Re: Request for Anodyne® Therapy/MIRE™ Clinical Data

Thank you for your inquiry regarding clinical evidence on Anodyne® Therapy System. In accordance with the FDA's ***Good Reprint Practices***, enclosed are only clinical research studies that have been published in peer reviewed journals. Anodyne Therapy, LLC provided financial support for the conduct of some of these studies, this is noted on all applicable publications.

Some of the studies included in this research compendium contain information regarding uses of Anodyne® Therapy for conditions that are not included in the FDA-approved labeling for this device. The FDA cleared indications for use for the Anodyne® Therapy System are for:

Temporary relief of pain, stiffness and muscle spasm; and temporarily increasing local circulation.

Anodyne® Therapy should not be used over an active cancer or directly over the womb in pregnancy. Additionally, the use of Anodyne® Therapy carries a *slight risk* for a superficial burn, which is minimized when proper protocols are followed.

If you have a question with regards to the data presented in any of these studies, we encourage you to contact the lead author as listed on the particular study in question. If this author is unavailable, please contact 1-800-521-6664 for additional information.

A Compendium of Clinical Evidence
on Monochromatic Infrared Photo Energy (MIRE™)
Anodyne® Therapy Systems

Peer Reviewed
Published Clinical Data

All data and cases presented in the compendium are the result of treatment with the Anodyne® Therapy System or the Equilight™ System, the veterinary version. No other devices or adjunctive therapies were used unless otherwise noted in the studies.

Peer-Reviewed Clinical Studies

These following studies have been published in medical journals that have a rigorous peer-review process. They are listed chronologically.

1. Horwitz L, Burke TJ, Carnegie DE. **Augmentation of Wound Healing Using Monochromatic Infrared Energy**. *Advances in Wound Care.* 1999;12:35-40.

2. Noble JG, Lowe AS, Baxter GD. **Monochromatic Infrared Irradiation (890): Effect of a Multisource Array upon Conduction in the Human Median Nerve**. *Journal of Clinical Laser Medicine and Surgery.* 2001;19:291-295.

3. Kochman AB, Carnegie DE, Burke TJ. **Symptomatic Reversal of Peripheral Neuropathy in Patients with Diabetes**. *Journal of the American Podiatric Medical Association.* 2002;92:125-130.

4. Prendergast JJ, Miranda G, Sanchez M. **Improvement of Sensory Impairment in Patients with Peripheral Neuropathy**. *Endocrine Practice.* 2004;10:24-30.

5. Leonard DR, Farooqi MH, Myers S. **Restoration of Sensation, Reduced Pain, and Improved Balance in Subjects with Diabetic Peripheral Neuropathy; A Randomized, Double Blind, Placebo Controlled Study**. *Diabetes Care*. 2004;27:168-172.

6. Kochman AB. **Monochromatic Infrared Photo Energy and Physical Therapy for Peripheral Neuropathy: Influence on Sensation, Balance and Falls**. *Journal of Geriatric Physical Therapy.* 2004;27:16-19.

7. Powell MW, Carnegie DE, Burke TJ. **Reversal of Diabetic Peripheral Neuropathy and New Wound Incidence: The Role of MIRE**. *Advances in Skin & Wound Care*. 2004;17(6):295-300.

8. DeLellis S, Carnegie DE, Burke TJ. **Improved Sensitivity in Patients with Peripheral Neuropathy: Effects of Monochromatic Infrared Photo Energy**. *Journal of the American Podiatric Medical Association.* 2005; 95(2):143-147.

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15. Mitchell, U, Myrer JW, Johnson AW, Hilton SC. **Restless Legs Syndrome and Near Infrared Light: An Alternative Treatment Option.** *Physiotherapy Theory and Practice.* 2010, Oct 26.

16. Mak, M, Cheing, G. **Immediate Effects of Monochromatic Infrared Energy on Microcirculation in Healthy Subjects.** *Photomedicine and Laser Surgery. 2012;30(2):1-8.*

17. Hsieh, R, Liao, W, Lee, W. **Local and Systemic Cardiovascular Effects from Monochromatic Infrared Therapy in Patients with Knee Osteoarthritis: A Double-Blind, Randomized, Placebo-Controlled Study.** *Evidence-Based Complementary and Alternative Medicine.* 2012; Article ID 583016.

18. Ammar, T. **Monochromatic Infrared Photo Energy in Diabetic Peripheral Neuropathy.** *International Scholarly Research Network* (ISRN) *Rehabilitation.* 2012; Article ID 484307.

19. Ahmed, E, Maayah,M,Mohammad Abu Asi, Y. **Anodyne Therapy Versus Exercise Therapy in Improving the Healing Rates of Venous Leg Ulcer**. *International Journal of Research in Medical Sciences. 2013;Aug;1(3):198-203.*

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SHORT REPORT

Augmentation of Wound Healing Using Monochromatic Infrared Energy

Exploration of a New Technology for Wound Management

Lon R. Horwitz, DPM, CWS; Thomas J. Burke, PhD; and Dale Carnegie, DPM

Abstract

VENOUS ULCERS, DIABETIC ULCERS, AND postamputation wounds are difficult to manage and often do not heal, even with aggressive medical management and conscientious patient compliance. The lack of consistent and favorable outcomes is a costly problem for the health care industry, patients, and physicians. With an aging American population, the opportunity to explore novel and cost-effective treatment strategies will likely increase during the next several decades.

It has recently been demonstrated that a commercially available, Food and Drug Administration-cleared monochromatic infrared energy (MIRE) modality increases nitric oxide (NO) in the blood and plasmas of normal adult subjects (authors' unpublished research). An elevation in NO has been suggested to be the basis of improved rates and quality of healing during L-arginine or nitroglycerin therapy in patients with wounds.[1-3] Dietary L-arginine, a source of NO via the constitutive isoform of the enzyme nitric oxide synthase (cNOS), increases the rate of wound healing following traumatic, thermal, and fracture injuries.[4-6]

It has been proposed that through this NO-mediated process, MIRE might prove beneficial in patients with venous and diabetic ulcers and in patients who exhibit slow rates of postamputation wound closure. The authors have evaluated the efficacy of wound healing during use of a commercially available MIRE device. The 5 patients discussed in this paper had wounds that were deteriorating or stagnant.

Purpose

The authors propose that the net result of increasing local amounts of circulating NO may be neovascularization, enhanced tissue perfusion, and successful wound healing.

Protocol

Approval for this protocol was obtained from the Colorado Multiple Institutional Review Board (COMIRB) prior to subject recruitment at the Denver Veterans Affairs Medical Center (DVAMC) and Denver Health Medical Center (DHMC) in Denver, CO. Subjects were recruited from patients attending the weekly DVAMC podiatric medical clinic or the DHMC physical medicine clinic. All had undergone months or years of conventional wound management (ie, alginate dressing [SORBASAN], a collagen gel [Kollagen], Unna's paste boot, silver sulfadiazine cream [Silvadene], wet-to-moist dressings, compression wraps), with little or no improvement in signs and symptoms, before initiation of the MIRE protocol.

Subjects with venous ulcers were recruited by one of the authors (L.R.H.) from the DVAMC clinic. They were given instructions on how to use the MIRE device at home. Subjects were to discontinue their previous conventional modalities, use the MIRE device for 30 minutes each day, redress the wound with a sterile saline wet-to-moist gauze dressing, apply a compressive elastic wrap, and return to the DVAMC podiatric clinic 1 week later. Each clinic visit was marked by thorough topical wound debridement and redressing with a wet-to-moist dressing, followed by application of a compressive elastic wrap around the wound and the lower extremity involved. Subjects were then seen twice a month or monthly for the next several months, depending on wound severity and progress toward healing. Wounds were photographed with a 35 mm camera. The photographs were scanned into a computer, and a commerically available image measurement and statistical software program was used to calculate the wound surface in square centimeters.The software can calculate area, perimeter, radius, and other measurements based on the ruler in the photograph.

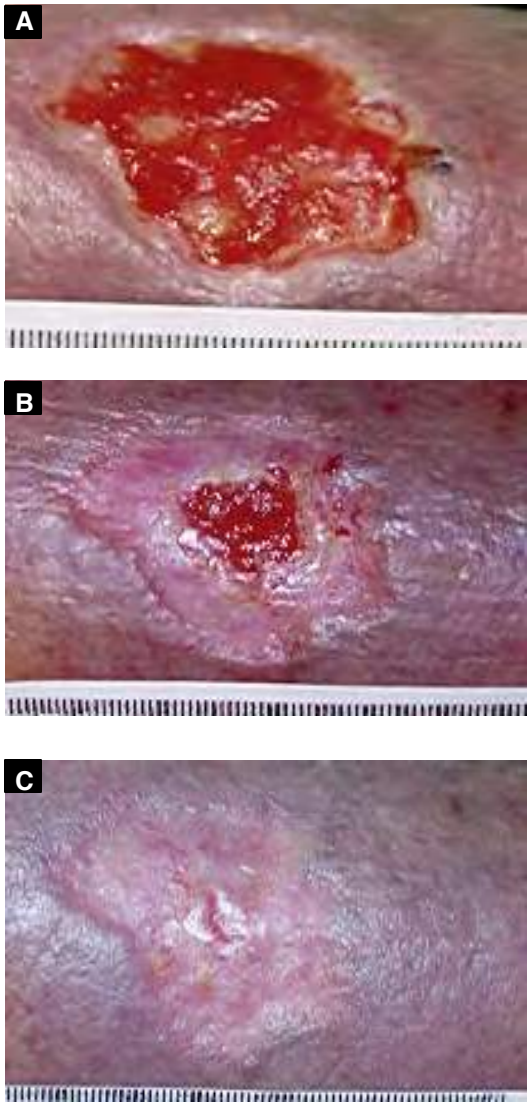
Subjects with ulcerations related to diabetes were recruited by one of the authors (D.C.) from the DHMC clinic. Their wounds were more recent or postsurgical in nature. Each clinic visit was marked by thorough topical wound debridement, a 30-minute treatment with the MIRE device, and redressing with a wet-to-moist gauze dressing. Patients were seen in the DHMC clinic weekly, then progressing to 2- to 3-week intervals, depending on wound severity and evidence of healing. Wounds were photographed with a 35 mm camera. As with the venous ulcers, the photographs were scanned into a computer and the wound surface area was calculated in square centimeters.

The author at the University of Colorado Medical School (T.J.B.) recruited the subject with a wound related to scleroderma. This subject was assessed and given a MIRE device for home use, with clinic visits scheduled every other week to monitor progress.

The MIRE device was cleared by the Food and Drug Administration in 1994 for the purpose of enhancing circulation and reducing pain. It delivers MIRE at 890 nanometers (nm) wave length (the only wave length the MIRE device emits) from each of 2 flexible pads containing 60 Gallium Aluminum Arsenide (GaA1As) diodes. The uniform average power emitted over the pad surface (22.5 cm^2) of the diode array was 9.0 milliwatts/centimeter squared (mw/cm^2), as measured with a Centronic OSD60-5T photodiode (Newberry, CA) Total energy density per 30-minute application (for each pad) was 43.2 Joules/centimeter squared (Jcm/cm^2). Of particular interest was the flexible nature of these pads, which allows placement on uneven body surfaces and at more than a single site. The design of the flexible pad allows the

Figure 1

PROGRESS OF WOUND HEALING IN SUBJECT 1



Venous ulcer measures 8.29 cm^2 on April 2, 1997 (photo A). 1.21 cm^2 on July 30, 1997 (photo B), and is resolved on October 29, 1997 (photo C).

infrared energy to be delivered perpendicular to and in contact with the involved site.

Subject 1

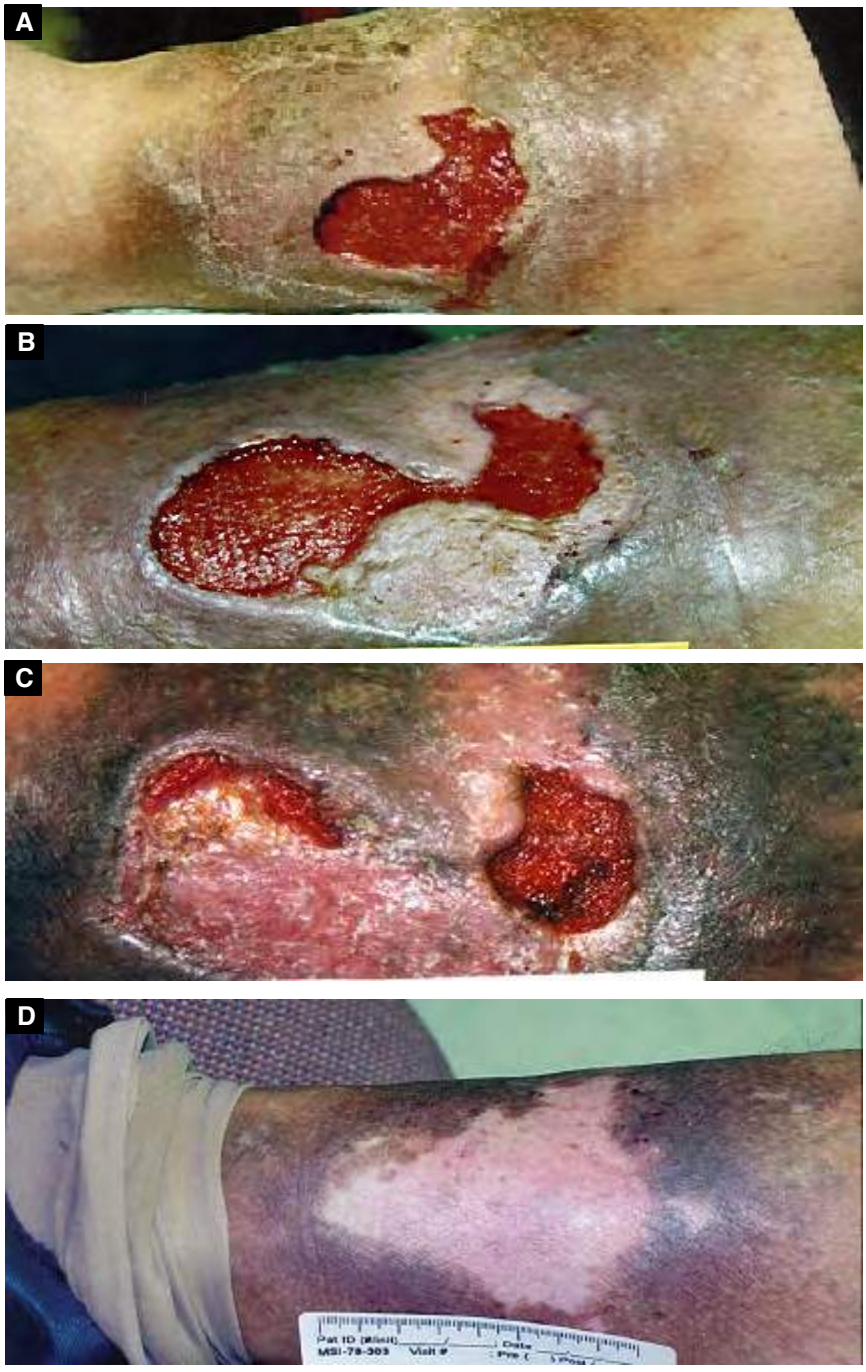
This 60-year-old, nondiabetic, Caucasian male had a painful venous ulcer, which had initally appeared in 1958, on his right lower leg. The subject enrolled in the study on March 12, 1997, after failed therapy with Unna's paste boot, an alginate dressing (SORBSAN), a collagen gel (Kollagen), and compression sock therapy over several weeks. On April 2, 1997, the ulcer's area measured 8.29 cm^2. The patient's protocol was daily use of the MIRE device at home for 30 minutes per day, after showering and cleaning the ulcer with a mild saline solution, and continued use of compression therapy. On July 30, 1997, the lateral ulcer measured 1.21 cm^2, and it resolved on October 29, 1997 (Figure 1). As of August 26, 1998, there have been no signs of tissue deterioration. The subject continues to be employed full-time, and he remarried during his study participation due to renewed self-image.

Subject 2

A 64-year-old, nondiabetic, obese, Caucasian male presented with a venous ulcer that had existed for 13 years. The wound was located at the lateral mid-calf on his left leg and was neither deteriorating nor progressing toward healing with conventional modalities (Unna's paste boot, a skin protectant spray [GRANULEX], a hydrocolloid dressing [DuoDERM], and silver sulfadiazine cream [Silvadene]). This subject was provided with an MIRE device for home use. Direct contact application was self-administered for 30 minutes every day prior to wet-to-moist dressing changes. A compression bandage was used for its therapeutic value and its ability to hold the dressings in place. Progress was monitored with weekly clinic visits

Figure 2

PROGRESS OF WOUND HEALING IN SUBJECT 2



Venous ulcer measures 21.34 cm^2 on October 25, 1995 (photo A), 9.78 cm^2 on December 6, 1995 (photo B), 1.61 cm^2 and 3.41 cm^2 on April 10, 1996 (photo C), and is resolved with no breakdown on May 28, 1998 (photo D).

initally. As the ulcer healed, progress was monitored with monthly clinic visits. The wound area was 21.34 cm^2 at the initiation of the MIRE protocol on October 25, 1995 (Figure 2).

Eleven months later (September 11, 1996), use of the MIRE was discontinued, with the wound area measuring 1.3 cm^2. Wet-to-moist dressings were applied every day, along with compression wrap therapy, and clinical debridement was performed every 4 weeks. On May 28, 1998, long-term follow-up revealed healthy pink, full-thickness, intact skin, absence of hemosiderin deposition, and no open lesion. Compression sock therapy was instituted for long-term management of lower extremity venous disease. The subject is now employed full-time and has achieved his goal of playing softball.

Results with Diabetic Ulcers

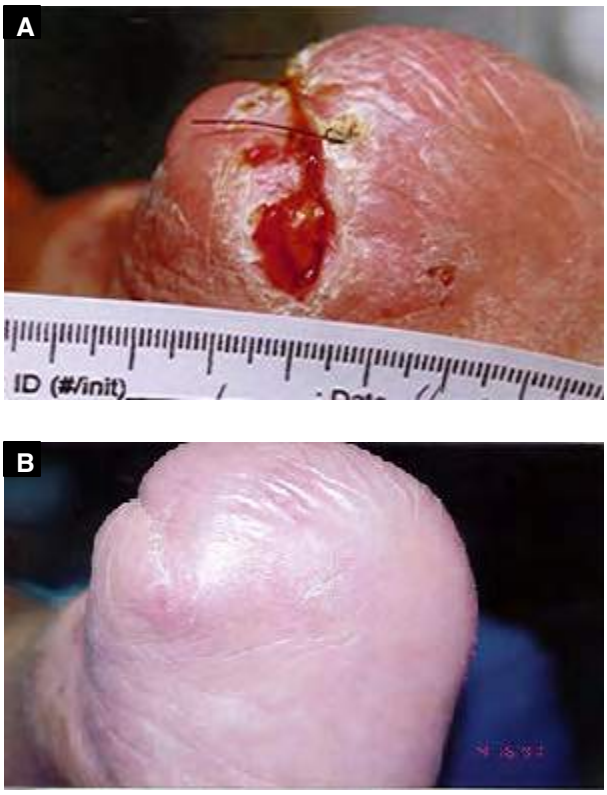
Subject 3

A 64-year-old African American female with Type I diabetes presented with wound dehiscence 2 months after a left great toe amputation. She was assessed and instructed on the use of the MIRE device at home. She began therapy on November 25, 1996. The distal pedal wound was 1.81 cm^2 (Figure 3), and a 2-year-old dorsal wound (not shown) was 7 cm^2. The MIRE device was administered for 30 minutes every other day, followed by wet-to-moist dressings, and the subject was monitored with clinic visits at the DHMC every other week. After the first 6 weeks, the interval between clinic visits was extended to 2 to 3 weeks. This subject became weight-bearing on February 12, 1997 - the first time in 2 years - and was fitted with an orthotic. Monochromatic infrared energy usage was discontinued after 5 months of management, and complete closure of the distal and dorsal wounds was achieved.

This subject also had a wound on her right heel that had been present for 7 months and was deteriorating with conventional management. After wound debridement, tendon exposure was noted. Outpatient therapy began on October 16, 1996, when the heel ulcer measured 2.26 cm^2. She used the MIRE device at home, and she was followed with twice-a-month clinic visits. By April 16, 1997, there was no clinical evidence of an open wound. This subject was able to join her husband on a fishing trip for the first time in 2 years.

Figure 3

PROGRESS OF DISTAL WOUND HEALING IN SUBJECT 3



Wound dehiscence measures 1.81 cm^2 on November 25, 1996 (photo A) and is resolved on April 16, 1997 (photo B).

Subject 4

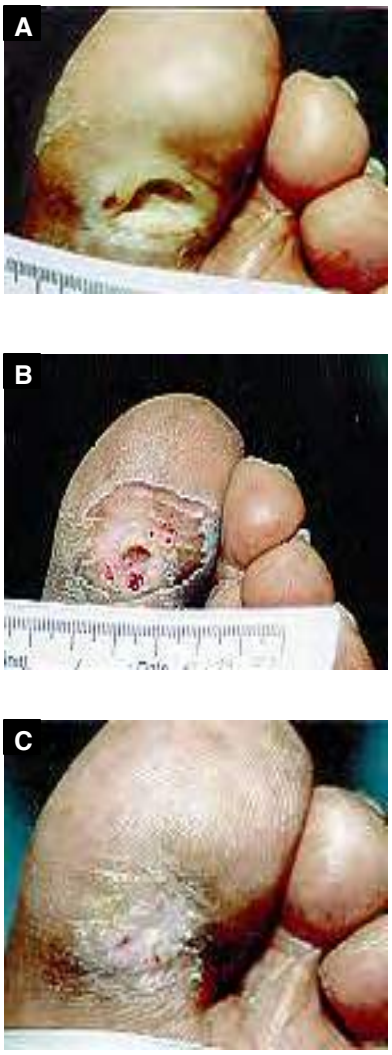
This 64-year-old African American male with Type I diabetes presented with a foreign body embedded in his left great toe. The foreign body was surgically excised, and this subject subsequently was discharged. One month later, the subject was referred to the physical medicine clinic at DHMC with a non-healing ulcer, 2 cm in diameter, penetrating down to bone at the surgical site. The subject refused amputation of the left great toe. Treatment involved weekly topical debridement, daily saline soaks with wet-to-moist dressings, and use of the MIRE device for 30 minutes once a week in the outpatient clinic. A transparent dressing (OpSite) was placed over the wound to avoid contamination. A visiting nurse applied a wet-to-moist saline dressing each day. After 3 weeks, sensation in the left great toe returned, edema greatly diminished in the hallux, and there was noticeable improvement in granulation tissue within the ulcer cavity. During the final 6 weeks, the subject was treated 3 times with the MIRE device. Four months after surgery, the ulcer had healed with neither scarring nor callus tissue (Figure 4).

Results with a Scleroderma-Related Ulcer

A 45-year-old Caucasian female presented with a 13-year history of scleroderma. In November 1997, she developed a painful ulcer on the middle finger of her right hand. Conventional

Figure 4

PROGRESS OF WOUND HEALING IN SUBJECT 4



Wound area of this diabetic ulcer measures 0.64 cm^2 on September 3, 1997 (photo A) and 0.18 cm^2 on October 29, 1997 (photo B). The ulcer is resolved on December 3, 1997 (photo C).

therapy yielded no improvement over the next 4 months. At-home MIRE treatments of 30 minutes twice a day began on March 14, 1998. Within 2 weeks, the lesion had completely healed (Figure 5).

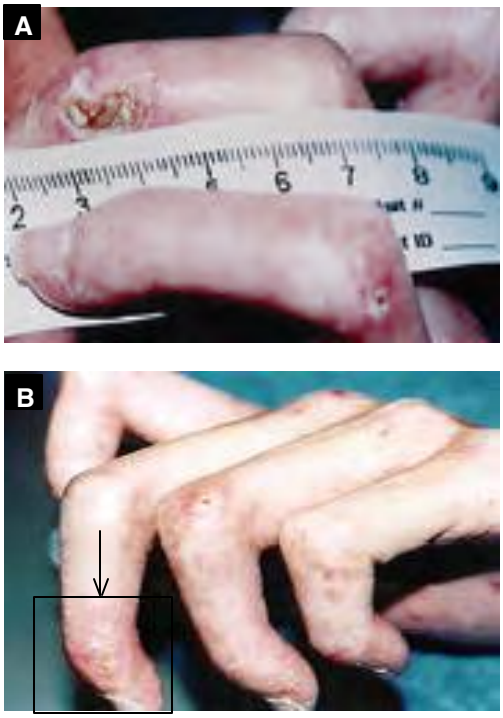
Discussion

Monochrmatic infrared energy was effective in healing a variety of wounds that either had become stagnant or had deteriorated with conventional management. Because virtually all other interventions were discontinued, these results suggest that MIRE, perhaps the specific wave length of 890 nm, could have been responsible. In addition, the design of the pads that maintained the focused energy density perpendicular to the wound site and the large surface area of the diode array may have contributed to the results achieved. In 3 cases (subjects 1, 2, and 3), the healed wounds have not recurred during 1 to 2 years of follow-up evaluation, despite the cessation of MIRE exposure. The ease of pad placement, which does not involve the stress of continuous hand positioning, is subject-friendly and contributed to the subject compliance required in this study.

It recently has been demonstrated that application of this particular MIRE device to the skin for 30 minutes increases plasma NO in nondiabetic subject volunteers, as measured with a Sievers Instrument, Model 280, Nitric Oxide Detector (authors' unpublished data). NO is a potent endogenous vasodilator that can be liberated from tightly bound hemoglobin on exposure to various wave lengths of energy.[7] In the patients described here, the use of MIRE on refractory wounds may have involved elevations in local and systemic NO. Recently, Schindl et al[8] reported increased circulation in the feet of diabetic patients with microangiopathy after using a visible red monochomatic energy device with an energy density of 30 J/cm^2. The circulatory effects were sustained even after the use of the device was discontinued. Bioavailable NO has beeen shown to enhance arterial perfusion, by vasodilation, at a site of previous vascular compromise.[9]

Figure 5

PROGRESS OF WOUND HEALING IN SUBJECT 5



Wound area of this ulcer related to scleroderma measures 0.44 cm2 on March 13, 1998 (photo A). The ulcer is resolved on March 27, 1998 (photo B).

NO is a powerful anabolic agent,[10] and it is thought to be the molecule that accounts for the wound healing efficacy of oral supplementation with L-arginine[1] or topical nitroglycerin[2], both of which are sources of NO. In addition, the healing process may be accelerated by increasing circulatory NO-a potent vasodilator.[11] Shorter wave lengths in the ultraviolet range also have been shown to promote vasodilation through release of NO.[12] NO levels were not measured in the subjects described in this paper. However, the enhanced healing suggests that some subjects had the capacity to generate local increases of NO in response to MIRE expo-

sure. It is important to recognize that 2 of the subjects in this DVAMC study had venous ulcers for many years and that no previous therapy had effected wound closure and/or healing. Thus, it is unlikely that the ulcers would have healed without external intervention.

NO is bound to the cysteine 93 of the beta chain of hemoglobin during the passage of red blood cells through the lungs.[13] In addition to oxygen, hemoglobin also transports NO throughout the body. NO is thought to aid in vascular perfusion by dilatation of arterioles, thus enhancing tissue oxygenation, nutrient delivery, and removal of waste products of metabolism.

MIRE appears to accelerate healing at local sites where the MIRE pad is placed. This may be accomplished by liberating NO from hemoglobin or possibly from other nitrosylated compounds.[13] Although NO has a short half-life, usually less than 3 seconds,[14] the body's circulation provides a continuous supply of red blood cells containing NO. Thus, there is an uninterrupted delivery of red blood cells containing NO to the site where the MIRE pads are placed. Once MIRE exposure is initiated, the local effect would be continuous release of NO from hemoglobin, vasodilation, angiogenesis, enhanced tissue perfusion, and less ischemia. There also may be an anabolic effect that manifests itself as improved tissue remodeling.[10]

Use of MIRE in the subjects described in this paper appeared to have contributed to improving their quality of life, as described earlier. Enhanced dermal tissue repair and fewer visits to wound care providers potentially allows an overall savings of health care dollars, wound supplies, and physician and patient time. The MIRE device is a novel technology that has been demonstrated to be a noninvasive, portable, drug-free method for potentially healing chronic wounds resistant to conventional modalties.

Additional research is needed to show whether MIRE is independently responsible for wound healing. Originally, the research described in this paper was designed as a COMIRB-approved, randomized, placebo-controlled, double-blind study. However, it soon became apparent to the participating medical professionals which patients were using active versus placebo MIRE devices. For ethical reasons, all patients using the placebo devices were switched to active MIRE devices. AWC

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Monochromatic Infrared Irradiation (890 nm): Effect of a Multisource Array upon Conduction in the Human Median Nerve

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ABSTRACT

***Objective*: Antidromic conduction studies in the human median nerve were used to assess the neurophysiological effects of irradiation of the skin overlying the nerve using a novel treatment unit comprising a multisource monochromatic infrared diode array (Equilight, Denver, CO). *Materials and Methods*: Healthy human volunteers ($n = 40$) were recruited and randomly allocated to one of four groups: control, placebo, or one of two treatment groups (1.7 and 4.0 J/cm^2). After baseline recordings of negative peak latency (NPL) were completed on the nondominant arm, subjects were treated according to group allocation. Recordings were subsequently repeated at 5-min intervals over a 45-min period. *Results*: Analysis of negative peak latency difference scores (ANOVA) demonstrated significant differences in NPL between groups and over time ($p < 0.05$). While in the control and placebo groups NPL values remained relatively stable, in the two treatment groups such values decreased marginally, with the greatest effects observed in the 4.0 J/cm^2 group (e.g., at 5 min, differences in NPL [mean ± SEM]: control group, 0.02 ± 0.03 msec; treatment group 2, 4 J/cm^2, −0.07 ± 0.03 msec). Similar significant differences were observed in skin temperature; correlation analysis indicated a weak (but expected) positive linear relationship between skin temperature and nerve conduction velocity ($r = 0.125$). *Conclusion*: These results suggest that irradiation at the parameters and under the conditions used here produce a direct neurophysiological effect. The magnitude of such effects are in keeping with previous findings using single source arrays at higher radiant exposures or thermal effects of the treatment unit.**

INTRODUCTION

SO-CALLED LASER THERAPY, the use of low-intensity lasers and superluminous diodes as a therapeutic modality at radiant exposures typically under 30 J/cm^2, has been investigated and clinically applied for nearly 30 years. Over this period, technological advances have led to the replacement of gaseous He-Ne systems with smaller, more portable laser-diode–based devices as the mainstay of treatment; additionally, multisource treatment arrays based upon clusters of diodes, which allow treatment of larger tissue areas, have become increasingly popular with clinical practitioners.[1] While this therapy has been promoted (and researched) as an effective treatment option for various pathologies such as delayed wound healing and pain,[1–3] controversy and skepticism has surrounded its use, particularly for the relief of pain.[4,5] Such controversy is based in part upon the lack of an obvious mechanism for the putative treatment effects associated with laser therapy;[4,6] as a result, a significant proportion of the studies completed to date within this field have aimed to establish definitively the basic physiological and biological processes that may underlie any claimed clinical benefits of laser therapy.

In assessing putative mechanisms of action, a number of studies have assessed the effects of irradiation upon various neurophysiological functions.[6–15] Findings from such studies in animals include reports of laser-generated or delayed action potentials *in vitro,*[7] and laser-mediated increases in conduction latencies in the isolated frog sciatic nerve (820 nm; 2.38–3.57 J).[8] In humans, most work to date has concentrated on assessment of the effects of laser upon peripheral nerve conduction, with variable effects reported.[9–14] While one of the earliest reports in this area noted an apparent increase in nerve conduction latency

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in the superficial radial nerve,[9] other studies in the same nerve have produced variable findings using He-Ne[10] or infrared diode irradiation.[11] Perhaps most interestingly, Kramer and Sandrin[12] compared He-Ne (632.8 nm, 10 mW), GaAlAs (780 nm, 12 mW) and placebo laser irradiation (using white light) and found no significant effects upon sensory latencies in the superficial radial nerve.

Studies at this center have similarly yielded variable results.[13,14] Infrared laser irradiation (830 nm; continuous wave [CW]; 9.6 J/cm^2) was found to produce a significant increase of approximately 0.4 msec in median nerve negative peak latency (NPL).[14] In contrast, no significant results were found using pulsed irradiation (73 Hz versus 5 kHz; 820 nm; 1.5 J/cm^2).[13] Interestingly, when the relevance of radiant exposures (830 nm; CW; 1.5–12 J/cm^2) upon conduction velocity in the human median nerve was investigated, a significant increase in negative peak latency was reported (magnitude of change = ~0.2 msec), but only for the lowest radiant exposure (i.e., 1.5 J/cm^2); such effects were coupled with a decrease in recorded skin temperature.[15] Finally, laser-mediated *decreases* in motor and sensory distal latencies after laser irradiation have also been demonstrated, using higher levels of radiant exposure (magnitude of change = ~0.18 msec); GaAlAs; 830 nm; 40 mW; CW; 1.2 J/point).[16]

While such investigations have been based upon the use of single source lasers or superluminous diodes, no study has yet attempted to quantify the putative effects of multisource treatment arrays. Thus, despite their increasing popularity over the last 10 years,[3,5] the precise effects of this type of device remain unknown. Therefore, the aim of this current study was to examine the effects of a multisource array upon median nerve conduction in humans, as this is a well-established and characterized model of nerve conduction. For this study, a novel flexible treatment device was used to optimize application of radiation to the skin overlying the nerve in the forearm.

MATERIALS AND METHODS

Preliminaries

Following approval by the University of Ulster's Research Ethics Committee, healthy human volunteers (n = 40; male and female; 20–40 years old) were recruited and screened for history or current signs/symptoms of neuromuscular disorders or peripheral neuropathy. The experimental procedure was explained to subjects, who were then asked to sign a simple consent form and randomly assigned to one of four experimental groups under single-blinded conditions. Subjects were randomly allocated to groups and remained supine for the duration of the experiment. The volar surface of the right forearm and hand was prepared using alcohol, and the stimulation and recording sites, at the elbow and second digit, respectively, were cleaned with a colloidal abrasive (Omniprep [Weaver, Aurora, CO]) to improve electrical conductance.

Recording procedures

A bipolar muscle stimulator was used to identify the median nerve at the elbow for the purposes of antidromic stimulation; a monopolar muscle stimulator was further used to map the course of the nerve along the forearm to the palmar surface of the hand to facilitate the accurate positioning of the treatment arrays (Fig. 1). A bar stimulating electrode was attached at the elbow, and two digital ring recording electrodes to the second digit, with the active electrode on the proximal phalanx and the reference electrode 3 cm distally on the middle phalanx. An earth electrode was also attached approximately 2 cm above the wrist, and all electrodes connected to a Mystro$^+$ electrophysiological stimulation and recording system (Medelec Ltd., Surrey, U.K.) The nerve was stimulated supramaximally (at 20%) using 100-μsec pulses, delivered at a frequency of 1 Hz; averaged responses to a train of 16 pulses were recorded and stored digitally for subsequent analysis. Recordings were taken at 2-min intervals until three consecutive readings showed constant negative peak latencies (less than 0.01 msec). Once stabilized in this way, action potentials were recorded at 5-min intervals for the reminder of the experimental period (i.e., 45 min).

Ambient and skin temperature were recorded concomitantly throughout the procedure at 1-min intervals. For this, one ambient probe and one skin thermistor (model EU-U-V3-2; Grant Instruments Ltd., Cambridge, U.K.) were used, with the latter attached to the skin overlying the mid-point between the elbow and the wrist. All were connected to a Squirrel data logger

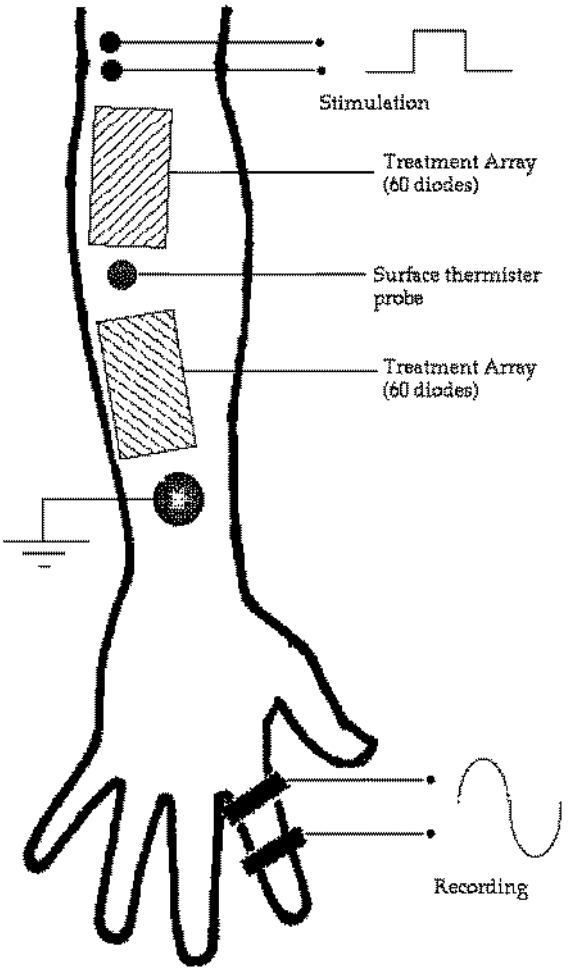

FIG. 1. Experimental procedure, showing electrical stimulation, electrode placement, and area of irradiation.

(Squirrel meter, 1200 series; Grant Instruments Ltd.) interfaced with a microcomputer; both thermistors were sensitive to temperature changes of ±0.05°C.

Irradiation parameters

A multisource monochromatic treatment unit (Equilight, Denver, CO) was used to irradiate the skin overlying the course of the nerve, after baseline recording of NPL was complete. This device produced infrared radiation (890 nm; pulsed at 270 Hz; average irradiance set at 0.42 mW/cm^2) via two multisource arrays, each containing 60 diodes (irradiation area: 22.5 cm^2 per array); the unit was applied to deliver radiant exposures of 1.7 J/cm^2 (treatment group 1) or 4.0 J/cm^2 (treatment group 2) dependent upon group allocation.

For the placebo condition, the procedure was repeated as for the 4 J/cm^2 group (treatment group 2) without activating the unit, thus allowing no active radiation to be delivered. Furthermore, the device was hidden from the subjects' view in all groups, in order to maintain blinding conditions.

Analysis

NPL, that is, the time (msec) from onset (stimulus artefact) to the maximum negative deflection of the recorded action potential, or negative peak latency, was measured by an independent investigator. To allow for variation between subjects' baseline values, NPL difference scores were calculated for each subject by subtracting initial NPL values (time = 0 min) from subsequent measurements. Ambient and skin temperature readings were treated similarly. All such results were analyzed using repeated measures analysis of variance (ANOVA) and appropriate *post hoc* Fisher tests to determine whether any differences between conditions were statistically significant. The significance level was set at $p < 0.05$ for all tests. All statistical analyses were completed using the Statview statistical analysis package (Abacus Concepts Inc., Berkley, CA).

Ambient temperature

Shift in ambient temperature of more than ±0.5°C in any one experiment was used as the basis for exclusion of relevant data for that subject. This did not occur for any of the subjects. Beyond this, analysis of collected ambient temperature data indicated no significant differences between groups.

RESULTS

Figure 2 shows NPL differences (msec; means ± SEM) plotted against time in minutes for control, placebo, and both treatment groups. Although values in the control and placebo groups increased slightly over the 45 min of the experiment, NPLs in the two treatment groups *decreased* over the same period. Statistical analysis (ANOVA) of these data indicated significant differences among groups ($p = 0.0281$), over time ($p = 0.012$), and an interactive effect ($p = 0.0066$). *Post hoc* Fisher tests further showed significant differences between control and treatment 2, treatment 1, and placebo, as well as treatment 2 and placebo groups at the 5-min interval. At 10-, 15-, 20-, and 45-min points, significant differences were found between treatment group 2 (i.e., 4 J/cm^2) versus control and placebo groups.

Concomitant skin temperature recordings for all four groups are summarized in Figure 3, which shows temperature differences (°C; means ± SEM) plotted against time in minutes. At baseline (i.e., 0 min), the mean skin temperature value for all groups was 31.42 ± 0.18°C (mean ± SEM), and at the 45-min

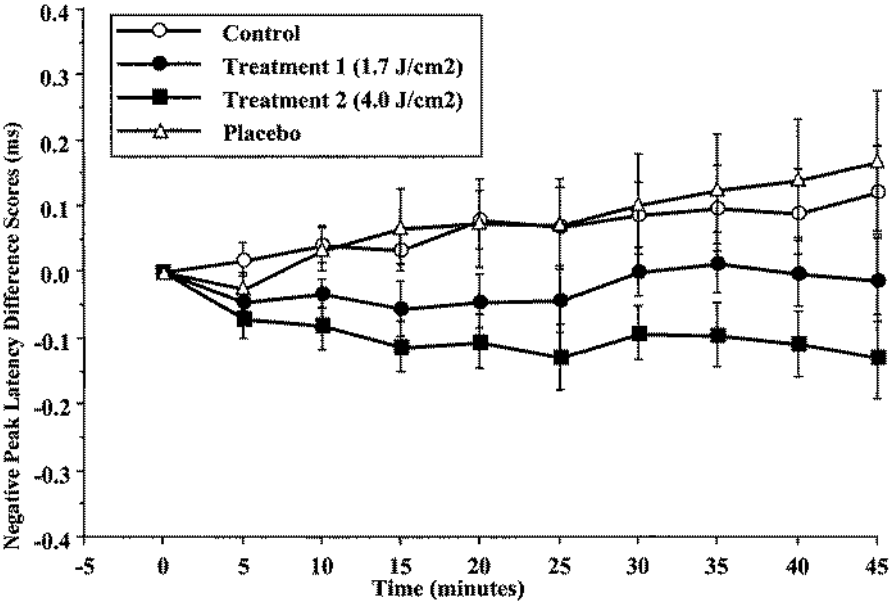

FIG. 2. Negative peak latency difference scores (NPLDs; msec) against time in minutes (points represent means ± SEM; $n = 10$ for all groups).

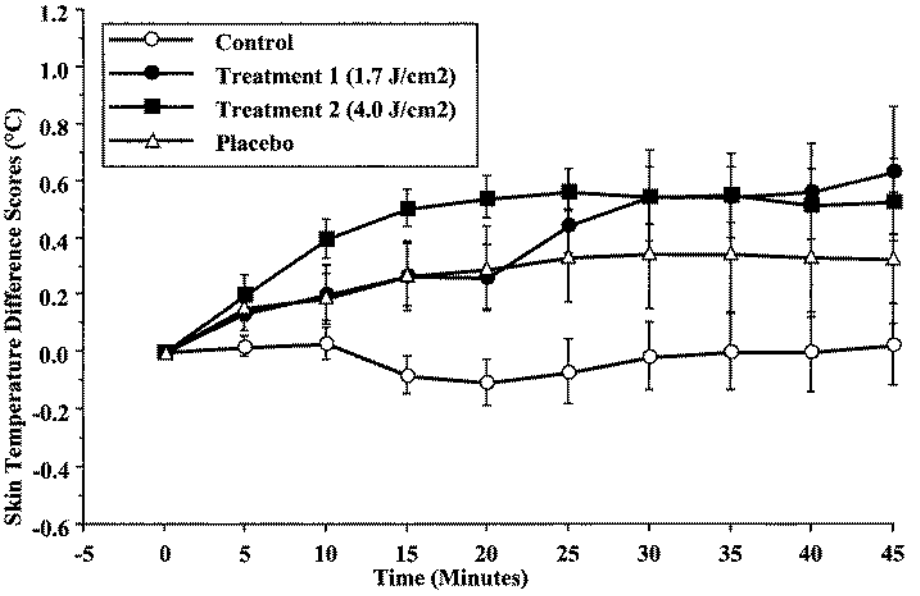

FIG. 3. Skin temperature difference scores (°C) against time in minutes (points represent means ± SEM; $n = 10$ for all groups).

time point the mean value was 31.8 ± 0.2°C (mean ± SEM). Results for the control group remained relatively stable over the experiment period; in contrast, skin temperature for both treatment groups and the placebo group increased. Statistical analysis confirmed that there were significant differences in skin temperature among groups ($p = 0.007$), over time ($p = 0.0001$), and an interactive effect between the time points and experimental groups ($p = 0.0289$). *Post hoc* Fisher tests further showed significant differences between control and both treatment groups at the 10- and 30-min points. At 15, 20, and 25 min, *post hoc* Fisher tests showed significant differences among control and the other three experimental groups.

In summary, while there were some differences seen between groups, the most consistent findings indicated that the 4.0 J/cm^2 treatment group demonstrated significant (and the greatest) decreases in negative peak latency values, coupled with increases in skin temperature values.

DISCUSSION

Despite nearly 30 years of research and clinical application, there is still considerable debate regarding the efficacy of laser therapy, in part due to the lack of an obvious mechanism of action underlying the claimed effects of such devices.[5] In the laboratory, previous studies have demonstrated variable effects of irradiation upon nerve conduction, based exclusively upon single source devices;[8,9,13,14] the effects of irradiation using multisource arrays have not previously been investigated. Previous research at this center has examined the effects of irradiation of the current multisource array (0.18, 0.54, and 1.45 J/cm^2; GaAlAs, 890 nm) upon wound healing in murine skin; that study concluded that irradiation at these parameters did not affect the rate of wound healing (0.18 and 0.54 J/cm^2) but rather seemed to produce an inhibitory effect (1.45 J/cm^2).[17] Therefore, the aim of the current study was to examine the neurophysiological effects of such multisource monochromatic infrared irradiation upon conduction in the human median nerve; previous investigations in this nerve have demonstrated direct neurophysiological effects of laser irradiation.[8,13–16]

Analysis of negative peak latencies in the current study indicate that monochromatic infrared irradiation of the volar forearm overlying the nerve can significantly alter nerve conduction. In the present study, irradiation at the parameters indicated resulted in a *decrease* in latency, and thus an increase in conduction velocity. Further analysis showed that the effects of irradiation were relatively long lasting: decreases in NPL lasted for the duration of the experimental period (up to 45 min).

The finding of concomitant increases in skin temperature may provide an explanation for the observed findings, as it has been well recognized that a variation in tissue temperature will cause a corresponding alteration in nerve conduction velocities.[18–20] This is interesting as the irradiation parameters (1.7 and 4.0 J/cm^2) used in the present study would typically be classified as low intensity and, therefore, essentially athermal. The concomitant increase in skin temperature reported here contrasts with the findings of previous studies. Basford et al.,[16] similarly demonstrated a laser-mediated decrease in motor and sensory latency of the median nerve (1.25 J/point; 890 nm; CV; infrared), but found no significant alterations in skin temperature. In contrast, Greathouse et al.[11] reported significant *reductions* in skin temperature following laser irradiation at 20 or 120 sec to five 1-cm^2 segments along the course of the superficial radial nerve. As a result, Greathouse and colleagues[11] discounted the observed (significant) increases in conduction, positing that unacceptable fluctuations in room temperature had produced the effects upon skin temperature and nerve conduction; this has been subsequently challenged by Baxter et al.[14] Such an explanation is clearly not applicable in the current study, as ambient temperature remained stable, and skin tem-

perature differences did not occur in the control group. It must therefore be assumed that changes in the measured skin temperature were treatment mediated; however, the precise mechanism underlying this effect is unknown. This notwishstanding, a conductive heating effect cannot be discounted as the treatment arrays were found (even at the relatively low settings used here) to produce a mild level of heat. One possible explanation may lie in the high level of total energy delivered over the course of the nerve in the current study; at 164 J for treatment group 2 (i.e., 4 J/cm^2), this would be over 10-fold greater than levels used in previous experiments (based upon single point sources). Given such high levels of delivered energy, a significant increase in skin temperature might reasonably be expected in the treatment groups, along with a parallel increase in nerve conduction velocity. Correlation analysis between skin temperature difference score values and NPL difference score values did provide evidence for such a relationship ($r = -0.562$); in other words, an increase in skin temperature was accompanied by a decrease in NPL and therefore representative of an increase in median nerve conduction velocity. This observation suggests that the effects observed in the current study may have been based upon a thermal mechanism, rather than the result of a direct photobiological effect. However, this is largely speculative. More detailed investigation is required before this can be definitively demonstrated.

In the final analysis, the present study has demonstrated a significant effect upon nerve conduction *in vivo*. However, analysis of results indicates that infrared irradiation delivered by this device may have produced a thermal rather than the expected photobiological effect. The significance of such an effect in the clinical application of this therapy has yet to be defined and requires further research; in particular, the (marginal) thermal effects reported here may be produced, and possibly more simply and effectively, with other electrophysical agents.

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Symptomatic Reversal of Peripheral Neuropathy in Patients with Diabetes

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Forty-nine consecutive subjects with established diabetic peripheral neuropathy were treated with monochromatic near-infrared photo energy (MIRE) to determine if there was an improvement of sensation. Loss of protective sensation characterized by Semmes-Weinstein monofilament values of 4.56 and above was present in 100% of subjects (range, 4.56 to 6.45), and 42 subjects (86%) had Semmes-Weinstein values of 5.07 or higher. The ability to discriminate between hot and cold sensation was absent (54%) or impaired (46%) in both groups prior to the initiation of MIRE treatment. On the basis of Semmes-Weinstein monofilament values, 48 subjects (98%) exhibited improved sensation after 6 treatments, and all subjects had improved sensation after 12 treatments. Therefore, MIRE may be a safe, drug-free, noninvasive treatment for the consistent and predictable improvement of sensation in diabetic patients with peripheral neuropathy of the feet. (J Am Podiatr Med Assoc 92(3): 125-130, 2002)

Diabetic peripheral neuropathy is partly a consequence of diabetes-mediated impairment in blood flow to, and resultant hypoxia of, nerves.[1] There is no treatment to reverse the neurologic deficit of this disease manifestation, although capsaicin cream, tricyclic antidepressants, and valproic acid are efficacious in diminishing pain.[2] Studies have demonstrated some increase in conduction velocity with the use of aldose reductase inhibitors.[3] Due to the notable problems in feasibility, logistics, and efficacy that accompany each of these approaches, additional research into preventing and treating diabetic neuropathy has become a major research focus of the American Diabetes Association, the Juvenile Diabetes Foundation, and the National Institutes of Health.

Diabetic peripheral neuropathy is considered to be a progressive disease. Impaired sensation in the feet becomes evident several years after the onset of diabetes.[4] Ultimately, the loss of feeling can result in one or more ulcerations of the foot. If the degree of sensory impairment reaches a level in which the subject is insensate to the Semmes-Weinstein 5.07 monofilament, there is a very high likelihood of ulceration, followed by amputation.[5] Therefore, improving blood flow in the feet of patients with diabetes could help restore sensation; furthermore, restoration of adequate circulation may reverse neuropathy and thus delay the onset of ulcerations that often lead to amputation.

In the authors' practices, many patients have been treated with monochromatic near-infrared photo energy (MIRE) in a protocol designed to heal otherwise recalcitrant ulcers, including venous stasis and diabetic ulcers of the lower leg.[6] MIRE is also used to facilitate the progress of patients treated with physical therapy after musculoskeletal and soft-tissue injuries, as it has been cleared by the US Food and Drug Administration under 510k for increasing circulation and reducing pain. In many instances, patients being treated for a variety of problems at the outpatient Physical Therapy Department of The Medical Center of Aurora, Colorado, have told their therapists that they could feel warmth during MIRE application, although they had been unable to discern differences

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in temperature prior to MIRE treatment. These reports usually occurred several days after treatment began.

To investigate whether sensation returned in the lower extremities during MIRE treatment, a prospective study was performed on subjects with diabetes in whom the loss of sensory perception could be easily documented. The sole complaint of the subjects was neuropathy; none had lower-extremity ulcers. At the end of the 30-day trial, all 49 subjects had partial restoration of feeling in their feet. To the authors' knowledge, this is the first highly successful, noninvasive, drug-free therapy that restores, at least temporarily, neural sensation in subjects with diabetes.

Materials and Methods

All of the subjects in the study were treated at the Physical Therapy Department of The Medical Center of Aurora, Colorado. The subjects ranged from 35 to 80 years of age; 25 had type 1 diabetes and 24 had type 2 diabetes (Tables 1 and 2). On the basis of the Semmes-Weinstein monofilament test, all had peripheral neuropathy. The ability to detect hot *versus* cold was also absent or impaired in all subjects. No novel treatments or pharmaceuticals that would have uniquely modified circulation in the lower extremities were employed for 30 days prior to beginning this study. No changes were made in the standard of medical care associated with diabetes for these subjects, including insulin or oral hypoglycemic agents, diet, blood pressure medications, or exercise. The Semmes-Weinstein test is often used as an adjunct to gait-testing analysis in a physical therapy department and such information can guide the therapist in reeducating the muscles of the lower leg despite ongoing neuropathy.[7] The present study included patients with diabetes whose Semmes-Weinstein, hot-*versus*-cold discrimination, and gait analysis values were abnormal. In an outpatient physical therapy department, the goal is to rehabilitate patients as quickly as possible. None of the following clinical research tools were used: transcutaneous partial pressure of oxygen, vibratory sensation measuring instrumentation, or reflex measuring devices.

MIRE is delivered from a series of 60 gallium aluminum arsenide diodes in a flexible pad (diode array) placed on the foot or lower leg. The device used in this study was the Anodyne Therapy System (Anodyne Therapeutics LLC, Denver, Colorado). Four diode arrays were used and each application lasted 30 minutes. One diode array was placed on the distal posterior aspect of the tibia in an effort to alter circulation in the posterior tibial artery, and a second diode array was placed over the anterior distal tibia in an effort to affect the dorsalis pedis artery. The third and fourth diode arrays were placed on the dorsal and ventral surfaces of the foot. This was done to each foot. If the posterior tibia region was uncomfortable for the subject, two diode arrays were placed on the plantar surface of each foot.

Several sizes of Semmes-Weinstein monofilaments (3.22, 3.84, 4.08, 4.17, 4.31, 4.56, 4.74, 4.93, 5.07, 5.18, 5.46, 5.88, 6.10, and 6.45) were used to determine the absolute level of neurological impairment. The monofilaments were randomly applied to three test sites: the great toe, plantar arch region, and fourth toe. The same locations were tested at each visit. The filament was applied until it began to bend and it was held in place for approximately 1.5 seconds. Each site was tested three times. Care was taken to test areas in which the keratin layer was the least thick. The response to the filament testing was based on the subjective response of the subject, who was asked to say "now" when the filament could be felt. In addition, the subject was queried as to the location on the foot where the monofilament was sensed to assure objectivity of the measurements taken.

Hot-*versus*-cold testing was done at the same test sites on the feet. Response to the hot-*versus*-cold testing was determined from the subject's reports as to whether he or she could correctly identify the hot or cold bar at three sites. The responses were graded as absent (0 of 3 correct answers at all sites); impaired (correct discrimination at one or two sites); or intact (correct discrimination at all three sites). One of the authors (A.B.K.) performed all sensory tests and applied the diode arrays to each subject.

Results

The data for subjects with type 1 and type 2 diabetes were grouped and analyzed by repeated measures analysis. Values were reported as mean ± SD and significance was accepted at $P < .05$.

The ages of the subjects, type of diabetes (type 1 or 2), Semmes-Weinstein values, and hot-*versus*-cold discrimination ability prior to beginning the study and after MIRE treatments are shown in Tables 1 and 2. As indicated in Table 3, subjects with type 1 diabetes (60.4 ± 12.8 years of age) were approximately 12 years younger than the type 2 subjects (72.5 ± 5.5 years of age).

Baseline Semmes-Weinstein deficits were virtually identical for type 1 (5.49 ± 0.52) and type 2 (5.44 ± 0.47) subjects (Table 3). There were 13 subjects with type 1 diabetes and 13 type 2 subjects who had no ability to discriminate between hot and cold prior to MIRE treatment (Tables 1, 2, and 4).

Table 1. Data for Subjects with Type 1 Diabetes (N = 25)

Age (years)	Semmes-Weinstein Monofilament Values			Hot-*versus*-Cold Discrimination	
	Baseline	6 MIRE Treatments	12 MIRE Treatments	Baseline	12 MIRE Treatments
70	4.93	4.31	4.08	Impaired	Intact
71	5.07	4.56	4.17	Impaired	Intact
69	5.88	4.93	4.17	Absent	Impaired
72	5.07	4.31	4.08	Impaired	Intact
54	5.07	4.17	3.84	Impaired	Intact
64	5.46	5.07	4.56	Absent	Impaired
50	4.93	4.17	4.08	Impaired	Intact
54	5.18	4.56	4.31	Impaired	Impaired
52	5.88	5.07	4.31	Absent	Impaired
45	5.07	4.31	4.08	Impaired	Intact
72	5.88	4.74	4.31	Absent	Impaired
58	5.88	4.93	4.31	Absent	Impaired
68	6.10	5.18	4.93	Absent	Impaired
75	5.88	5.07	4.31	Absent	Impaired
68	5.18	4.74	4.31	Impaired	Impaired
42	5.07	4.56	4.17	Impaired	Intact
36	5.88	4.93	4.31	Absent	Impaired
54	5.07	4.56	4.08	Impaired	Intact
78	5.88	5.07	4.31	Absent	Impaired
72	5.46	4.93	4.17	Absent	Impaired
76	6.45	5.46	4.93	Absent	Impaired
58	6.45	5.18	4.74	Absent	Impaired
35	4.56	4.08	3.22	Impaired	Intact
71	6.10	5.18	4.56	Absent	Impaired
48	4.93	4.56	4.31	Impaired	Impaired

Note: Semmes-Weinstein monofilament to which subjects were insensate at baseline and after 6 or 12 MIRE treatments.

After 12 MIRE treatments, 100% of the type 1 subjects had Semmes-Weinstein monofilament values below 5.07 (Fig. 1). Mean Semmes-Weinstein values for all 25 type 1 subjects were 4.26 ± 0.34 after 12 MIRE treatments (Table 3). Because the Semmes-Weinstein scale is a $\log_{10}$ scale, this result demonstrates that subjects who could only detect a force of approximately 20 g prior to MIRE were now able to detect a force of approximately 2 g.

Figure 2 documents a similar response to MIRE treatment in the somewhat older type 2 diabetic subjects. After 12 MIRE treatments, 100% of the type 2 subjects had Semmes-Weinstein values below 5.07, and the mean for all 24 subjects was 4.45 ± 0.32 (Table 3). These results reflect an average of 85% improvement in sensory perception from approximately 20 g to 3 g following MIRE treatment. The mean Semmes-Weinstein values before and after 12 treatments with MIRE for all of the subjects are shown in Figure 3. Whereas 42 of 49 subjects (21/25 type 1, 21/24 type 2) had values at or above 5.07 prior to initiating the study, after 12 MIRE treatments none had values higher than 4.93 (Tables 1 and 2).

After 12 MIRE treatments, 9 of 12 (75%) subjects with type 1 diabetes converted from impaired hot-*versus*-cold sensation to an intact ability to discriminate hot from cold (Table 1), and 4 of 11 (36%) subjects with type 2 diabetes were able to discriminate hot *versus* cold after 12 MIRE treatments (Table 2).

Discussion

The results of the present study suggest that there is a potentially effective therapy currently available that will, at least temporarily, reverse diabetic peripheral neuropathy in all patients as documented by the Semmes-Weinstein monofilament.

The insensitivity to a 5.07 (10 g) Semmes-Weinstein monofilament is "reliable and may be superior to biothesiometry in screening for patients at risk for foot ulceration since sensitivity is the more important parameter," as pointed out by Kumar et al.[8] Recently, Mayfield and Sugarman[9] noted: "The Semmes-Weinstein monofilament is currently the best choice for screening for clinically significant neuropathy because it is portable, inexpensive, painless, easy to administer, acceptable to the patient, and provides good predictive ability for the risk of ulceration and amputation." In this study, 42 of 49 subjects had loss of protective sensation (Semmes-Weinstein value of

Table 2. Data for Subjects with Type 2 Diabetes (N = 24)

	Semmes-Weinstein Monofilament Values			Hot-*versus*-Cold Discrimination	
Age (years)	Baseline	6 MIRE Treatments	12 MIRE Treatments	Baseline	12 MIRE Treatments
70	4.56	4.17	3.84	Impaired	Intact
72	5.07	4.74	4.17	Impaired	Impaired
75	4.56	4.17	4.08	Impaired	Intact
73	4.93	4.31	4.08	Impaired	Intact
78	5.46	5.46	4.93	Absent	Impaired
75	5.46	4.93	4.31	Absent	Impaired
58	5.18	4.93	4.56	Impaired	Impaired
78	5.46	4.93	4.31	Absent	Impaired
80	5.88	5.18	4.93	Absent	Impaired
78	5.46	4.93	4.31	Absent	Impaired
68	6.10	5.18	4.56	Absent	Impaired
72	5.88	5.18	4.56	Absent	Impaired
72	5.46	4.93	4.31	Absent	Impaired
75	5.07	4.56	4.17	Impaired	Impaired
65	5.18	4.93	4.56	Impaired	Impaired
73	6.10	5.46	4.93	Absent	Impaired
72	5.07	4.31	4.08	Impaired	Intact
73	5.88	5.18	4.56	Absent	Impaired
74	5.46	5.18	4.93	Impaired	Impaired
76	6.10	5.18	4.56	Absent	Impaired
73	5.18	4.93	4.31	Impaired	Impaired
58	5.88	4.74	4.17	Absent	Impaired
78	6.10	5.18	4.74	Absent	Impaired
74	5.07	4.56	4.31	Impaired	Impaired

Note: Semmes-Weinstein monofilament to which subjects were insensate at baseline and after 6 or 12 MIRE treatments.

Table 3. Subject Characteristics and Semmes-Weinstein Monofilament Values (Mean ± SD)

Diabetes Type	N	Age (years)	Baseline	6 Treatments	12 Treatments
Type 1	25	60.4 ± 12.8	5.49 ± 0.52	4.74 ± 0.38	4.26 ± 0.34[a]
Type 2	24	72.5 ± 5.5	5.44 ± 0.47	4.84 ± 0.36	4.45 ± 0.32[a]

Note: Baseline indicates patient characteristics before MIRE treatment.
[a] $P < .0001$ *versus* baseline.

Table 4. Subject Characteristics and Hot-*versus*-Cold Sensation Discrimination

	Baseline			12 Treatments		
Diabetes Type	Absent	Impaired	Intact	Absent	Impaired	Intact
Type 1 (N = 25)	13	12	0	0	16	9
Type 2 (N = 24)	13	11	0	0	20	4

Note: Data are presented as values for subjects with the indicated deficit per total number of subjects. Baseline indicates patient characteristics before MIRE treatment.

5.07 or greater) at baseline, yet MIRE treatment was able to reverse neuropathic impairment to below 5.07 in every subject. Improving sensation to this degree reduces the risk of an eventual foot ulceration or amputation.

The present study shows that MIRE treatment in an outpatient setting can reverse, at least temporarily, the sensory deficits in all diabetic subjects treated so far. Admittedly the trial was small and lasted only a month. However, there were no restrictions as to subject selection, and subjects were not required to alter any aspect of their lifestyle, dietary intake, or drug or exercise regimen.

Although no placebo was used, this outpatient

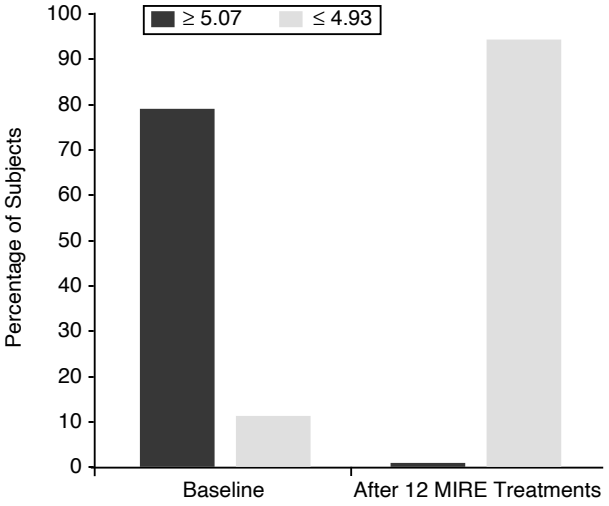

Figure 1. Percentage distribution of patients with type 1 diabetes (N = 25) with Semmes-Weinstein monofilament values ≥ 5.07 and ≤ 4.93 before (left) and after (right) 12 MIRE treatments.

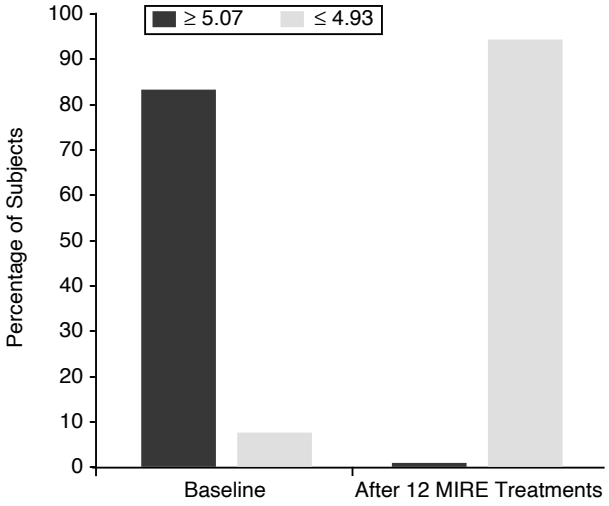

Figure 2. Percentage distribution of patients with type 2 diabetes (N = 24) with Semmes-Weinstein monofilament values ≥ 5.07 and ≤ 4.93 before (left) and after (right) 12 MIRE treatments.

clinical study was performed in a setting in which the goal is to expedite patient recovery. Historically, diabetic peripheral neuropathy of long duration does not reverse spontaneously. Moreover, the usefulness of placebo arms in objective studies has recently been questioned.[10]

The physiologic basis of the improvement in neural function may be due, in part, to improved circulation related to the localized release of nitric oxide. However, it is emphasized that in this outpatient study, neither nitric oxide nor any of its surrogates were measured directly. Accordingly, any possible involvement of nitric oxide is purely speculative. However, nitric oxide might be involved for the following reasons:

1) It is well recognized that photo energy can modulate circulation, as evidenced by the early work of Nobel laureate Robert Furchgott,[11] although the precise biological effects of MIRE are less well understood. Recently, experimental studies in rats have demonstrated that 890 nm near-infrared photo energy, virtually identical to MIRE, increases blood flow partly through an effect mediated by endothelial nitric oxide synthase or nitric oxide; the vasodilation was sustained for several hours even after the photo energy was removed.[12]

2) Red blood cells are able to store large amounts of nitric oxide,[13] partly in the form of nitrosothiols,[14] and the absorption of this wavelength of photo energy by hemoglobin is well documented.[15] Thus, vasodilation mediated by photo energy may be due, in part, to the localized release of nitric oxide from the red blood cells continuously passing through vessels exposed to the MIRE.[12, 16]

3) Glycosylated hemoglobin, characteristic of diabetes, avidly binds nitric oxide.[17] This suggests that even the smaller-than-normal amounts of nitric oxide produced by patients with diabetes[18, 19] may not be easily released from red blood cell hemoglobin at mi-

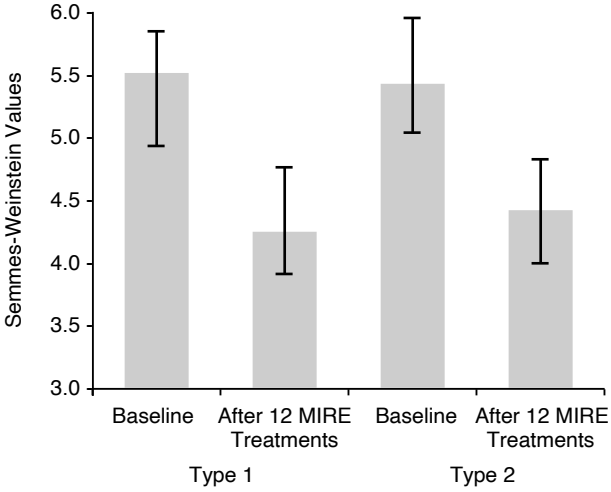

Figure 3. Semmes-Weinstein monofilament values (Mean ± SD) in all subjects before and after 12 MIRE treatments. $P < .0001$.

crocirculatory sites. Perhaps MIRE enables the nitric oxide to be released from glycosylated hemoglobin more easily.

Conclusion

The results of this study suggest that in an outpatient setting MIRE consistently has the effect of improving neural function in patients with diabetes. Future studies should be directed at assessing whether nitric oxide may be involved in these outcomes and at the long-term duration of the improvement in sensory deficits that were observed with this 1-month treatment protocol.

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Original Article

IMPROVEMENT OF SENSORY IMPAIRMENT IN PATIENTS WITH PERIPHERAL NEUROPATHY

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ABSTRACT

Objective: To report the findings in 27 patients with peripheral neuropathy (21 with lower extremity sensory impairment associated with diabetic peripheral neuropathy and 6 with other causes), who received treatment with monochromatic near-infrared photoenergy (890 nm) delivered by the Anodyne Therapy System (ATS).

Methods: All enrolled patients exhibited abnormal sensory perception (either hyperesthesia or hypoesthesia) based on a qualifying examination with the Neurometer CPT (current perception threshold) (baseline CPT). The patients received 10 ATS treatments (each lasting 40 minutes) during a 2-week period and then underwent CPT retesting to determine the extent of improvement of sensory impairment in myelinated and unmyelinated sensory fibers of the peroneal nerve.

Results: All patients obtained improvement in sensory impairment in comparison with baseline CPT measures, and 16 of the 27 patients achieved normal sensory responses in all nerve fiber subpopulations. Ten patients had been tested previously (initial CPT) and did not exhibit spontaneous improvement in sensory impairment during a mean period of 27 months before baseline CPT. After receiving the ATS treatments, however, this group of patients showed improvement in comparison with both initial CPT results and baseline CPT.

Conclusion: On the basis of the data from this study, the ATS seems to be a safe and effective treatment to improve sensory impairment associated with peripheral neuropathy due to diabetes and other causes. **(Endocr Pract. 2004;10:24-30)**

Abbreviations:
ATS = Anodyne Therapy System; **CPT** = current perception threshold; **DPN** = diabetic peripheral neuropathy; **HbA1c** = hemoglobin A1c; **SD** = standard deviation; **SWM** = Semmes-Weinstein monofilament

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INTRODUCTION

Sensory impairment is a common consequence of the nerve damage associated with diabetes and other causes. In patients with diabetes, it is referred to as diabetic peripheral neuropathy (DPN). Sensory impairments associated with DPN often begin as tingling, or a "stocking and glove sensation," and often progress toward pain. At some stage of progression of DPN, patients exhibit diminished sensation to light touch, vibration, and temperature, placing them at high risk for lower extremity ulcers, amputations, and falls. In some patients, symptoms are not appreciated or are ignored, attributing their lifestyle accommodations to aging. Frequently, patients with DPN first present to a clinician with hypersensitive symptoms similar to those in nerve fiber inflammation or neuritis. As the disease state progresses, the symptoms manifest as loss of nerve fiber function or hyposensitivity and sometimes as anesthesia, wherein the nerve fibers are unresponsive to various stimuli (1). Sensory impairments associated with diabetes have been thought to be progressive and irreversible (2) and possibly caused by microvascular dysfunction (3).

A recent study reported temporary reversal of neuropathic symptoms associated with DPN with the use of a near-infrared modality, the Anodyne Therapy System (ATS) (4). That study evaluated sensory deficits with use of graded sizes of Semmes-Weinstein monofilament (SWM) as its primary endpoint. The SWM test is widely used, and the failure to sense the SWM 5.07 is clinically recognized as highly predictive of foot ulceration and lower extremity amputation (5). Sole use of the SWM 5.07 is a gross measure of sensory impairment, and the SWM test is able to measure only diminished sensation (hypoesthesia). The purpose of the current study was to determine whether quantifiable changes in sensory impairment, both hyperesthetic and hypoesthetic, are demonstrable in patients with neuropathy after treatment with the ATS by using the Neurometer CPT (current perception threshold), an established neurodiagnostic tool (1,6,7).

MATERIALS, METHODS, AND PATIENTS

Measurement Apparatus and Protocol

We used the Neurometer CPT sensory nerve conduction threshold (Neurotron, Inc., Baltimore, MD) electrodi-

agnostic examination to obtain objective and quantitative measures of the functional integrity of the peroneal sensory nerve fibers. The Neurometer CPT emits transcutaneous electrical stimuli through a pair of gold-plated electrodes that, when placed over the great toe, quantifies neuroselective CPT of the peroneal nerve fibers. The test site is stimulated with three different sinusoidal frequencies of electrical stimuli. These frequencies—2,000 Hz, 250 Hz, and 5 Hz—evoke a response from different subpopulations of sensory nerve fibers—large myelinated, small myelinated, and small unmyelinated fibers, respectively—which constitute 90% of the sensory nerve fibers.

Neurometer testing is a fully automatic, forced-response test of patient response to randomly generated outputs of electrical stimuli in milliamperes. Because neither the testing professional nor the patient can influence the test outcome, it is a doubled-blind evaluation of sensory nerve function. CPT values are calculated and printed at each of the three sinusoidal frequencies (2,000 Hz, 250 Hz, and 5 Hz) in numerical units. Each numerical unit represents 0.01 mA of output intensity that was necessary to evoke a patient response. For example, a CPT measure of 100 units denotes that a stimulus output intensity of 1.0 mA was needed to evoke a patient response.

The Neuval CPT Evaluation and Database program (CPT software) allows analysis of CPT test data in several ways. First, CPT test results are compared with normative values (Table 1) to determine whether the patients have either abnormally low (hyperesthetic) or abnormally high (hypoesthetic) CPT values in comparison with healthy subjects for each nerve subpopulation. Second, the CPT software calculates a range analysis within each nerve subpopulation, ranging from −2 (moderate hyperesthesia) to +4 (profound hypoesthesia) and with a score of 0 being normal. Severity scoring is as follows: 4 = profound hypoesthesia, indicating no response to the stimulus at a maximal output of 999 mA; 3 = severe hypoesthesia, which indicates a CPT above the healthy normal range and 4 or more standard deviations (SD) above the mean; 2 = moderate hypoesthesia, which indicates a CPT above the healthy normal range and 3 to 4 SD above the mean; 1 = mild hypoesthesia, which indicates a CPT above the healthy normal range and 2 to 3 SD above the mean; and 0 = no detection of abnormality. Third, the CPT software provides a grade severity, ranging from 0 to 12, and an associated commentary classification. A grade severity of 0 indicates that the patient's response shows no abnormal measures in any nerve fiber subpopulation. The maximal level of abnormality is a grade severity of 12, which indicates that all nerve subpopulations are completely hypoesthetic.

We determined CPT values before and after performance of the treatment protocol with the ATS to obtain quantitative measures of sensory nerve responses, which were then clinically analyzed with use of the CPT software. Posttreatment CPT testing was done within 1 hour after the last ATS treatment in 19 patients, but 8 patients were retested between 3 and 96 days after the last ATS treatment.

Treatment Protocol

We used the ATS model 480 (Anodyne Therapy LLC, Tampa, FL) to deliver ATS treatments. The ATS consists of the following: (*1*) a 12-V DC power source, (*2*) a control unit, and (*3*) eight flexible therapy pads, on which are mounted 60 superluminous gallium-aluminum arsenide diodes that are connected to the power source by means of insulated leads. The diodes mounted on the flexible therapy pads emit photoenergy in the near-infrared spectrum (890 nm) that is pulsed 292 times per second, having a duty cycle (time on) of 50%. The power density is 8 mW/cm^2, and the average power per flexible therapy pad is 480 mW.

The flexible therapy pads of the ATS were placed in contact with each patient's skin during the treatment period. Specifically, one therapy pad was placed on the dorsal and one on the plantar aspect of the foot as well as one on the lateral and one on the medial aspect of both lower extremities, immediately above the ankle in each patient. All but one patient (who received only 5 treatments) received a total of 10 treatments delivered during the course of 2 weeks. Each treatment lasted 40 minutes. No adverse symptoms or events were noted in any patient.

Table 1
Normal Values for Current Perception Threshold

Stimulus	Range		Mean	Standard deviation
	Minimum	Maximum		
5 Hz	18	170	78	31.9
250 Hz	44	208	123	38.8
2,000 Hz	179	523	330	79.5

Study Subjects

Patients, recruited from the clinical endocrinology practice of one of us (J.J.P.), who presented with clinical symptoms of peripheral neuropathy, including either hyperesthetic or hypoesthetic symptoms based on CPT testing, were offered treatment. No patient willing to undergo treatment and posttreatment CPT testing during the period from March 2002 through September 2002 was excluded for any reason, regardless of the extent of the sensory impairment, the duration of the condition, or comorbidities. Thus, these data are reported on an intention-to-treat basis. Twenty-seven patients (18 men and 9 women; mean age, 73 years [range, 61 to 89]) agreed to receive treatment and undergo diagnostic testing. Of this group, 21 patients had a diagnosis of DPN, and 6 patients had neuropathy attributable to nondiabetic causes. Three patients were diagnosed with type 1 diabetes, and 18 were diagnosed with type 2 diabetes. The duration of diabetes before treatment was a mean of 16 ± 11 years (range, 1 to 30). Pretreatment routine laboratory testing revealed that none of the six nondiabetic patients had hyperglycemia. Of this group, three patients (ages 74, 75, and 83 years) had hypothyroidism, one patient (age 79 years) had hypoglycemia, one (age 74 years) had peripheral vascular disease, and one (age 74 years) had hypercholesterolemia. All had normal blood pressure, and homocysteine levels were less than 9.0 µmol/L in all six patients.

Recent hemoglobin A1c (HbA1c) data, available for 17 of the 21 patients with diabetes, indicated that these patients exhibited reasonably good glycemic control (mean ± SD, 6.9 ± 1.4%); no patient was excluded on the basis of available HbA1c. During the treatment protocol, there was no change in medications taken by any of the patients.

Of interest, 10 patients (9 with diabetes and 1 without diabetes) had undergone prior CPT examination and CPT software analysis (initial CPT), a mean of 27 months before the baseline CPT conducted at the beginning of this study. Comparison of the sensory impairment findings in these 10 patients (the "conventional management group") between the initial CPT and baseline CPT, during which they received standard care for their condition, was separately analyzed to determine any changes in their sensory impairment both before and after ATS treatment.

Statistical Analysis

Data were analyzed by paired and unpaired *t* test where appropriate and by repeated measures with a null hypothesis that treatments would have no effect on either (*1*) numerical CPT measure of nerve fiber response to stimulation at 2,000 Hz, 250 Hz, or 5 Hz or (*2*) clinical analysis with use of the CPT software. *P* values of less than 0.05 were considered significant. The statistical package used was StatView (Abacus Concepts, Inc., Berkeley, CA). Values are reported as means ± 1 SD.

RESULTS

Conventional Management Group

The 10 patients in the conventional management group (7 men and 3 woman) had a mean age of 74 ± 6 years at baseline testing. Between initial CPT and baseline CPT, the patients in this group remained reasonably constant in the severity of their neuropathic symptoms in all nerve fiber groups tested, as reflected in the CPT numerical scores (2,000 Hz = 615 ± 279 to 683 ± 286; 250 Hz = 290 ± 291 to 286 ± 278; and 5 Hz = 224 ± 290 to 152 ± 217; no statistically significant changes). Grade severity, already elevated at initial CPT, had also increased modestly but not significantly (6.3 ± 4.6 to 8.3 ± 2.1; $P = 0.16$) when measured again at baseline CPT. No patient whose grade severity was "abnormal" at initial CPT had improvement to "normal" at baseline CPT, an indication that these patients had not experienced a spontaneous or medical treatment-related improvement in sensory impairment with standard care. Consistent with reported pathologic features of this condition, individual sensory impairment remained the same or worsened.

After ATS treatment, this conventional management group demonstrated significant improvement ($P<0.05$) in sensory impairment based on CPT numerical scores at 2,000 Hz (476 ± 120) compared with baseline CPT (683 ± 286). Changes in mean CPT values at 250 Hz and 5 Hz after ATS treatment, however, were not statistically significant ($P = 0.14$ and $P = 0.4224$, respectively).

Each of the 10 patients presented at baseline CPT with an abnormal grade severity (maximum, 12.0). After ATS treatment, grade severity determined with the CPT software decreased significantly to 2.7 ± 3.9 in comparison with initial CPT (6.3 ± 4.6) and with baseline CPT (8.3 ± 2.1) ($P<0.03$ and $P<0.002$, respectively). The mean reduction in grade severity from initial CPT to posttreatment CPT was 3.5 grade severity points ($P<0.03$), a 56% reduction. After treatment, 6 of the 10 patients (60%) in the conventional management group attained a grade severity score of 0, indicating no abnormalities in any sensory nerve fiber subpopulation. Associated commentary classification ranged from very mild hyperesthetic to profound sensory loss; nonetheless, 8 of the 10 patients (80%) showed improvement with ATS treatment.

In a comparison of posttreatment CPT with baseline CPT, 9 of the 10 patients (90%) demonstrated an improvement in grade severity and thus an improvement in sensory impairment after treatment. The mean reduction in grade severity from baseline CPT to posttreatment CPT in these 10 patients was 5.6 ($P<0.002$), a 67% improvement.

Range analysis (maximum, 4.0) after treatment (2,000 Hz = 0.7 ± 0.9; 250 Hz = 0.7 ± 1.2; and 5 Hz = 0.0 ± 0.0) was decreased when compared with initial CPT (2,000 Hz = 1.8 ± 1.5; 250 Hz = 1.3 ± 1.5; and 5 Hz = 1.1 ± 1.5) and baseline CPT (2,000 Hz = 2.0 ± 1.7; 250 Hz = 1.7 ± 1.3;

and 5 Hz = 0.3 ± 1.0). A statistically significant decrease, however, was apparent only between baseline CPT and after treatment at 2,000 Hz ($P<0.03$).

Full Patient Cohort

In the overall study group of 27 patients, the CPT numerical scores for 2,000 Hz, 250 Hz, and 5 Hz were abnormal at baseline CPT (Fig. 1). Specifically, mean scores were 657 ± 297, 324 ± 289, and 193 ± 251, respectively, which were higher than the maximal normal scores (shown in Table 1). After treatment, CPT scores decreased significantly at 2,000 Hz to 481 ± 195 ($P<0.001$) and at 250 Hz to 221 ± 213 ($P<0.02$) but not at 5 Hz (153 ± 246; $P<0.423$). The 5-Hz scores varied substantially both before (range, 9 to 999) and after (range, 13 to 999) treatment.

The CPT numerical scores assessed at 2,000 Hz were within normal ranges (see Table 1) in only 5 of the 27 patients at baseline (Fig. 2). After treatment, 20 of the 27 patients exhibited a normal sensory response to stimuli at 2,000 Hz. The CPT numerical scores were within normal ranges in only 10 of the 27 patients when tested with 250 Hz at baseline, but the number increased to 19 of the 27 patients after ATS treatment. Finally, 16 of the 27 patients exhibited responses within normal ranges to 5 Hz at baseline, and this number increased to 24 of the 27 patients after treatment. Of the 27 patients, 26 (96%) experienced a reduction in overall grade severity of sensory impairment, the mean (Fig. 3) decreasing from 8.3 ± 2.1 at baseline to 3.2 ± 4.2 after ATS treatment ($P<0.0001$)—a 61% improvement. After ATS treatment, 16 of the 27 patients (59%) had a grade severity of 0, indicating normal sensory responses in all nerve fiber subpopulations.

Posttreatment range analysis (2,000 Hz = 0.59 ± 1.18; 250 Hz = 0.55 ± 1.08; and 5 Hz = 0.42 ± 1.20) was substantially less than at baseline CPT (2,000 Hz = 2.08 ± 1.57; 250 Hz = 1.29 ± 1.29; and 5 Hz = 0.92 ± 1.20). These decreases were statistically significant at 2,000 Hz ($P<0.001$) and at 250 Hz ($P<0.002$) but not at 5 Hz.

DISCUSSION

The effect of ATS treatments to improve sensory perception, supported by the data from this study, is extraordinary in light of the marginal success of current medical or pharmacologic interventions in reducing sensory impairment, particularly that associated with DPN. By a comparison of baseline CPT with posttreatment CPT, these data offer quantifiable objective evidence that all sensory nerve fiber subpopulations had improved function, regardless of whether the nerve fiber originally was hyperesthetic or hypoesthetic.

Although ATS treatments resulted in improvements in sensory perception of stimuli at 2,000 Hz, 250 Hz, and 5 Hz, the changes were statistically significant only at 2,000 Hz and 250 Hz. Range analysis on these patients suggests that large and small myelinated nerves may have been affected to a greater extent than small unmyelinated nerves, inasmuch as the nerve fiber response to 5 Hz was less impaired than were responses to 2,000 Hz and 250 Hz at baseline CPT. Small nerve fiber dysfunction has been reported more often than large fiber dysfunction in DPN (8,9). One possible explanation for this result is that CPT values for the 5-Hz frequency have greater variability than the other frequencies, which is supported by these data. As a result, a larger number of patients would have to be examined at this frequency to obtain a statistically significant result. These data also seem to support recently published findings in more than 2,000 patients that indicate that response to a stimulus at 5 Hz may not be predictive of hypersensitivity and early neuropathy among those with diabetes (10).

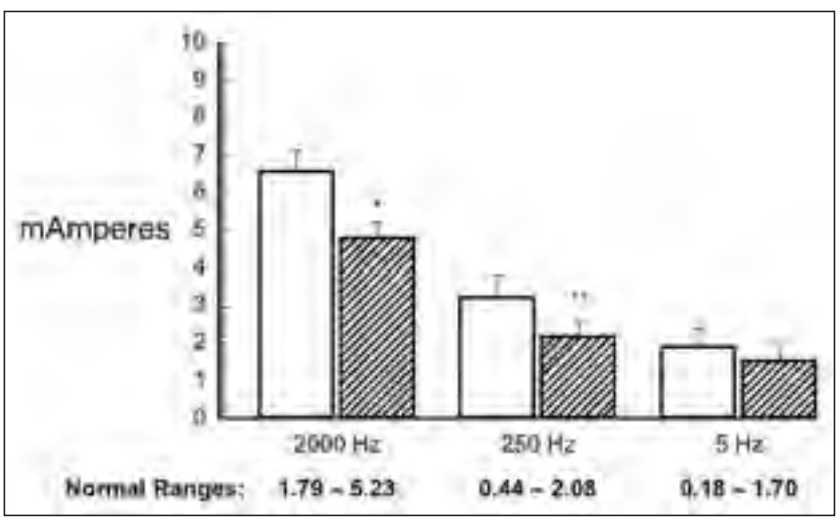

Fig. 1. Effect of treatment with Anodyne Therapy System on current perception threshold scores in milliamperes (means ± standard errors). Baseline (*open bars*) and after treatment (*hatched bars*). Normal ranges for each current are shown at bottom. * = $P<0.001$ versus baseline; ** = $P<0.02$ versus baseline.

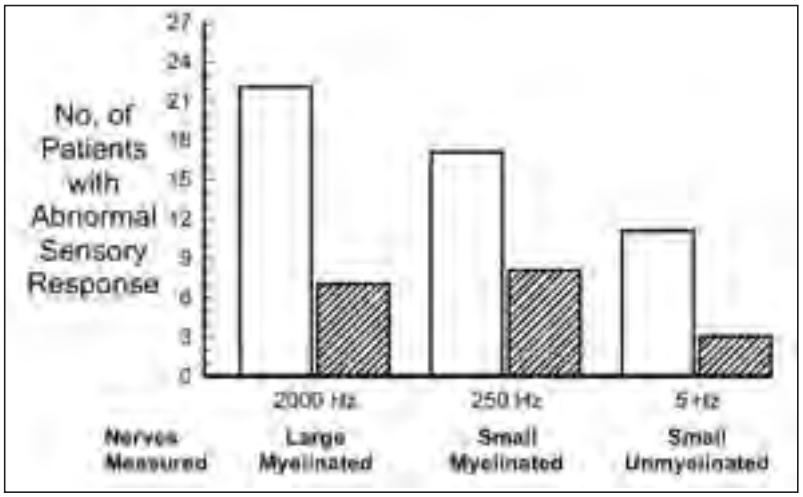

Fig. 2. Number of patients with abnormal sensory response to current perception threshold testing before treatment (baseline; *open bars*) and after treatment (*hatched bars*) with Anodyne Therapy System.

Among the patients with diabetes, these results seemed unrelated to changes in blood glucose control because HbA1c levels before treatment were, for the most part, well controlled. Additionally, because HbA1c tests the average glucose levels for the prior 3 months, no change would be expected within the 2- to 3-week treatment protocol that would account for the sensory improvement that was observed.

No correlation was found between outcome of ATS treatment and either the duration of the diabetes or the type of diabetes; this result suggests that the duration of sensory impairment and the type of diabetes are not predictive of responses to treatment. Review of the data does suggest that those patients with the highest level of impairment (in the sense of having one or more nerve fibers that were completely hypoesthetic) might expect less profound improvement than those who exhibited no nerve fibers that had reached the completely hypoesthetic state. Moreover, the improvement in sensory perception was also observed in patients without diabetes; therefore, the cause of the neuropathic impairment may be irrelevant to the effectiveness of this treatment protocol.

Because medications that might have been considered an additional variable in the current study were not changed during the treatment protocol, the likelihood that a unique medication affected these results is minimal. Inclusion criteria were extremely broad and were based solely on the existence of sensory impairment and willingness of patients to undergo treatment and diagnostic evaluation. Indeed, the level of sensory impairment of the patients at baseline CPT was extremely broad, ranging from anesthetic hypoesthetic to very mild hyperesthetic. Thus, bias in terms of patient selection was minimized. CPT testing is a double-blind procedure in its evaluation of nerve fiber impairment; hence, investigator or patient bias can be ruled out as contributing to these results. Because all patients received actual treatment with the ATS, the potential for a placebo effect cannot be completely discounted. In the medical literature, however, no evidence suggests that DPN spontaneously reverses. This hypothesis is fully supported by these data, in that none of the patients in the conventional management group exhibited spontaneous reversal of the sensory impairment during a mean period of 27 months of medical management of their condition.

A growing body of evidence suggests that DPN may be related, in part, to endothelial dysfunction and an impaired microcirculation to the peripheral nerves (11-14). Clearly, one important consequence of the progressive vascular disease that characterizes patients with diabetes is a reduction in capillary blood flow to the tissues of the feet (15). Part of this reduction is due to the formation of arteriovenous shunts that carry arterial blood to the low-pressure venous circulation rather than into the capillaries. Recently, several studies demonstrated that a circulation-induced increase in oxygenation and nutrition both promotes new nerve growth and, in existing nerves, reestablishes nerve membrane potential that has been altered by hypoxic conditions associated with poor blood flow in patients with diabetes (16,17). Similar acute and sustained increases in local blood flow have been achieved by using a single diode emitting photoenergy in the near-infrared spectrum in a rat model (18). Because enhanced circulation is produced by some near-infrared devices as well as the ATS system, a microcirculatory increase seems to be the most plausible mechanism of action with respect to improvement in sensory perception noted in this study, although we have not directly evaluated this hypothesis.

It is important to consider the validity of CPT analysis, the endpoint used in this study. CPT was chosen to measure changes in sensory impairment in this study for several reasons, including the following factors: (*1*) painless, noninvasive, ease of use; (*2*) double-blinding of test results to evoked stimuli; (*3*) high sensitivity (0.001 mA);

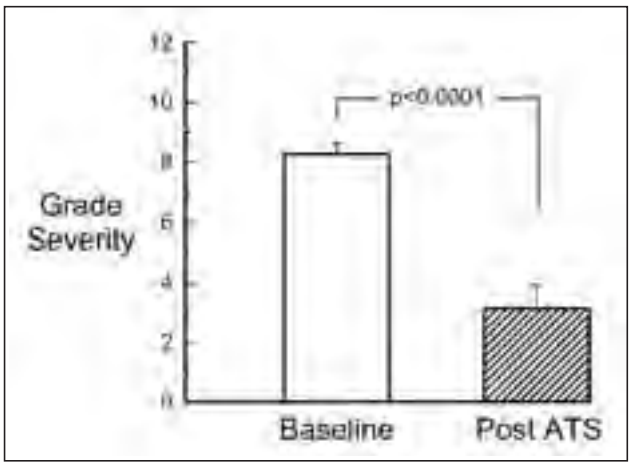

Fig. 3. Grade severity of sensory impairment after treatment with Anodyne Therapy System (*ATS*) (*hatched bar*) in comparison with baseline (*open bar*) in 27 patients with peripheral neuropathy.

(*4*) ability to measure response of 90% of the nerve fibers (including large myelinated, small myelinated, and small unmyelinated fibers, which might be selectively affected by neuropathic symptoms); (*5*) existence of normative values; (*6*) availability of CPT software analysis of severity grades of impairment; (*7*) reports of both hyperesthetic and hypoesthetic nerve fiber function; (*8*) irrelevance of skin thickness, edema, or ambient or skin temperatures to the test results; (*9*) ability of nerves to serve as their own controls; and (*10*) acceptance of CPT analysis by a wide variety of clinicians, including the American Association of Clinical Endocrinologists. Additionally, CPT analysis had been used as a primary endpoint in at least 15 previously published clinical studies that have examined nerve function. As is the case with other methods of testing, CPT is subject to some limitations. To our knowledge, the ability of CPT to measure functional abnormalities of selective nerve fibers has not been validated by pathologic examination. Additionally, no correlating data between sensory impairment as measured by CPT and clinical endpoints of neuropathic foot ulceration and amputation are currently available. Insensitivity to the SWM 5.07 has been studied extensively and is widely accepted as having a strong correlation with risk of neuropathic ulceration and amputation (19). In addition, at least one report has described a correlation between an abnormal response to the biothesiometer and an increased risk of neuropathic foot ulceration (20).

In view of the high correlation between sensory impairment associated with peripheral neuropathy, particularly DPN, and lower extremity ulcers, amputations, and falls (21,22), effective treatment options for this condition are a priority of the research community. Thus far, these efforts have yielded suboptimal results. Accordingly, a widely held belief in mainstream medicine is that the sensory impairment associated with DPN remains irreversible and progressive. Excellent ("tight") glucose control is medically accepted as a method to delay the onset and progression of DPN. Additionally, current standards of care include patient education, periodic foot examinations, and special diabetic footwear to reduce the incidence of foot wounds and amputations, which are highly correlated with DPN.

The only report of significant improvement in sensory impairment associated with DPN is based on a surgical intervention known as peripheral nerve decompression, wherein the four medial ankle tunnels related to the tibial nerve and its medial, lateral, plantar, and calcaneal branches are decompressed (23). Interestingly, patient follow-up postoperatively indicates a substantially reduced incidence of neuropathic foot ulcers and amputations, which are objectives of the US Surgeon General in "Healthy People 2010" (24).

CONCLUSION

The current data strongly suggest that ATS treatments, delivered in the manner described, significantly improve sensory impairment associated with peripheral neuropathy, at least temporarily. These results were consistent among patients of both sexes and various ages, irrespective of the cause of the sensory impairment or the duration of the diabetes. Therefore, these findings may be generalizable to the patient population at large. Importantly, sensory impairment associated with DPN, at least as measured by insensitivity to the SWM 5.07, is strongly correlated with the occurrence of neuropathic foot ulcers and amputations. On the basis of data published by Dellon (25), significant improvements in sensory impairment associated with DPN achieved by peripheral nerve decompression reduce the incidence of neuropathic foot ulcers and amputations. By inference, improvements in sensory impairment associated with DPN after treatment with ATS, because they appear to be as significant as those with surgical decompression, may likely have the same effect on the incidence of ulcers and amputations, if the observed clinical effect is durable. The durability of ATS treatments was not evaluated as part of our current study. We plan to reevaluate this group of patients with CPT testing to determine the durability of clinical effect observed both with ongoing treatments and after cessation of treatment.

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Restoration of Sensation, Reduced Pain, and Improved Balance in Subjects With Diabetic Peripheral Neuropathy

A double-blind, randomized, placebo-controlled study with monochromatic near-infrared treatment

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OBJECTIVE — Diabetic peripheral neuropathy (DPN) has been thought to be progressive and irreversible. Recently, symptomatic reversal of DPN was reported after treatments with a near-infrared medical device, the Anodyne Therapy System (ATS). However, the study was not controlled nor was the investigator blinded. We initiated this study to determine whether treatments with the ATS would decrease pain and/or improve sensation diminished due to DPN under a sham-controlled, double-blind protocol.

RESEARCH DESIGN AND METHODS — Tests involved the use of the 5.07 and 6.65 Semmes Weinstein monofilament (SWM) and a modified Michigan Neuropathy Screening Instrument (MNSI). Twenty-seven patients, nine of whom were insensitive to the 6.65 SWM and 18 who were sensitive to this filament but insensitive to the 5.07 SWM, were studied. Each lower extremity was treated for 2 weeks with sham or active ATS, and then both received active treatments for an additional 2 weeks.

RESULTS — The group of 18 patients who could sense the 6.65 SWM but were insensitive to the 5.07 SWM at baseline obtained a significant decrease in the number of sites insensate after both 6 and 12 active treatments ($P < 0.02$ and 0.001). Sham treatments did not improve sensitivity to the SWM, but subsequent active treatments did ($P < 0.002$). The MNSI measures of neuropathic symptoms decreased significantly (from 4.7 to 3.1; $P < 0.001$). Pain reported on the 10-point visual analog scale decreased progressively from 4.2 at entry to 3.2 after 6 treatments and to 2.3 after 12 treatments (both $P < 0.03$). At entry, 90% of subjects reported substantial balance impairment; after treatment, this decreased to 17%. However, among the group of nine patients with greater sensory impairment measured by insensitivity to the 6.65 SWM at baseline, improvements in sensation, neuropathic symptoms, and pain reduction were not significant.

CONCLUSIONS — ATS treatments improve sensation in the feet of subjects with DPN, improve balance, and reduce pain.

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Diabetic peripheral neuropathy (DPN) is relatively common complication of long-term diabetes (1) and is thought to be progressive and irreversible (2). DPN may be characterized by perceived numbness and diminished sensation and/or pain (3). Diminished sensation associated with DPN presents a significant risk factor for subsequent diabetic ulcers and nontraumatic amputations (4,5) as well as for falls among the elderly (6). As such, DPN presents both a substantial economic cost to the health care system and potentially debilitating consequences for those affected.

Current medical treatment algorithms stress the importance of delaying the onset of DPN through excellent blood glucose control (7). After the onset of DPN resulting in diminished sensation, medical management focuses on the implementation of secondary measures for prevention of foot wounds and amputations such as intensive foot-care education and periodic professional foot evaluations (8). Extensive research into likely pharmacological agents designed to either delay the onset of DPN or reverse mild to moderate symptoms after onset is ongoing. Whereas there are encouraging reports (9), a satisfactory pharmacological treatment option has yet to present itself.

Recently, symptomatic reversal of DPN was reported (9) with the use of a noninvasive medical device, the Anodyne Therapy System (ATS). Although the reported results were quite significant, the study was not controlled nor was the investigator blinded. We initiated this study to determine whether treatments with the ATS would improve sensation diminished due to DPN under a sham-controlled, double-blind protocol.

RESEARCH DESIGN AND METHODS

— Twenty-seven subjects met entry requirements for this institutional review board–approved study and completed the treatment protocol. To be eligible, all subjects were required to exhibit a diagnosis of either type 1 or type 2 diabetes and a diagnosis of peripheral neuropathy based on patient history and physical examination. Additionally, all subjects had to be insensate to the 5.07

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Abbreviations: ATS, Anodyne Therapy System; DPN, diabetic peripheral neuropathy; LOPS, loss of protective sensation; MNSI, Michigan Neuropathy Screening Instrument; SWM, Semmes Weinstein monofilament; VAS, visual analog scale.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Semmes Weinstein monofilament (SWM) on at least two of five test sites on the plantar surface of both feet (great toe, fourth toe, and three sites on the metatarsal area), indicative of their having established DPN and loss of protective sensation (LOPS). All subjects were also subjected to additional testing with the 6.65 SWM to further quantify the extent of their sensory loss. Subjects were excluded if they exhibited uncontrolled hypertension, prior history of knee or back surgery, active malignancy, or were pregnant or likely to become pregnant.

Evaluation measures

The primary endpoint in this study was observed change in sensitivity to the SWM 5.07 at the five tested sites. Secondary measures were changes in patient response to a modified Michigan Neuropathy Screening Instrument (MNSI) patient questionnaire and a physician foot examination (10).

The SWM tests were conducted by pressing the monofilaments at the five testing locations in random fashion avoiding heavily callused areas. With the subjects blindfolded, the monofilaments were pressed against the skin at each location until they bent and held in place for 1–2 s. The subjects were asked to respond "yes" if they felt the monofilament and further asked to describe the location on the foot where they sensed the monofilament. The same physician conducted all tests done with each subject to avoid interobserver bias.

The MNSI questionnaire provides a graded patient response of neuropathic symptoms. In general, a higher score represents more neuropathic symptoms. For purposes of this study, we omitted the questions "Have you ever been advised that you have neuropathy" and "Have you ever had an amputation," because the inclusion criteria included a diagnosis of neuropathy and ambulatory status. Thus, the maximum possible score was 11. To determine variation in subject response to active and sham treatment, the questionnaire was modified to elicit responses for both the left and right leg. Because those with diminished sensation associated with DPN often exhibit balance impairment (6), we added a question "Do you ever feel off balance or feel like you are going to fall?" Lastly, we asked the subjects to rate their pain level on a 10-point visual analog scale (VAS).

The MNSI physical examination is a graded clinical examination of the *1*) appearance of the foot as being normal or abnormal, *2*) presence or absence of foot ulceration, *3*) ankle reflexes as being either present, present with reinforcement, or absent, *4*) semiquantitative vibration perception of the great toe to a 128-Hz tuning fork as being either present, reduced, or absent, and *5*) light touch sensation of the great toe to the SWM 5.07 monofilament. The evaluation of the great toe with the SMW 5.07 was omitted from the clinical examination portion because a more thorough examination of five points on the plantar aspect of the foot was already documented in each subject.

Treatments were administered with the ATS Model 480, supplied for this study by its manufacturer (Anodyne Therapy, Tampa, FL). The ATS is a medical device consisting of a base power unit and therapy pads containing 60 near-infrared (890 nm) gallium aluminum arsinide diodes used to increase circulation by dilating arteries and veins. Inactivating the diodes so that no near-infrared photo energy was emitted and inserting heaters preset at 37°C created sham devices of identical appearance. Thus, neither the investigators nor the subjects could discriminate active from sham devices either visually or by temperature. Active versus inactive therapy pads were marked as A and B during the placebo phase of this study with only the manufacturer knowing active from sham. Active ATS units were preset to deliver 1.3 $J \cdot cm^{-2} \cdot min^{-1}$ of photo energy. Sham devices delivered only warmth at 37°C and no photo energy.

Treatment protocol

All subjects initially received treatment with both active and sham ATS therapy pads at our clinic three times per week for 40 min each visit for 2 weeks (six treatments) as described below. This was followed by six active treatments of the same duration administered to both limbs during the following 2 weeks. During each of the 12 40-min treatments, four ATS diode therapy pads were placed on each lower limb as follows: one on the top and one on the bottom of the foot and one on each side of the calf just above the ankle. Subjects were randomized so that irrespective of the degree of impairment in sensation noted at initial SWM evaluation, one lower limb received a sham treatment and the other an active treatment for the first six 40-min sessions. Sham-controlled treatments were administered only during the first 2 weeks of the protocol, because the results of a previously reported study (9) showed that a measurable change in sensitivity to the 5.07 SWM could be expected with this treatment protocol. Furthermore, we believed that extending the protocol to 1 month to deliver 12 sham treatments would have adversely affected recruitment and retention of subjects in this study. Fourteen of the subjects received initial active treatments on the left leg and the remainder on the right leg, and sham treatments were simultaneously given on the opposite leg. Neither the clinical staff nor the subjects knew which leg was receiving the active treatment. Patients returned to the clinic 3 days after the sixth treatment, were retested with the SWM, and then both limbs received the first of a series of six active treatments.

Thus, SWM testing, patient questionnaires, and physical examinations were conducted before entry into the study, just before initiation of the seventh treatment session (i.e., 3 days after completing the sixth treatment), and within 3 days after completing the twelfth treatment session, on each lower extremity.

Statistics

Data were analyzed by paired and unpaired Student's *t* test where appropriate and by repeated measures with a null hypothesis that treatments would have no effect on either *1*) increasing the number of sites sensitive to the 5.07 SWM, *2*) the numerical score on the MNSI questionnaire, *3*) physician foot examination, or *4*) self-reported pain. Significance was accepted when $P < 0.05$. The statistical package StatView from Abacus Concepts (Berkley, CA) was used. Values are expressed as mean ± 1 SD.

RESULTS — The 27 subjects who were insensitive to the SWM 5.07 were stratified into two groups (group 1 and group 2) based on their ability to sense the SWM 6.65. Group 1, consisting of 18 subjects, was able to sense the SWM 6.65 at all tested sites. Group 2, consisting of nine subjects, was unable to sense the SWM 6.65, which requires 30 times the bending force of the SWM 5.07, at no less than one tested site. Thus, group 2 subjects presented with a more profound level of sensory impairment than those in

Table 1—*Subject characteristics at initial evaluation (pretreatment)*

Subject no.	Age (years)	Sex	Weight (lbs)	Type	Duration (years)
Group 1*	61 ± 12		212 ± 35		
1	62	F	207	2	10
2	58	F	151	1	33
3	57	M	234	2	30
4	78	M	219	2	9
5	52	F	251	2	22
6	70	M	220	2	4
7	62	M	225	2	7
8	41	M	297	2	5
9	61	M	260	2	2
10	69	M	180	2	12
11	48	M	235	2	9
12	48	F	190	1	38
13	70	F	198	2	5
14	35	M	200	2	3
15	61	F	190	2	2
16	67	M	215	2	3
17	82	M	173	2	4
18	72	M	200	2	2
Group 2*	64 ± 9		218 ± 38		
1	75	M	275	2	5
2	76	F	176	2	15
3	53	M	250	2	30
4	68	F	162	2	7
5	67	M	215	2	5
6	48	M	211	2	1
7	67	M	193	2	30
8	66	M	225	2	6
9	60	M	260	2	2

*Data are means ± SD.

group 1. Other than for the level of sensory impairment, the subjects in these two groups were substantially homogenous in terms of age, sex, and weight.

Subject demographics (Table 1)

Average age of the subjects was 61 ± 12 years in group 1 and 64 ± 9 years in group 2 (NS). All but 2 of the 27 subjects had type 2 diabetes.

SWM (Table 2)

Group 1 subjects. At initial evaluation, there was no difference in sensitivity to the 5.07 SWM between the feet that initially received active treatments and the feet that received sham treatment for the first six sessions (NS). Six active treatments with the ATS reduced the number of sites insensitive to the SWM 5.07 ($P <$ 0.02 vs. baseline), but the foot treated with the sham diodes did not demonstrate a significant decrease (NS). Six additional active treatments (12 active treatments total) resulted in a further improvement in sensation as the ability to detect the 5.07 SWM increased significantly ($P < 0.001$ vs. baseline). Six active treatments administered after initial sham treatments resulted in improved SWM 5.07 sensitivity ($P < 0.002$ vs. baseline).

Group 2 subjects. At initial evaluation, group 2 subjects exhibited profound diminished sensation, as evidenced by both the inability to sense the SWM 6.65 at one or more sites and by the average number of sites insensitive to the SWM 5.07 compared with group 1 subjects (Table 2). Neither 6 nor 12 active treatments significantly decreased the number of sites insensate to the SWM 5.07. After the initial 6 active treatments and after 12 treatments, no sites became sensitive to the 5.07 SWM (NS versus baseline). Likewise, among group 2 patients, sham treatment did not significantly affect sensitivity to the SWM 5.07 (Table 2).

MNSI patient questionnaire (Table 3)

Group 1 subjects. At initial evaluation, there was no difference to the modified MNSI patient questionnaire score (maximum 11) for the foot that initially received active treatments (4.7 ± 1.8) as compared with sham treatments (4.7 ± 1.9) (NS). Six active treatments resulted in a reduction of the MNSI score ($P =$ 0.0001 vs. baseline). Six additional treatments with active diodes resulted in a further reduction in the MNSI score ($P <$ 0.05 vs. baseline). There was also a statis-

Table 2—*Number of sites on the plantar surface of the foot that were insensate to SWM 5.07 (10 g) before (baseline) and after 6 and 12 ATS treatments (active diodes versus placebo)*

Baseline	After 6 treatments	After 12 treatments
Group 1 (sensate to 6.65 SWM)		
3.5 ± 1.0	2.4 ± 1.5 (with active diodes) $P < 0.02$	1.9 ± 1.7 (active diodes) $P < 0.001$
3.6 ± 1.1	3.0 ± 1.5 (sham diodes) (NS) $P < 0.09$	2.3 ± 1.8 (active diodes) $P < 0.002$
Group 2 (insensate to 6.65 SWM)		
4.7 ± 0.5	4.0 ± 1.7 (with active diodes) (NS) $P = 0.21$	3.7 ± 1.7 (active diodes) (NS) $P = 0.10$
4.4 ± 0.7	4.0 ± 1.7 (sham diodes) (NS) $P = 0.27$	3.9 ± 1.7 (active diodes) (NS) $P = 0.28$

Data are means ± SD. Five sites were tested on each foot. *P* values are compared with baseline in that limb. All subjects completed 12 treatment sessions with either active or sham diode arrays. In group 1 ($n = 18$), these 18 subjects were insensate to the 10-g, 5.07 SWM but were sensate to the 6.65 SWM. In group 2 ($n =$ 9), these nine subjects were insensate to the 5.07 and were also insensate to the 6.65 SWM at one or more sites on the foot.

Table 3—*MNSI scores before and after 6 and 12 treatments with the ATS*

	Baseline	After 6 treatments	After 12 treatments
MNSI questionnaire scores (maximum 11)			
Group 1 ($n = 18$)			
Active diodes	4.7 ± 1.8	3.5 ± 1.7 ($P < 0.0001$)	3.2 ± 1.5 ($P < 0.001$)
Sham diodes	4.7 ± 1.9	3.8 ± 1.5 ($P < 0.01$)	3.7* ± 1.9 ($P < 0.05$)
Group 2 ($n = 9$)			
Active diodes	3.7 ± 1.4	3.0 ± 1.6 (NS)	3.0 ± 1.3 (NS)
Sham diodes	3.6 ± 1.6	3.3 ± 1.5 (NS)	3.1* ± 1.4 (NS)
MNSI foot examination scores (maximum 4)			
Group 1 ($n = 18$)			
Active diodes	1.5 ± 0.5	1.4 ± 0.7 (NS)	1.3 ± 0.6 (NS)
Sham diodes	1.6 ± 0.5	1.3 ± 0.7 (NS)	1.3* ± 0.6 (NS)
Group 2 ($n = 9$)			
Active diodes	2.1 ± 0.7	1.9 ± 0.6 (NS)	1.8 ± 0.6 (NS)
Sham diodes	2.1 ± 0.7	1.9 ± 0.6 (NS)	1.8* ± 0.6 (NS)

Data are means ± SD. Sham treatments (sham diodes) for the first 6 sessions were followed by treatment with active diodes for sessions 7 through 12. *These feet received active ATS treatments for sessions 7 through 12.

tically significant decrease in the MNSI after six sham treatments ($P < 0.01$ vs. baseline). The "sham" foot, treated for the final six sessions with active diodes demonstrated a reduction in the MNSI score ($P < 0.05$ vs. baseline).

Group 2 subjects. Treatment with active diodes for six sessions did not result in a statistically significant decrease in the MNSI (NS versus baseline) nor did six additional treatments with active diodes (NS versus baseline). There was no statistically significant decrease in the MNSI score after six sham treatments (both values are NS versus baseline).

Foot examination (Table 3)

Group 1 subjects. At baseline examination, only 2 of the 18 group 1 subjects had feet with an abnormal appearance (dry skin or Charcot), and only one had an ulcer. Thus, reported abnormalities, if any, in the foot examination would be due mainly to changes in either ankle reflexes or semiquantitative vibratory sensation. Foot examination score did not significantly change with either 6 or 12 active treatments. Likewise, the foot examination did not change significantly with either six sham treatments or the subsequent administration of six active treatments (both values are NS versus baseline).

Group 2 subjects. Foot examination score at initial evaluation for the group 2 subjects indicated more significant impairment compared with the group 1 subjects (Table 3). As in the group 1 subjects, there was no significant change in foot examination scores after either active or sham treatments.

Pain

Group 1 subjects. Overall self-reported pain (VAS) in the group 1 subjects, which was not reported by extremity, decreased from 4.2 ± 2.3 at baseline to 3.2 ± 1.9 after the first 6 treatments (i.e., active diodes on one leg and sham on the opposite leg; $P < 0.03$) and to 2.3 ± 1.7 after 12 treatments ($P < 0.0001$ vs. baseline).

Group 2 subjects. VAS in the group 2 subjects was much more variable than in group 1. Whereas self-reported pain decreased over the month-long trial, this was not statistically significant due to the wide variation in VAS and the small number of subjects. Pain averaged 4.2 ± 3.9 at baseline, 2.6 ± 2.3 after 6 treatments, and 2.00 ± 2.3 after 12 treatments (NS versus baseline for both 6 and 12 treatments).

Balance improvement

Group 1 subjects. The questionnaire required a yes or no response to the following question: "Do you feel off balance or feel like you are going to fall?" At initial evaluation, 16 of the 18 group 1 subjects (89%) answered this question affirmatively. After six treatments, only seven subjects answered affirmatively (39%), and after 12 treatments, only three subjects answered affirmatively (16.7%). After 12 treatments, balance impairment was no longer reported by 81% of the subjects.

Group 2 subjects. Most subjects (seven of nine; 78%) in group 2 also answered the balance impairment question affirmatively before the start of treatment. After six treatments, only four of nine subjects (44%) answered this question affirmatively. However, no further improvements were noted after 12 treatments as four of nine subjects continued report balance impairment. Thus, after both 6 and 12 treatments, self-reported balance impairment was no longer reported by 43% of the group 2 subjects.

CONCLUSIONS — The results of the present study demonstrate that treatments with near-infrared photo energy delivered in the manner specified in the study protocol resulted in a significant decrease in the average number of sites insensitive to the 5.07 SWM in diabetic subjects with LOPS who had not progressed to profound sensory loss, defined as their inability to detect a much larger monofilament (Table 2). After 12 such treatments, the average number of sites insensitive to the SWM 5.07 among subjects in group 1 decreased to less than two sites, representing almost a 50% improvement in sensation. Comparatively, six sham treatments did not significantly decrease the number of foot sites insensitive to the SWM 5.07, but statistically significant sensory improvement was noted when these feet later received six active treatments.

We did not observe a significant improvement in sites sensitive to the SWM 5.07 in those subjects (group 2) with LOPS who also presented with profound sensory loss, as characterized by their inability to detect a SWM 6.65 (300 g) at one or more tested sites after either active or sham treatment. There may have been some improvement in sensory perception of monofilaments, sized between 5.07 and 6.65, but we did not perform tests using intermediate-sized monofilaments in the context of this study.

DPN, as documented by the failure to sense a 5.07 SWM at two sites on either foot, is considered as LOPS and recognized as a "localized illness of the foot" (11). The present results suggest that ATS treatments in those subjects who had not progressed to

profound sensory loss, namely group 1, may result in at least a temporary restoration of protective sensation.

Subject response to the MNSI questionnaire showed that neuropathic symptoms decreased among those with LOPS (group 1) after 6 to 12 active treatments with the ATS. This was not the case in the group 2 subjects who exhibited profound sensory loss in addition to LOPS, even though they had lower self-reported neuropathic symptoms at entry. Based upon physician examinations, neither ankle reflexes nor vibratory sensitivity to a 128-Hz tuning fork significantly improved during the course of 12 active treatments with the ATS in either group 1 or group 2 subjects. Based on these data, we would tentatively conclude that administration of 12 ATS treatments only improves light touch sensation as measured by the SWM 5.07.

Self-reported pain (VAS) decreased significantly in group 1 subjects after both 6 and 12 treatments, but there was no significant reduction in the group 2 subjects after either 6 or 12 treatment sessions. Thus, 6 to 12 active treatments with ATS may be able to reduce pain but only in those whose DPN has not evolved to profound sensory loss. However, several of the subjects with profound sensory loss did self-report diminished pain during the course of the treatment protocol. Due to the limited number of subjects ($n = 9$), the pain response attenuation for the entire group did not reach statistical significance. Pain reduction might be significant among those with profound sensory loss if the sample was larger.

The only lifestyle change that we addressed was in subject-reported balance impairment. Both group 1 and group 2 subjects exhibited substantial improvement in self-reported balance after the initial six treatments (56.3 and 42.9%, respectively). No further improvement was reported among the group 2 subjects after 12 treatments, but group 1 subjects reported additional improvement (81% of subjects reporting improvement overall). The association between DPN and increased incidence of falls in diabetic subjects has been well documented (6). Although there are certainly factors other than DPN that contribute to falls, the improvement in balance may offer an opportunity for fall-related risk reduction in this population despite the severity of their sensory impairment before treatment.

This study did not include an examination of the biological mechanism through which the improvements in sensation demonstrated after treatment with ATS were obtained. Because both the active and placebo diode pads emit a comparable thermal effect, it is apparent that the results were not simply due to warmth.

The data obtained in this study are limited in some important respects. The 5.07 SWM, although validated and very widely used as a diagnostic tool, determines a gross measure of sensory loss in those with DPN. More discreet quantitative sensory tests would be helpful in determining the exact degree of sensory improvement experienced after the administration of ATS treatments (12). Furthermore, changes in pain and balance were only secondary endpoints in this study, and the study design did not permit us to measure pain reduction or balance improvement in active compared with sham treatment of individual limbs. An alternative study design that would evaluate subjects receiving either active or sham treatment on both limbs, rather than by extremity as in this study, would address this question. Additionally, objective measures of balance, such as the Tinetti Assessment Tool (13), would provide more objective data on actual improvements in gait and balance. Interestingly, a preliminary report showing improved Tinetti Assessment scores and a reduced risk of falling in elderly subjects treated with ATS was recently published (14). Lastly, the present study only evaluated treatment effect after 6 and 12 treatments and did not include analysis of the durability of ongoing treatment. However, the results of this study are so encouraging that we have obtained institutional review board approval to extend this study to include additional quantitative sensory tests and measures of durability.

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Monochromatic Infrared Photo Energy and Physical Therapy for Peripheral Neuropathy: Influence on Sensation, Balance, and Falls

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ABSTRACT

Purpose: Elderly patients are at high risk for falls due, in part, to the loss of sensation in the lower extremities. This study examined the effectiveness of a comprehensive therapy intervention that included monochromatic infrared photo energy for improving foot sensation, balance, and fall status. **Methods:** Thirty-eight patients, average age 78 years, participated in this study. All patients lacked protective sensation in the lower extremities (documented by the Semmes Weinstein 5.07 monofilament), demonstrated a significant fall risk based on Tinetti scores, and had a history of falling. Patients participated in a mean 12 treatments that consisted of infrared photo energy, neuromuscular re-education, balance and strength training, and stretching exercises. **Results:** Comparisons of patients' status pre- and post- treatment showed that they improved significantly in lower extremity sensation and balance and that they experienced fewer falls. **Conclusion:** A comprehensive therapy intervention that includes infrared photo energy has the potential to improve sensation and balance and to reduce fall frequency. These results should be of great interest to patients with peripheral neuropathy, health care providers who treat these patients, and the payor community that incurs the cost of treatment.

Key Words: infrared photo therapy, neuropathy, falls, balance, impairments

INTRODUCTION

One in every 3 persons over the age of 65 falls each year.[1,2] Among those over 65, falls are the leading cause of injury, deaths, and hospital admissions for trauma.[3,4] Falls among the elderly are a significant health care concern with associated costs exceeding $20 billion annually.[5] The most significant consequence of falls is hip fracture.[6] In 1996 there were approximately 340,000 hospitalizations for hip fractures[7] and 50% of the older adults were unable to return home or live independently after their hospitalization.[8] By 2020, the cost of falls in the United States is expected to rise to $32 billion per year.[9]

Falls are a consequence of numerous intrinsic (patient centered) and extrinsic (environmental) factors. Intrinsic factors contributing to falls include gait and balance deficiencies, neurological and musculoskeletal impairments, psychoactive medication use, dementia, and visual impairment.[10] The literature also suggests a high correlation between fall occurrence and diminished sensation among patients with diabetic peripheral neuropathy and neuropathy from other causes such as chemotherapy, alcohol abuse, and peripheral vascular disease.[11-13] In fact, individuals with Type 1 diabetes and neuropathy are reported to be 15 times more likely to fall than their diabetic counterparts who do not yet exhibit peripheral neuropathy.[14] Additionally, the risk of injury from falls in elderly patients exhibiting neuropathy may exceed 50%, far more than that of the elderly population as a whole.[15]

The early stages of diabetic peripheral neuropathy are often characterized by pain and tingling. Five years after initial diagnosis of diabetic peripheral neuropathy, diminished appreciation of temperature and/or pressure is evident in the feet of virtually all of these patients.[16] The progressive sensory loss associated with diabetic peripheral neuropathy makes it very difficult, if not impossible, for physical therapists to achieve meaningful improvements in balance, reductions in fall risk, and a decrease in falls (even when using interventional strategies that have proven successful in elderly patients without neuropathy). For this reason, physical therapy interventions designed to reduce the risk of falls in patients with diabetic peripheral neuropathy have focused primarily on development of compensatory strategies such as using canes, walkers, and managing extrinsic (environmental) fall risks.

Kochman et al recently reported that it is possible to significantly improve foot sensation in diabetic patients with peripheral neuropathy, including those with loss of protective sensation. They used a noninvasive medical device, the Anodyne® Therapy System (ATS), which emits monochromatic near infrared photo energy (MIRE™).[17] Their results are a dramatic departure from those of other interventions that have been unable to restore protective sensation in patients with diabetic peripheral neuropathy. The present study was conducted to determine whether the increased sensation achieved using the ATS, integrated with appropriate balance focused physical therapy interventions, would be able to reduce balance/gait deficiencies and reduce the risk of falls in an elderly population.

METHODS

Patients

This study employed data from the records of 38 consective patients attending an inpatient physical therapy clinic. Institutional review board approval was obtained for use of the data. The mean age of the patients was 78 ± 9.4 years (range: 56 to 97). Fifteen patients were male and 23 were female. Twenty-seven patients had a primary diagnosis of diabetic peripheral neuropathy, 6 exhibited distal polyneuropathy associated with long-term use of alcohol, and 5 exhibited impaired distal sensation due to peripheral vascular disease (PVD).

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Measurements

Assessment of impaired foot sensation was documented objectively using a 5.07 Semmes Weinstein Monofilament (SWM). Patients were asked to respond with 'Now' when they were able to sense randomly applied pressure by this monofilament on the great toe, third toe, and the plantar arch. Application of the SWM was conducted in accordance with recommended testing protocols including avoidance of heavily calloused areas, avoidance of patient prompting, and visually blinding the patients to the sites being tested. Consistent with Medicare guidelines, insensitivity to the SWM 5.07 monofilament at either 2 or 3 of the tested sites was considered to be impaired sensation and loss of protective sensation.[16]

Balance and gait abnormalities were assessed using the Tinetti Assessment Tool.[9] This is a widely recognized objective instrument for determining balance and gait deficiencies and assessing the risk of future falls. Higher Tinetti scores (maximum 28) correlate inversely with risk of falls. Individuals with Tinetti scores under 19 are considered to be at the highest risk for falls, those with scores between 19 and 24 are considered to have a moderate risk of falling, and those with scores 24 and above are considered to be at low risk for falls. All patients presented with a Tinetti score of 20 or less and thus were characterized as having a known fall risk.

All patients were interviewed to determine a prior history of falls during the 3 months immediately prior to evaluation and treatment. At least one fall during this 3-month pretreatment period was documented for all patients. Seventy-nine percent of the patients experienced two or more falls during the prior 3 months; several had fallen 4 to 6 times.

Intervention

The ATS used in this study is a photo diode (wave length 890 nm) based photon therapy modality that was cleared by the FDA in 1994 for temporarily increasing local circulation and reducing pain. The ATS has been used extensively in the physical therapy department since its purchase by our hospital.[17] Previous research has documented improved wound healing[18] and increased nerve conduction velocity[19] with use of monochromatic infrared energy. The interventional protocol consisted of a daily 30 to 40 minute treatment with the ATS (2 diode containing therapy pads, 1 on the medial and 1 on the lateral side of each lower extremity) followed by physical therapy depending on the assessed needs of the individual patient. The physical therapy interventions consisted of static and dynamic balance retraining, neuromuscular re-education, strength training, and stretching of the ankle plantar flexors and hip flexors. Patients received treatment with ATS and physical therapy until sensation and Tinetti scores increased. The number treatments ranged between 6 and 20. Typically, 12 treatments were required, but those who exhibited less balance impairment required fewer treatments (6) and those with profound balance impairment required as many as 20 treatments.

At the conclusion of treatment patients were examined again using the 5.07 SWM and the Tinetti scale. Subsequently, and with no further ATS or physical therapy interventions, all patients were contacted to determine if they experienced a fall during the 3 months after the completion of treatment.

Data Analysis

After the calculation of descriptive statistics, differences in pre- and post-treatment status were compared using Wilcoxon matched pairs signed ranks tests. Significance was accepted when $P<0.05$.

RESULTS

At baseline, all of the 38 patients exhibited loss of protective sensation assessed by the SWM 5.07 monofilament. The mean number of sites sensitive to the SWM 5.07 (out of 3 tested sites) was 0.9 ± 0.3. The mean Tinetti score was 11.2 ± 4.5 at entry (range: 5 to 20), well below a score of 19, the cut off value below which patients have the highest risk for falls. Finally, the mean number of falls experienced by all patients over the previous 3 months was 2.6 ± 1.4 (range: 1 to 6); there was a total of 98 falls in the 38 patients during the 3 months prior to pretreatment examination.

At the conclusion of the 12.7 ± 2.9 interventions (range 6-20) with the ATS and appropriate physical therapy, all patients demonstrated restoration of protective sensation as determined by the SWM 5.07 monofilament. Specifically the patients were able to sense a mean of 2.7 ± 0.4 of the 3 sites on the foot ($P < 0.0001$). After treatment patients' Tinetti scores were 21.6 ± 3.4. Each patient demonstrated a higher Tinetti score (Figure 1) with a mean improvement of 10.4 ± 3.9 points (range: 4 to 21). This increase was significant ($P < 0.0001$). Additionally, 29 of 38 patients reduced their Tinetti fall risk category by at least one level (for instance, from high risk of falling to moderate risk) and 12 of these experienced a 2-level reduction in fall risk category (Figure 1). Finally, follow up patient interviews showed that only 4 patients experienced a single fall each during the 3-month period following therapy (Figure 2). The average falls per patient (0.1 ± 0.3) represented a significant decrease ($P < 0.0001$).

DISCUSSION

In the present study, it was hypothesized that comprehensive physical therapy intervention consisting of using both

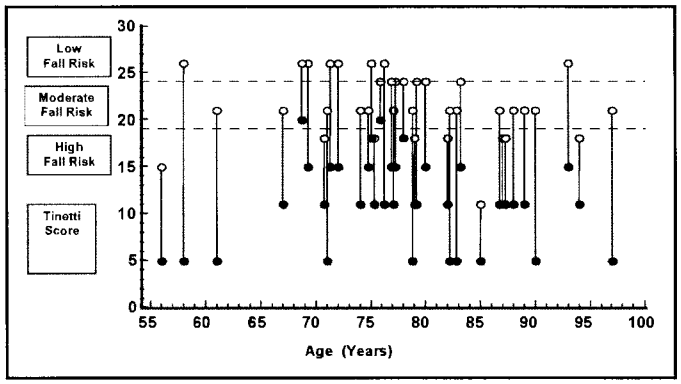

Figure 1. Tinetti scores increase in every patient regardless of age. Filled circles indicate Tinetti scores before ATS and PT interventions and open circles indicate scores after interventions.

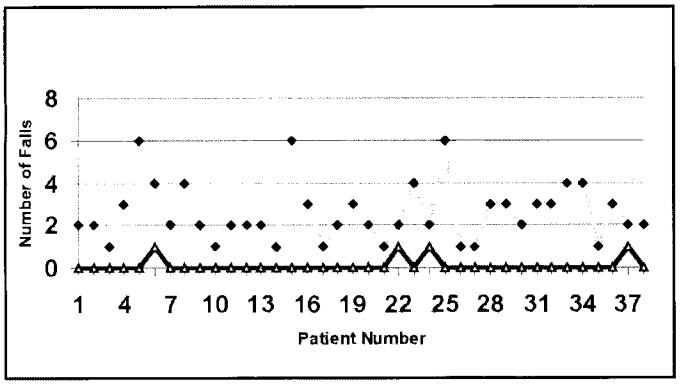

Figure 2. Number of falls by each patient is decreased in the 3 months after combined ATS and PT interventions (triangles) compared to the 3 months before (diamonds).

the ATS to improve sensation and appropriate physical therapy to improve balance, motor control, strength, and flexibility could reduce both fall risk and the post-treatment falls in an at-risk population. This hypothesis was intuitive since interventional strategies that are not accompanied by increased foot sensation in patients with distal neuropathy have produced limited benefit in fall related outcomes.[20]

All patients obtained objective improvement in foot sensation, which was accompanied by significant reduction in objectively measured fall risk (mean Tinetti improvement 10.2 points). Further, this increased sensation and reduced fall risk resulted in a 93% reduction in the actual incidence of falls during the 3 months after treatment when compared to the fall history during the 3 months prior to treatment. Prior to treatment the 38 patients had reported 98 falls and during the 3 months after intervention only 4 falls were reported.

We used the ATS to increase circulation and improve foot sensation in the patients. The ATS is a photon energy based therapeutic device that delivers solely near infrared photo energy (890 nm) produced by diodes. Photo energy, while of limited but rapidly increasing use in the United States, is a well-recognized therapeutic agent internationally, based on published clinical and scientific evidence.[21] Photon therapy is used clinically to increase circulation, reduce pain, and promote healing for a wide variety of conditions.[21] While the underlying mechanism of action is not completely understood, effectiveness is based upon scientific and physiologic parameters including wavelength, energy density, absorption, and duration of treatment[21] and similar wavelengths do increase microcirculation.[22] While there are other photon therapy devices available for use in the United States, we used the ATS due to availability, our staff's years of clinical experience with the ATS, and the existence of a published clinical study that demonstrated the efficacy of ATS in symptomatically reversing diabetic peripheral neuropathy.[17]

Historically, physical therapy interventions designed to reduce the number of falls in elderly patients, particularly those with distal neuropathy, have resulted in minimal success.[23,24] However, Richardson and colleagues[25] have reported that a 3- week exercise program designed to increase rapidly available distal strength and balance in patients with peripheral neuropathy was able to improve unipedal and tandem stance times by a mean of 6 seconds each and functional reach by a mean of 1 inch. However, no analysis of postintervention falls or a broader analysis of changes in gait and balance under a Tinetti and similar test were undertaken. While the therapy intervention in this study included many of the exercises employed in the Richardson study,[25] our protocol included a broader range of gait and balance interventional strategies. Unfortunately, the differences in measures undertaken in our study and the Richardson study[25] make comparison of the therapeutic results and net health outcomes impossible.

Of interest, in this study the loss of protective sensation was due to 3 different etiologies, suggesting that this approach may work to the advantage of the therapist in treating patients with impaired lower leg sensation and proprioception due to various etiologies.

Decreased microcirculation apparently underlies sensory impairment in diabetic patients[26] and is the contributor to wounds and amputations.[27] It is likely that the alcohol and PVD mediated decreases in sensation also are due to poor microcirculation to the endoneurial surface of nerve bundles. These data suggest that improving local circulation and foot sensation, at least with the use of the ATS, improves the efficacy of several important physical therapy interventions designed to improve balance, muscle strength, and gait. This comprehensive treatment approach to balance deficiencies associated with diabetic peripheral neuropathy and other sensory neuropathies is apparently able to significantly improve balance and gait, significantly reduce objective measures of fall risk and, at least for a period of 3 months after treatment reduce the number of actual falls.

Certain limitations of the study design should be considered when analyzing these conclusions. These data were based upon an IRB approved review of patient's charts, thus there was no control. Additionally, concomitant analysis of the utilization of psychoactive drugs and other intrinsic falls risks was not performed. Incidence of falls was only analyzed for brief periods of 3 months before and after interventions. Lastly, the study methodology did not permit us to analyze gains that were attributable to physical therapy alone and those related to the increases in foot sensation resulting from the use of the ATS. Further studies should consider matched controls to: (1) determine the relative effectiveness of the combination of ATS with physical therapy compared to physical therapy alone, (2) control for other intrinsic risks for falls, and (3) follow up on fall outcomes beyond 3 months.

CONCLUSIONS

Based on these clinical data, ATS is able to improve foot sensation, and when used in conjunction with physical therapy is able to significantly improve balance and gait, reduce objective fall risk, and reduce the incidence of falls in an elderly population when comparing 3 month periods immediately before and immediately after intervention.

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Reversal of Diabetic Peripheral Neuropathy and New Wound Incidence: The Role of MIRE

Mark W. Powell, MD; Dale E. Carnegie, DPM; and Thomas J. Burke, PhD

ABSTRACT

OBJECTIVE: To determine if improved foot sensitivity to the Semmes-Weinstein 10-g (5.07) monofilament, originally impaired because of diabetic peripheral neuropathy, might be associated with a reduced incidence of new diabetic foot wounds.

DESIGN: Retrospective cohort study using a health status questionnaire.

SUBJECTS: Sixty-eight individuals over age 64 with diabetes, diabetic peripheral neuropathy, and loss of protective sensation who had clinically demonstrable increases in foot sensation to the Semmes-Weinstein monofilament after treatment with monochromatic near infrared photo energy.

MAIN RESULTS: After reversal of diabetic peripheral neuropathy following treatment with monochromatic near infrared photo energy, only 1 of 68 patients developed a new diabetic foot wound, for an incidence of 1.5%. Comparatively, the incidence previously reported in the Medicare-aged population with diabetes was 7.3%.

CONCLUSIONS: Improved foot sensitivity to the Semmes-Weinstein monofilament in patients previously suffering from loss of protective sensation due to diabetic neuropathy appears to be associated with a lower incidence of new diabetic foot ulcers when compared with the expected incidence in the Medicare-aged population with diabetes.

CLINICAL RELEVANCE: Therapeutic interventions that effectively improve foot sensitivity that has been previously diminished due to diabetic peripheral neuropathy may substantially reduce the incidence of new foot wounds in the Medicare-aged population with diabetes.

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Of the more than 18 million individuals in the United States who have diabetes, 15% are over age 65.[1] Health care costs in this age-group are often borne by Medicare. The direct cost of diabetes was estimated at $78 billion in 1997,[2] growing to $91 billion in 2002.[3] Over 51% of that $91 billion was spent on patients older than age 65.[3] Treatment for one of the complications of diabetes—lower extremity ulcers—cost Medicare $1.5 billion in 1995.[1] By 2001, the cost for treatment of diabetic foot ulceration and associated amputations had climbed to an estimated $10.9 billion.[4]

Fifteen percent or more of people with diabetes sustain 1 or more foot wounds during their lifetime,[5] and they are 15 times more likely to suffer a nontraumatic lower extremity amputation than people without diabetes.[6] As a result, reduction in the incidence of foot wounds and nontraumatic amputations among people with diabetes is an objective of Healthy People 2010.

Diabetic peripheral neuropathy (DPN), or sensory nerve dysfunction, is typically determined in a clinical setting by diminished sensation to the Semmes-Weinstein 10-g (5.07) monofilament (SWM) or by diminished vibration perception threshold (VPT) in the foot. DPN is widely considered a significant risk factor for diabetic foot wounds.[7] Patients with diabetes who show sensitivity to the SWM rarely develop these wounds.[8] As the severity of DPN progresses toward loss of protective sensation (LOPS), including insensitivity to the

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SWM, so does the risk of foot ulceration.[9]

DPN has been documented in more than 80% of patients who have 1 or more diabetic foot ulcers[10]; it is also a factor in more than 80% of all nontraumatic, lower extremity amputations performed on patients with diabetes.[11] DPN can be identified in the intact, contralateral limb in more than 97% of lower extremity amputees.[12] Although abnormal sensory nerve function has been detected in the contralateral limb of diabetic amputees, it is not present in age-matched amputees without diabetes.[13]

In a study examining the effectiveness of therapeutic shoes in preventing reulceration in patients with diabetes, Reiber et al[14] reported that more than 93% of all foot wounds that developed during the study were found in patients who were insensitive to the SWM. The inability to detect the SWM and a VPT of 25 volts (V) or more—indicators of sensory nerve dysfunction—have been shown to have similar sensitivity[15] and a high correlation to each another.[15] They have also been found to be predictive of diabetic foot wounds.[16] Young et al[16] reported that in a group of patients with no prior foot ulcers, fewer than 4% of patients with a VPT less than 25 V developed a foot wound, compared with almost 19% of those with a VPT of 25 V or more; this represents a five-fold increase in incidence. No recurrent ulcers were seen in the group with a VPT of less than 25 V; however, 30 recurrent foot wounds were noted in patients with a VPT of 25 V or more.

Several studies have discussed the incidence of diabetic foot wounds, with the most exhaustive examination by Harrington et al.[1] They analyzed Medicare claims data from the 1995 and 1996 Standard Analytic Files (SAF) 5%, which is a scalable database containing the complete claims representative of 5% of the Medicare population. Based on the analysis, Harrington et al[1] determined that the incidence rate of wounds in patients over age 65 was 7.3%. Abbott et al[17] reported a 7.2% incidence rate over 1 year in a sample of 1035 patients with diabetes (average age 60; range 23 to 70). Pham et al[18] found an incidence of 11.6% in a group of 248 high-risk patients with diabetes (age 58 ± 12) who exhibited, among other risk factors, sensory nerve dysfunction based on both SWM and VPT testing.

For the present study, it was estimated that the expected annual incidence rate of new diabetic foot wounds among a Medicare-aged population would be 7.3%. This value was used to compare the results of the patient cohort in the present study.

With the incidence of diabetic wounds so closely associated with DPN, increasing foot sensitivity to the SWM in such patients should theoretically reduce the incidence of diabetic foot wounds. The lack of treatment to improve foot sensation in patients with DPN, as measured by either sensitivity to the SWM or VPT, however, has prevented evaluation of such a hypothesis.

Two recent studies [19,20] suggest that temporary increases in foot sensitivity to the SWM are possible through the application of monochromatic near infrared photo energy (MIRE) to patients with diabetes who presented to their health care professional with an already significant LOPS associated with DPN. To date, no long-term evaluation has been conducted to determine any changes (increase or decrease) in the incidence of new foot wounds in patients who had clinically demonstrable evidence of improved sensory nerve function following application of this noninvasive modality.

The present study details outcomes in 68 patients who showed increased sensitivity to the SWM after being treated with MIRE. Between 10 and 15 months after sensation had improved, patients were queried about the incidence of new diabetic foot wounds. These patients were questioned about other outcomes as well, including number of falls, fear of falling, and activities of daily living. Responses to questions concerning these other functional outcomes, however, are outside the objectives of this report.

METHODS

Insurance records of the only 2 durable medical equipment suppliers offering the MIRE device (Anodyne Therapy System; Anodyne Therapy LLC, Tampa, FL) were reviewed to obtain a list of patients to whom a health status questionnaire would later be administered. Only patients with diabetes and LOPS, whose insurance claims reflected a diagnosis of both diabetes (ICD-9 codes 250.61 or 250.62) and peripheral neuropathy (ICD-9 code 357.2), and who received therapy with the MIRE device between January 1, 2002, and May 31, 2002, were eligible for the study. Prior to providing information to the authors, all patient identifiers were removed by the suppliers; patients had authorized the release of medical information relative to their diagnosis and the therapeutic benefits resulting from MIRE treatment. Medical records for each patient, including written physician orders and treatment notes, were reviewed to confirm the initial diagnosis of DPN with LOPS and subsequent improvement of their sensory nerve dysfunction, as measured by improved sensitivity to the SWM after treatment with MIRE.

Patients who already had a diabetic foot ulcer when they first started using the MIRE device were excluded from the study. This would permit an analysis of the development of new foot ulcers over the next year (mean 12.5 months) of treatment with the MIRE device at home. Patients age 64 or younger were excluded to permit analysis of Medicare-aged patients only.

Table 1.
POST SURVEILLANCE QUESTIONNAIRE

1. **Prior to using Anodyne:**
   a. Did you ever experience a wound on your foot? *(Yes, No)*
   b. If so, did the wound heal in less than 8 weeks? *(Yes, No)*
   c. Did you ever have a lower extremity amputation? *(Yes, No)*
   d. Did you feel off balance to the extent that you feared falling when you walked? *(Yes, No)*
   e. How many times did you fall during the 12 months prior to the time you started using Anodyne? *(None, 1 time, or 2 or more times)*
2. **Since using Anodyne:**
   a. Have you experienced a wound on your foot? *(Yes, No)*
   b. If yes, did the wound or wounds heal in less than 8 weeks? *(Yes, No)*
   c. Have you had a lower extremity amputation? *(None, Toe(s), Partial Foot, Total Foot, Below Knee, Above Knee)*
   d. Do you feel that your balance has improved and that you now have less fear of falling when you walk? *(Yes, No)*
   e. How many times have you fallen since beginning to use Anodyne? *(None, 1 time, or 2 or more times)*
   f. Compared to what you were able to do most days before using Anodyne, how would you compare what you are now able to do most days? *(A lot less, a little less, about the same, a little more, a lot more)*

Of the original pool of eligible patients, 119 patients qualified for the study, having met the criteria of (1) DPN and LOPS but no current lower extremity ulcers, (2) age 65 or older, and (3) improved foot sensation after use of the MIRE device. An 11-question post-treatment health status surveillance questionnaire was sent to these patients. The questionnaire asked about foot wounds, amputations, fall history, fear of falling, and activities of daily living before and after increased foot sensitivity (Table 1). The prevalence of foot wounds preceding improved sensitivity to the SWM was determined by patient responses to question 1a. Responses to question 2a established the incidence of new ulcers after increased sensitivity to the SWM.

Three interviewers attempted to contact each of the 119 patients at least 3 times to elicit responses to the health status questionnaire. Of the 119 community-dwelling patients, who had been using the MIRE at home for an average of 12.5 months, 68 (57%) agreed to answer the questionnaire.

The 68 patients had been treated by 51 physicians. Before providing the MIRE device to these patients, the durable medical equipment suppliers had received signed certificates of medical necessity from the attending physicians certifying a diagnosis of DPN and LOPS and the fact that these conditions can be reversed with regular use of MIRE.

The MIRE device used by these patients consists of a power unit connected to several therapy pads, each containing 60 luminous diodes that emit monochromatic near infrared (890 nanometers) photo energy.[21] Physicians had instructed their patients to place the MIRE therapy pads in direct contact with the skin on the bottom of the feet for 30 to 40 minutes per day for 2 months. After 2 months, the attending physicians reevaluated their patients to determine whether objective improvement in foot sensation was noted. If so (and if the patient desired ongoing access to the MIRE device for home treatment), the physicians signed a second certificate of medical necessity for lifetime use. The second certificate of medical necessity certified that foot sensation had substantially improved after treatment with the MIRE device. This was accompanied by chart notes documenting the clinical improvement in foot sensation. Patients were instructed to treat themselves at home for 30 to 40 minutes per day, 2 to 7 days a week.

Statistical analysis

Results were analyzed by a paired 2-tailed *t* test with a null hypothesis that improvement in sensory nerve dysfunction, as measured by increased sensitivity to the SWM, would not decrease the incidence of new foot wounds below a rate of 7.3%. Patients served as their own controls. The 2-tailed *t* test was used because no assumption was made a priori as to whether the incidence of new foot wounds would be higher or lower. A 2-tailed *t* test is more conservative than a 1-tailed *t* test. Significance was accepted when $P < .05$. All values are expressed as mean ± 1 standard deviation.

RESULTS

Mean age of the 68 diabetic respondents (37 male, 31 female) was 76.6 years (range 64 to 92; Table 2). Twenty-two patients were 80 years or older. The mean duration since the improvement in the sensory nerve function of these community dwellers, as certified by their attending physicians, averaged 12.5 months (range 10.5 to 15 months). These patients had ongoing access to the MIRE device at home during this time.

In the years before obtaining increased foot sensitivity, 19% of patients (13 of 68) had experienced a foot wound (Table 3). This finding is similar to the expected prevalence among individuals with diabetes, which has been reported to be 15%.[1] Patients stated that only 15% of those wounds healed within 8 weeks. Accordingly, the study population was considered to represent the diabetic population in terms of prevalence of diabetic foot wounds and time to wound healing, as reported by Harrington et al.[1]

Only 1 foot wound developed in the study population after

Table 2.
PATIENT DEMOGRAPHICS

Patients contacted by phone	119
Patients who answered questionnaire	68
Response rate	57%
Males	37
Females	31
Age (years)[a]	76.6 ± 6.3
Average months after reversal of DPN	12.5 ± 1.3

a = mean ± SD; DPN = diabetic peripheral neuropathy

these patients experienced increased foot sensitivity. The wound occurrence was considered typical because of risk factors associated with sensory nerve dysfunction. This incidence rate is less than 1.5% (1 in 68 patients). A higher rate, 7.3%, is more common, according to the literature.[1]

Another patient reported a topical burn to the dorsal aspect of the foot after he fell asleep for several hours while self-treating with the MIRE device. Such extended use while sleeping is inconsistent with the manufacturer's written warnings.

DISCUSSION

Sensory nerve dysfunction, as documented by either the SWM or the VPT test, is considered a late consequence of progressively compromised blood flow to the nerves of the lower extremities of individuals with diabetes. Studies have shown that however measured, sensory nerve dysfunction is a major contributory factor to foot wounds[8] and amputations[11,22] in this population. The findings of the present study corroborate those that document a high prevalence of wounds in patients with diabetes who have DPN and LOPS.

In addition, the survey results suggest that improvement of sensory nerve dysfunction, as measured by increased sensitivity to the SWM, may be accompanied by a reduced incidence of new diabetic foot ulcers. In the 68 patients who responded to this survey, the reported number of new diabetes-related wounds was less than 1.5% per year. Clinically published data suggest that an incidence rate of 7.3% should be expected when patients have DPN or LOPS.

Young et al[16] reported that strategies to improve foot sensation in patients with diabetes, who initially had diminished protective sensation, might reduce the incidence of diabetic foot wounds in those without significant sensory nerve dysfunction (VPT of less than 25 V) to under 4%. This outcome could significantly impact the costs associated with treating diabetic foot wounds, as reported by Shearer et al,[5] who concluded, "If all individuals with reduced vibration detection were identified and a new preventative strategy could reduce their risk of ulceration and amputations to levels experienced by those with normal vibration detection, US health payers could save up to $11.8 billion and save 333,000 life-years and 428,000 quality adjusted life-years (discounted) over the next 10 years."[5] These conclusions were based on discounting the cost and benefits to present values at a rate of 3%.

Interestingly, data from the present study indicate that before DPN was reversed, only 15% of wounds had healed in less than 8 weeks. After reversal of DPN, the diabetic foot ulcer and the topical burn discussed above healed within 8 weeks. This time to healing compares favorably with reported times for wound closure among patients with diabetes.[1] No conclusions can be drawn about this observation; it is both outside the objective of the present study and is not sufficiently supported by the sample size and study methodology. However, it may encourage future investigation.

The study has certain limitations. The sample size of 68 patients is less than the number included in the several studies that were used to benchmark these results.[17,18] Improved sensory nerve function was substantiated through analysis of written physician orders and supporting treatment notes. However, both the prevalence of diabetic foot wounds before treatment and the incidence of new diabetic foot wounds after improvement in sensory nerve function are based solely on patient response to the questionnaire. Similar methodology has been used in other studies related to falls[23, 24] or wounds.[25] It is possible that patient recall of a wound may be inaccurate or that an interviewer may have introduced bias in soliciting answers to questions. However, patients should have been able to accurately answer questions that formed the basis of the inquiry about old and new wounds. An attempt to minimize interviewer bias was made by using 8 separate interviewers.

Sensory nerve dysfunction is only 1 risk factor associated with diabetic foot wounds; no multivariate analysis of known comorbid risks for wounds was undertaken. Therefore, it is possible that some of the reported reduction in wound incidence resulted from other variables. Finally, no control group was used in this evaluation. The purpose of this study was to document changes in the incidence of diabetic foot wounds among patients whose sensory nerve function improved and compare them with an already extensive research database; this database served as a historical control.

This study shows an association between improved foot sensation in patients with LOPS due to DPN and a subsequently reduced incidence of foot wounds. Significant conclusions, however, about the relationship between these 2 variables can be derived only through an additional well-designed, randomized, controlled trial that addresses the acknowledged limita-

Table 3.
WOUND INCIDENCE BEFORE AND AFTER REVERSAL OF DPN WITH MIRE

	1 year Prior to DPN Reversal	1 Year After DPN Reversal	Improvement %	*P* Value
Wounds				
Prevalence	19%[1]			
Healed in 8 weeks	15%	100%	667%	
Incidence	7.3% [2]	1.5%	79%	<.0001

1 Prevalence was measured during the entire period prior to reversal of DPN. Actual prevalence was higher because patients with existing wounds at the time the MIRE device was ordered were excluded from analysis.
2 Historical incidence in the Medicare population as reported by Harrington et al.[1]

tions of the present study, including size of the study population. A future investigation should include an examination of any cost savings related to reduced incidence of new wounds, which would allow a cost benefit analysis of the method used to obtain improved foot sensitivity.

A larger population of patients with diabetes, treated with MIRE for several months to years, has been identified. Medicare carriers will be asked to assist with access to the relevant data in the Centers for Medicare and Medicaid Services Common Working File as part of a new analysis.

CONCLUSION

Increased sensory nerve function in patients previously diagnosed with DPN and LOPS, based on use of the SWM after continued access to the MIRE device in the home, seems closely related to a significant reduction in the expected incidence of new diabetic foot wounds. The actual reported incidence rate during continued MIRE use appears to be quite low and may be equal to or less than that previously reported for patients who have yet to experience disease-related sensory nerve dysfunction. These results support the conclusions reached by Shearer et al[5] that improvement in sensory nerve function in patients previously diagnosed with DPN and LOPS may have major socioeconomic and quality of life benefits for those with diabetes. This may offer potentially significant cost savings to the Medicare system and other health care organizations. ●

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Improved Sensitivity in Patients with Peripheral Neuropathy

Effects of Monochromatic Infrared Photo Energy

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The medical records of 1,047 patients (mean age, 73 years) with established peripheral neuropathy were examined to determine whether treatment with monochromatic infrared photo energy was associated with increased foot sensitivity to the 5.07 Semmes-Weinstein monofilament. The peripheral neuropathy in 790 of these patients (75%) was due to diabetes mellitus. Before treatment with monochromatic infrared photo energy, of the ten tested sites (five on each foot), a mean ± SD of 7.9 ± 2.4 sites were insensitive to the 5.07 Semmes-Weinstein monofilament, and 1,033 patients exhibited loss of protective sensation. After treatment, the mean ± SD number of insensate sites on both feet was 2.3 ± 2.4, an improvement of 71%. Only 453 of 1,033 patients (43.9%) continued to have loss of protective sensation after treatment. Therefore, monochromatic infrared photo energy treatment seems to be associated with significant clinical improvement in foot sensation in patients, primarily Medicare aged, with peripheral neuropathy. Because insensitivity to the 5.07 Semmes-Weinstein monofilament has been reported to be a major risk factor for diabetic foot wounds, the use of monochromatic infrared photo energy may be associated with a reduced incidence of diabetic foot wounds and amputations. (J Am Podiatr Med Assoc 95(2): 143-147, 2005)

Diabetes mellitus affects more than 15% of the US population older than 65 years.[1] The direct cost of this illness, which affects more than 17 million people, was recently estimated to be more than $91 billion annually, with more than half of this spent on those older than 65 years.[2] Lower-extremity foot wounds and amputations represent a significant portion of this cost.[3,4] Reductions in the incidence rates of these conditions to minimize the human and financial burden associated with diabetic foot wounds and amputations is one of the objectives of the US Surgeon General as stated in *Healthy People 2010*.[5]

Foot wounds are highly correlated with a loss of sensation in the lower extremities. Peripheral neuropathy is typically defined in a clinical setting as diminished sensation to the 5.07 Semmes-Weinstein monofilament in the foot. Recently, the Centers for Medicare and Medicaid Services determined that insensitivity to the 5.07 Semmes-Weinstein monofilament at two or more of five tested sites on either foot is considered to be loss of protective sensation and a localized illness of the foot.[6] Diabetic peripheral neuropathy is widely considered to be a very significant risk factor for diabetic foot wounds,[7] and lower-extremity ulcers occur much less frequently in diabetic patients who do not exhibit peripheral neuropathy.[8,9]

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Until recently, no treatments have been effective in improving foot sensation after it has been compromised owing to peripheral neuropathy. As a result, physicians who treat these patients have only been able to determine those who are at high risk of lower-extremity ulcers and amputations and then to prescribe accommodative risk-reduction strategies, including patient education, frequent visits to their physicians, orthotic devices for off-loading, and diabetic shoes. Unfortunately, patient compliance has been less than exemplary, and these risk-reduction strategies have met with sporadic success.[10]

Even after using risk-reduction strategies, patients with diabetic peripheral neuropathy remain at higher risk of lower-extremity wounds than those without it. For example, Reiber et al,[10] in their evaluation of the effectiveness of diabetic shoes, reported that more than 93% of all foot wounds during the study occurred in patients with diabetic peripheral neuropathy. (The incidence of wounds in their study population was approximately 11%.)

Two recent studies[11, 12] suggest that at least temporary increases in foot sensitivity to the 5.07 Semmes-Weinstein monofilament can be documented following the application of monochromatic infrared photo energy (MIRE; Anodyne Therapy LLC, Tampa, Florida) to diabetic patients who presented to their health-care professionals with an already significant loss of protective sensation associated with diabetic peripheral neuropathy. Another study[13] of patients with peripheral neuropathy showed that use of MIRE was associated with an increase in sensory nerve function based on testing conducted with the Neurometer CPT sNCT (Neurotron Inc, Baltimore, Maryland). Although one of these studies was randomized, double blind, and placebo controlled[12] and another used double-blind neurophysiologic testing,[13] the sample sizes were comparatively small. The present article details the improved foot sensation after treatment with MIRE in 1,047 patients (790 with diabetes mellitus) for whom sensory data had been collected in the course of medical treatment.

Research Design and Methods

The insurance claims of two durable medical equipment suppliers that offer the Anodyne Therapy System (Anodyne Therapy LLC), a piece of durable medical equipment that delivers MIRE, were reviewed to obtain a list of patients who had been treated with MIRE in physicians' offices and therapy clinics throughout the United States. The suppliers removed all patient identifiers in the data prior to submitting them to the investigators for purposes of this review and analysis. The Anodyne Therapy System delivers MIRE through therapy pads, each containing 60 superluminous diodes (890 nm of near-infrared wavelength), which are attached to a control unit that pulses the MIRE at 292 times per second.[14]

Before providing the Anodyne Therapy System to patients, these suppliers had received signed Certificates of Medical Necessity and chart notes (including, in most cases, the baseline 5.07 Semmes-Weinstein monofilament sensitivity value) from the attending physicians. These data supported both a diagnosis of peripheral neuropathy before and objective improvement after the patient had received a course of MIRE.

The suppliers maintained a searchable database containing a record of all claims filed, including *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) coding of the underlying conditions for which the Anodyne Therapy System had been ordered by referring physicians. The database, excluding any patient identifiers, was sorted to obtain a list of all patients who had a diagnosis of peripheral neuropathy based on ICD-9-CM code 357. The list was then stratified to obtain a list of those with type 1 or type 2 diabetes mellitus using ICD-9-CM codes 250.61 and 250.62, respectively. The period of inquiry was February 1, 2002, to January 23, 2004, and 2,070 patients treated with MIRE satisfied these criteria. Medical professionals who diagnosed peripheral neuropathy in their patients had been provided with pretreatment and post-treatment case report forms, which included a template of each foot on which were indicated five plantar sites to be assessed with the 5.07 Semmes-Weinstein monofilament before and after the application of MIRE. The five sites on the case report form were those recommended for evaluation of foot insensitivity by the National Institute of Diabetes and Digestive Diseases in "Feet Can Last a Lifetime,"[15] which had been incorporated into Centers for Medicare and Medicaid Services Decision Memorandum CAG-00059 issued on October 17, 2001,[6] and subsequently adopted in Centers for Medicare and Medicaid Services Program Memorandum AB-02-042 dated April 1, 2002. The suppliers had further advised the health-care professionals of the method of undertaking the Semmes-Weinstein monofilament evaluation consistent with "Feet Can Last a Lifetime," which included a "two-alternative, forced-choice method of evaluation" that has been validated as the most reliable method to test sensory input.[16] The medical records on file with the suppliers included 1,047 patient records containing completed case report forms, as previously described, of bilateral foot sensitivity data for the 5.07 Semmes-Weinstein monofilament before and after MIRE treatment.

Statistical Analysis

The results were analyzed using the paired two-tailed *t*-test with a null hypothesis that there would be no change in sensitivity (either an increase or a decrease) to the 5.07 Semmes-Weinstein monofilament following use of MIRE. Significance was defined as $P < .05$.

Results

The mean age of the study population (513 men and 534 women) was 73 years (range, 51–93 years) (Table 1). A total of 790 patients were diagnosed as having diabetic peripheral neuropathy, and 257 patients were diagnosed as having peripheral neuropathy associated with other etiologies. The mean number of sites insensitive to the 5.07 Semmes-Weinstein monofilament (bilaterally; a maximum of ten sites for both feet) was 7.9 before treatment and 2.3 after treatment ($P < .0001$). Of 1,047 patients, 452 (43%) exhibited insensitivity to the 5.07 Semmes-Weinstein monofilament at all ten sites before treatment with MIRE. At the conclusion of the initial MIRE treatments, these patients experienced a mean ± SD decrease of 6.9 ± 2.7 sites insensitive to the 5.07 Semmes-Weinstein monofilament, a 69% reduction in their sensory impairment ($P < .0001$) (Table 2). A total of 580 patients experienced a restoration of protective sensation after treatment with MIRE. Restoration of protective sensation was defined as having less than two sites on both feet insensitive to the 5.07 Semmes-Weinstein monofilament after MIRE treatment (Table 2).

Discussion

Until recently, peripheral neuropathy, particularly that associated with diabetes mellitus, was thought to be progressive and irreversible. Recent studies,[11-13] conducted in relatively small populations, have shown that symptomatic peripheral neuropathy is reversible with MIRE treatment. The present study shows that improvement can occur in a larger study population (1,047 community-dwelling patients with peripheral neuropathy) treated in routine clinical practice.

Notably, more than half of the patients who were initially diagnosed as having loss of protective sensation (56.1%) obtained at least a temporary return of protective sensation. Those with the most severe peripheral neuropathy (all ten sites insensitive to the 5.07 Semmes-Weinstein monofilament) had a striking restoration of sensation.

Figure 1 shows the number of insensate sites before and after treatment in this group of patients. Before treatment with MIRE, most of the patients exhibited a loss of sensation at nine or ten sites, and 75% of all patients had documented loss of sensation at six or more sites. After treatment, 50% of patients were insensate at none or only one or two sites and 75% were insensate at less than four sites. The change in distribution of insensitivity graphically demonstrates the MIRE treatment effect in this patient population.

The results of this analysis demonstrate that sensory loss associated with peripheral neuropathy, even when it has advanced to and beyond loss of protective sensation, is not necessarily irreversible. Moreover, most of these patients experienced a significant

Table 1. Demographic Characteristics of 1,047 Patients with Established Peripheral Neuropathy

	Value
Sex (No. [%])	
M	513 (49)
F	534 (51)
Diabetic peripheral neuropathy (No. [%])	790 (75)
Nondiabetic peripheral neuropathy (peripheral neuropathy associated with other etiologies) (No. [%])	257 (25)
Age (mean ± SD) (years)	73 ± 8.3
Insensate sites (mean ± SD) (No.)	7.9 ± 2.4

Table 2. Foot Sensitivity to the 5.07 Semmes-Weinstein Monofilament Before and After Treatment

	Value
All patients (No.)	1,047
Pretreatment insensate sites (mean ± SD) (No.)	7.9 ± 2.4
Post-treatment insensate sites (mean ± SD) (No.)	2.3 ± 2.4[a]
Decrease in insensate sites (mean ± SD) (No.)	5.6 ± 2.7[a]
Pretreatment patients with LOPS (No. [%])	1,033 (98.7)
Post-treatment patients who regained protective sensation (No. [%])	580 (56.1)
Post-treatment patients with LOPS (No. [%])	453 (43.9)
Pretreatment patients with all 10 sites insensate (No. [%])	452 (43)
Post-treatment insensate sites (mean ± SD) (No.)	3.1 ± 2.7[a]
Decrease in insensate sites (mean ± SD) (No.)	6.9 ± 2.7[a]

Abbreviation: LOPS, loss of protective sensation.
[a]$P < .0001$.

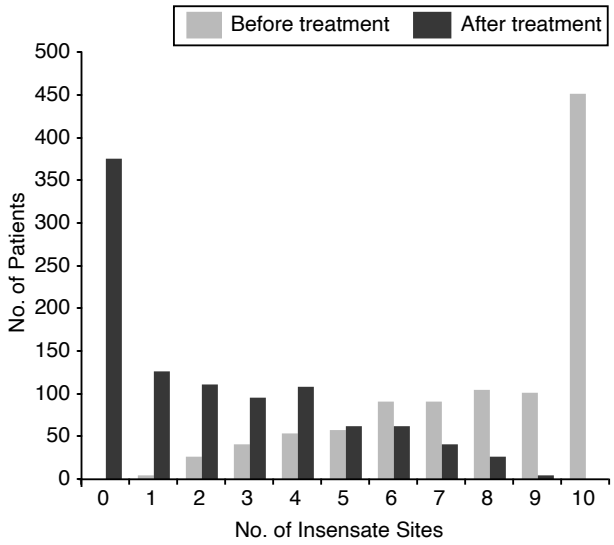

Figure 1. Number of patients with sites (on both feet) insensate to the 5.07 Semmes-Weinstein monofilament before and after treatment.

response to MIRE treatment. Improvement in sensation seems to occur even in patients with totally insensate feet (inability to sense the 5.07 Semmes-Weinstein monofilament at all tested sites). Because diabetic peripheral neuropathy is commonly associated with lower-extremity wounds and amputations as well as falls among people with diabetes mellitus, the sensory improvement reported in this study may also be associated with a decrease in these peripheral neuropathy–associated comorbidities. In fact, a reduced incidence of wounds has been reported in patients who have received nerve decompression surgery that resulted in improved sensory nerve function.[17] If additional studies support a relationship between improvement in sensory nerve function and a decreased incidence of wounds or falls (ie, peripheral neuropathy–attributable comorbidities), then interventions designed to improve this condition might offer significant benefit to these patients as well as a cost savings to the US health-care system.[3,4]

These observations and the conclusions derived must be analyzed in the context of certain limitations of the study design. For example, there was no control group against which the results of this study were measured. However, when a disease such as diabetic peripheral neuropathy is known to be progressive and irreversible, the use of historical controls from the published literature may be appropriate.[18] In the case of diabetic peripheral neuropathy, there have been no reports of either spontaneous reversal of this condition or efficacy of any nonsurgical intervention. Furthermore, these data were obtained from the records of patients who exhibited some improvement in their neuropathic symptoms. The data do not suggest that patients, before MIRE treatment, were early in their course of peripheral neuropathy or that they had a mild form of this condition. Rather, a significant proportion of patients, more than 75%, had well-defined peripheral neuropathy, a condition that would be the least likely to spontaneously reverse or to respond to pharmacologic treatment. However, we acknowledge that we cannot generalize these results to all patients with peripheral neuropathy. Clearly, there may be some patients who would not respond to MIRE treatment. Thus we conclude only that these 1,047 patients obtained objective improvement in foot sensitivity to the 5.07 Semmes-Weinstein monofilament after treatment with MIRE.

We also cannot totally discount physician or therapist bias, because the 5.07 Semmes-Weinstein monofilament, although objective, is only a patient-blinded test. These studies were initiated in February 2002, approximately 4 months after Medicare Decision Memorandum CAG-00059[6] was issued and all healthcare providers had been made aware of its implications for their patients by the suppliers and relevant professional associations. In addition, all of the patients knew that they were receiving active treatment. However, it is unlikely that the more than 300 evaluators systematically misinterpreted the sensitivity to the 5.07 Semmes-Weinstein monofilament before and after MIRE treatment.

The 5.07 Semmes-Weinstein monofilament is the most widely used testing method to clinically measure the existence of loss of protective sensation resulting from diabetes mellitus and to implement strategies to prevent foot ulceration and amputation. Mayfield and Sugarman[19] reported sensitivity of 85% to 100% and specificity of 34% to 100% depending on the number of sites tested and the testing method. In addition, Semmes-Weinstein monofilament testing has been reported to correlate with abnormal nerve conduction velocity testing, particularly as the extent of nerve impairment progresses.[20] However, the accuracy of this test depends on the method of testing and the achievement of maximal response from an alert and cooperative patient.[19] To maximize the validity of the test results, those performing Semmes-Weinstein monofilament testing were given case report forms adapted from "Feet Can Last a Lifetime,"[15] which recommends measuring five sites on the plantar aspect of the foot. In addition, these individuals were reminded to use the testing protocol contained in that publication, which is a two-alternative, forced-choice testing method that has been reported to minimize

patient bias.[16] Furthermore, this technique includes random testing sites on the feet and the avoidance of heavily callused and active wound sites.

Bias on the part of the evaluators should have been further minimized because none of the results were obtained with the goal of publishing the outcomes, which on analysis are consistent with recent published reports, one of which included randomization and double blinding.[11-13] Last, no multivariate analysis of these data was possible because this was a postmarket analysis of the efficacy of MIRE treatment. Because there are no known treatments for diabetic peripheral neuropathy in particular or for peripheral neuropathy in general, we cannot envision other variables that might have affected these outcomes.

Conclusion

Treatment with MIRE was associated with improved foot sensation to the 5.07 Semmes-Weinstein monofilament in a cohort of 1,047 patients initially diagnosed as having peripheral neuropathy. The extent of this improvement was substantial, even in patients with advanced loss of protective sensation. Because loss of protective sensation has been reported to be a major risk factor for diabetic foot wounds, an improvement in foot sensitivity obtained through the use of MIRE may also be associated with a reduced incidence of diabetic foot wounds and its sequelae, such as amputations.

Acknowledgment. More than 300 physicians and therapists who first documented peripheral neuropathy in their patients and then noted the improved sensation after treatment with MIRE. The detailed medical records supported their findings. Also, the staff of the two suppliers who worked with us to access their de-identified database and removed applicable patient identifiers from the records prior to our data review and analysis, and Amy Spirides, MBA, for assistance with the statistics and chart.

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Reversal of diabetic peripheral neuropathy with phototherapy (MIRE™) decreases falls and the fear of falling and improves activities of daily living in seniors

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Abstract

Objective: to determine whether restoration of sensation, impaired due to diabetic peripheral neuropathy (DPN), would reduce the number of falls and the fear of falling and improve activities of daily living (ADL) in a Medicare-aged population.
Design: retrospective cohort study of patients with documented, monochromatic near-infrared phototherapy (MIRE™)-mediated, symptomatic reversal of DPN.
Setting: responses to a health status questionnaire following symptomatic reversal of DPN.
Patients: 252 patients (mean age 76 years) provided health information following symptomatic reversal of diabetic neuropathy (mean duration 8.6 months).
Main results: incidence of falls and fear of falling decreased within 1 month after reversal of peripheral neuropathy and remained low after 1 year. Likewise, improved ADL were evident soon after reversal of peripheral neuropathy and showed further improvement after 1 year. Overall, reversal of peripheral neuropathy in a clinician's office and subsequent use of MIRE™ at home was associated with a 78% reduction in falls, a 79% decrease in balance-related fear of falling and a 72% increase in ADL ($P<0.0002$ for all results).
Conclusions: reversal of peripheral neuropathy is associated with an immediate reduction in the absolute number of falls, a reduced fear of falling and improved ADL. These results suggest that symptomatic reversal of diabetic neuropathy will have a substantial favourable, long-term socioeconomic impact on patients with DPN and the Medicare system, and improve the quality of life for elderly patients with diabetes and peripheral neuropathy.

Keywords: *diabetic peripheral neuropathy, MIRE™, falls, fear of falling, activities of daily living, Anodyne® therapy system, elderly*

Introduction

Diabetes affects more than 15% of the US population over 65 years of age [1]. The direct cost of diabetes exceeds $91 billion, with more than 51% of this being spent on those over 65 years of age [2]. One complication of diabetes is diabetic peripheral neuropathy (DPN), characterised by diminished sensation, with or without pain, in the lower extremities. DPN affects 30–100% of all long-term diabetic patients depending upon the clinical assessment(s) used to document DPN. DPN is acknowledged as a very significant risk factor for development of diabetic foot ulcers [3] and a major reason for the poor healing rates of these ulcers [4]. Additionally, DPN contributes to gait and balance problems, falls and the fear of falling [5–7]. More specifically, DPN is accompanied by postural instability, loss of available ankle strength, diminished proprioceptive thresholds both in foot and ankle inversion/eversion and in plantar flexion/dorsiflexion [8]. These complications result in a significant risk factor for falls in patients with DPN compared to diabetics who do not yet have DPN [9].

The risk of falls invariably increases with age and comorbidities [10, 11]. More than 30% of people over 65 years of age will fall one or more times per year [12] and the economic cost of falls exceeded $20 billion in 1994 [13]. Falls are the fourth leading cause of death in men between 65 and 85 years of age and the leading cause of death among both men and women over 85 [14]. Those with DPN have more impairments in balance [5, 7, 15, 16], an increased risk for falls [5], a higher absolute incidence of falls possibly exceeding 50% [5] and falls that result in injury than the elderly population in general [10]. The increased fear of falling in those with DPN decreases activities

of daily living (ADL) and increases the risk for subsequent falls in people over 65 years of age [17, 18].

While reversal of DPN would theoretically reduce the number of falls and/or fear of falling, and improve ADL, currently there are no pharmacologic treatments for DPN and the progressive health risks it presents that would allow testing of this hypothesis. Certain selected patients with DPN have responded well to a surgical procedure that releases the compression of nerves in the feet, but not all patients are candidates for surgery [19]. Several recent studies [20–26] have reported at least temporary symptomatic reversal of DPN during treatment with monochromatic near-infrared photoenergy, known as MIRE™, which was delivered non-invasively by the Anodyne® Therapy System (ATS; Anodyne Therapy LLC, Tampa, FL 33626, USA), an FDA cleared medical device [27]. To date no studies have examined whether these effects are sustained after treatment with MIRE™ in a clinic is stopped but is continued over time at home. The present study assessed the actual number of falls, the fear of falling, and ADL in 252 patients from 1 to 15 months after they had stopped receiving MIRE™ treatments in a clinic where improved sensation had been documented.

Methods

We administered a health status questionnaire to certain patients with DPN identified from the insurance billing records of two durable medical equipment (DME) suppliers, who had provided to patients an ATS, an item of DME delivering MIRE™, for use at home. The DME providers examined their database for all insurance claims filed under HCPCS code E0221with dates of service between January 2002 and 31 March 2003 and extracted all claims in which the prescribing diagnosis was diabetic neuropathy using ICD-9 codes 250.61 or 250.62 as indicative of either type 1 or type 2 diabetes, and ICD-9 code 357.2 as indicative of peripheral neuropathy. Next, the medical records, including written physician orders and treatment notes, for each patient were reviewed to confirm the initial diagnosis of DPN with loss of protective sensation (LOPS) and the subsequent improvement in sensation after treatment with MIRE™. The diagnosis was based on a history and physical documentation by the attending physicians. While many tests were described in the underlying clinical records, the presence of sensory impairment prior to the treatment and improvement after treatment were documented using the SWM 5.07 monofilament test. The SWM is recommended by the National Institutes of Health in Feet Can Last a Lifetime [28] and is the test of choice to determine LOPS by Medicare [29]. If a patient cannot feel the monofilament on two of five tested sites on either foot using a forced-choice test, they are considered by Medicare to have DPN.

Improvement in DPN symptoms following treatment with MIRE™ by physicians formed the basis for acquiring an ATS for use at home. This medical record review also indicated that neuropathic pain had decreased in many of these patients after instituting MIRE™ treatments. Lastly, claims for all patients younger than 64 years were excluded to permit analysis of only the Medicare-aged population.

Using these selection criteria, the medical records demonstrated clinical documentation for reversal of DPN after use of MIRE™ in 369 patients. The patients were contacted by the DME suppliers to ascertain if they would be willing to participate in a telephone questionnaire. The questionnaire elicited information regarding fall history, fear of falling and ADL, prior to and after reversal of DPN and LOPS.

The following questions with respect to the period prior to receiving successful treatment with the ATS (reversal of DPN and LOPS) were:

(i) Did you feel off balance to the extent that you feared falling when you walked?

(ii) How many times did you fall during the 12 months prior to the time you started using Anodyne®? (None, 1 time or 2 or more times).

Questions related to the period after reversal of DPN and LOPS were:

(iii) Do you feel that your balance has improved and that you now have less fear of falling when you walk?

(iv) How many times did you fall since the time you started using Anodyne®? (None, 1 time or 2 or more times).

(v) Compared to what you were able to do most days before using Anodyne®, how would you compare what you are now able to do most days? (A lot less, A little less, About the same, A little more, A lot more).

Evidence of balance impairment and fear of falling associated with DPN was determined based on the patient's response to question (i) and improvement after reversal of DPN was determined by response to question (iii). Falls associated with DPN were determined by the answer to question (ii) and a change in fall incidence after reversal of DPN was determined based on the answer to question (iv). Changes in ADL were determined based on the response to question (v). Lastly, the health status questionnaire included a comment section where the patients could relate, at their discretion, any additional information.

Eight interviewers attempted contact with the 369 successfully treated patients. Contact was attempted at least three times to maximise the number of responses. A total of 252 out of 369 (68%) community-dwelling patients completed the questionnaire, providing us with data covering a period of ATS usage ranging from 1 to 15 months (average 9 months) after reversal of DPN. For purpose of analysis, we then stratified these patients into five groups: those who had used ATS for (i) 1–3 months, (ii) 3–6 months, (iii) 6–9 months, (iv) 9–12 months and (v) 12 or more months after reversal of DPN.

Statistics

Data were analysed by paired two-tailed *t*-test with a null hypothesis that reversal of DPN would have no effect on (i) the number of falls, (ii) balance improvement and fear of falling or (iii) ADL irrespective of the numbers of months of ATS use. The two-tailed *t*-test was employed because we made no assumption (a priori) as to the direction changes would occur, if at all. Significance was accepted when $P<0.05$. The statistical package StatView™, from Abacus

Concepts, Inc., Berkley, CA, was used. Values are expressed as mean (SD).

Results

The mean age of the 252 patients (138 males) was 75.4 (6.6) years (range 64–101). Sixty-three patients were 80 years or older and 41 were between 64 and 69. Utilisation of the ATS at home by these community dwellers averaged 8.6 (4.2) months (range 1–15 months). Table 1 describes demographics for the 252 diabetic patients and Table 2 describes the outcomes in each of five groups (1–3 months, 3–6 months, 6–9 months, 9–12 months and 12+ months of ATS use). The following results were obtained.

Number of falls

During the year prior to clinical reversal of DPN, 73 of the patients (29%) had fallen and 53 of these (73%) experienced two or more falls. In the period after reversal of DPN, 57/73 (78%) patients reported a decrease in the number of falls ($P<0.0001$), either from one to none or from two or more to one or no falls. As anticipated, patients in the 1- to 3-month group showed the highest reduction in falls (100%); however those in the 12-month or longer group showed the second highest reduction in the number of falls (83%, Table 2). All groups reported a reduction in fall incidence. During the approximately 9 months after reversal of DPN, only 33/252 patients (13%) experienced a fall compared to 73/252 (29%) who had fallen during the year prior to reversal of DPN. This represents a 55% reduction in the number of patients reporting a fall after reversal of DPN ($P<0.0001$).

Fear of falling

Prior to reversal of DPN, 166 out of 252 patients (66%) reported being off balance to the extent that they feared falling when they walked. After reversal of DPN, 35 of these patients continued to report fear of falling when they walked whereas 131 of these patients (79%, $P<0.0001$) reported substantial improvement in balance and a reduced fear of falling. Patients in all groups reported a reduced fear of falling ranging from a high of 92% in the 1- to 3-month group to a low of 65% in the 12-month and greater group ($P<0.0001$ in all groups, Table 2).

Activities of daily living

After reversal of DPN, 182 out of 252 patients (72%, $P<0.0001$) reported they were able to at least 'do a little more most days' than they were when they suffered from DPN and 80 of these (44%, $P<0.0001$) reported being able to 'do a lot more most days' compared with when they suffered from DPN. Improvement in daily living was reported by patients in all groups with a high of 77% in the 6- to 9-month group and a low of 67% in the 3- to 6-month group ($P<0.0001$ for all groups). The percentage of patients able to do a lot more after reversal of DPN was highest in the 6- to 9-month group (59%) and was lowest in the 12-month and longer group (31%, $P<0.0001$ for all groups, Table 2).

Neuropathic pain

The medical records indicated that 220 out of 252 patients (87%, $P<0.0001$) obtained substantial reduction in neuropathic pain in addition to improved foot sensation after reversal of DPN. Reduction in pain was reported in all groups with a high of 95% in the 1- to 3-month group and a low of 76% in the 3- to 6-month group ($P<0.0001$ for all groups, Table 2).

Discussion

Prior studies have shown DPN to be a major contributory factor to balance impairment and falls in diabetic patients [10]. Our analysis confirmed the existence of both balance impairment and fall history in the diabetic patients we surveyed. Importantly, the present data demonstrate that reversal of DPN, at least with MIRE™, may substantially

Table 1. Patient demographics

Patients contacted by phone (*n*)	369	
Patients responding to questionnaire[a] (*n*)	252	
Percentage of patients responding	68	
Males	138	
Females	114	
Age (years)[b]	75.4 (6.6)	
Average months with reversal of DPN	8.6 (4.2)	
Patients who fell before reversal of DPN	73	
Patients with two or more falls	53/73	<0.0001
Patients with fewer falls after MIRE™	57/73	<0.0001
Total falls after MIRE™	13/252	<0.0001
Feared falling before reversal of DPN	166	
Feared falling after reversal of DPN	35	<0.0001
No longer feared falling after MIRE™	131	<0.0001
ADL after reversal of DPN		
Able to do a little more	182/252	<0.0001
Able to do a lot more	80/182	<0.0001
Pain reduced after reversal of DPN	220/252	<0.0001

n, number of patients; DPN, diabetic peripheral neuropathy; MIRE™, monochromatic near-infrared photoenergy; ADL, activities of daily living.
[a]Patients over 64 years and had used ATS for at least 1 month; [b]Means (SD).

Table 2. Outcomes in five groups of diabetic patients after MIRE™

	Months of home access to MIRE™ after reversal of DPN				
	1–3	3–6	6–9	9–12	12+
Number of patients	36	33	22	94	67
Months after MIRE™	1.2 (0.14)	4.0 (0.8)	6.7 (0.9)	10.1 (0.7)	13.3 (1.0)
Age	75 [8]	74 [7]	76 [6]	76 [7]	76 [6]
Male/female	23/14	20/13	9/13	44/50	40/27
Number who fell (B)	12	9	8	20	24
Two or more falls (B)	7/12	6/9	6/8	18/20	16/24
Number who fell (A)	2*	4**	7	9*	11*
Decrease in falls (%)	83	60	13	50	54
Reduced falls (%)	100	78	50	70	83
Fear (B)	26/36	21/33	16/22	57/94	46/67
Fear (A)	2/36*	6/33	4/22	7/57	16/67
Reduced fear (%)	92	70	75	88	65
ADL increase	25/36*	22/33*	17/22*	69/94*	49/94*
ADL % (A)	69	67	77	73	73
Some increase (ADL)	16/25	14/22	7/17	31/69	34/49
Increase in ADL (%)	64	64	41	45	69
A lot more (ADL)	9/25	8/22	10/17	38/69	15/49
Increase in ADL (%)	36	36	59	55	31
Pain reduction (%)	94*	80*	91*	85*	91*

DPN, diabetic peripheral neuropathy; B, before MIRE™; A, after MIRE™; Fear, fear of falling and/or balance problems; ADL increase, those with increased activities of daily living (ADL) after MIRE™; Some increase, able to do somewhat more after reversal of DPN; A lot more, able to do much more after reversal of DPN; Pain reduction, percentage of patients who reported a reduced pain level (visual analogue scale) after reversal of DPN.
*$P<0.0001$; **$P<0.01$.

(i) reduce the incidence of falls, (ii) reduce fear of falling and (iii) improve ADL in diabetic patients over 64 years.

A recent report [30] noted that the incidence of at least one fall in patients with DPN was 29%, the incidence of multiple falls was 21%, and most patients with DPN (66%) feared falling. The present data indicate that reversal of DPN is associated with dramatic reductions in both the frequency of reported falls (78%) and in the fear of falling (79%). Additionally, significant reductions in the frequency of reported falls and the fear of falling were apparent when patients had access to the ATS at home for 1–3 months after reversal of DPN; these reductions in falls remained evident up to 15 months after reversal of DPN. Although we know of no studies that report a reduction in falls, specifically in patients with DPN, it has been reported that a combination of group exercise, visual improvement strategies and home hazard reduction results in an estimated 14% reduction the annual fall rate [31]. Clearly, the 78% reduction in the number of falls in diabetic patients using the ATS, as documented in the present study, confirms earlier observations [23] and suggests the ATS may be an additional therapeutic intervention that may be of significant benefit in preventing falls among patients with DPN.

The prevalence of peripheral neuropathy of any aetiology in those aged 60–74 years (a somewhat younger cadre of seniors than those in the present study) has been estimated at 22% and it was suggested that this was likely to increase with age [5]. Moreover, the incidence of falls in this younger group was reported to be 50% [5]. Accordingly, the present data indicate that it may be possible to reduce this incidence of falls to approximately 10% in Medicare-aged seniors with peripheral neuropathy due to causes other than diabetes.

Richardson *et al.* [16] have reported that while exercise may reduce certain risk factors associated with falls in those with peripheral neuropathy, exercise itself has no significant effect in reducing the fear of falling. The data presented in this study suggest that restoring sensation may significantly reduce the fear of falling because 79% of the patients reported a diminished fear of falling. Because the fear of falling is an independent risk factor for a subsequent fall(s) within 20 months after a first fall [17, 18], our data suggest that it may be possible to reduce this risk factor.

The reduction in the fear of falling, and the decrease in neuropathic pain reported by 87% of all respondents, may have contributed to the 72% increase in activity level. One hundred and eighty-two patients reported an increased activity level and 80 (44%) reported being able to do much more on a daily basis after reversal of DPN. Increased activity among seniors, with or without diabetes, provides a wide range of net health benefits, economically, emotionally and physically. The present results suggest that reversing DPN and concomitantly reducing its associated pain may be expected to increase daily activity levels in those over 65 years of age, including those over 80 years of age, who showed similar improvements as the study group as a whole.

We acknowledge certain limitations in our study. For example, although reversal of DPN and decreases in neuropathic pain were objectively substantiated through analysis of written physician orders and supporting treatment notes, we relied solely on patient response to determine the incidence of falls, fear of falling and changes in ADL after reversal of DPN. Similar methodology is often used in studies related to falls [5, 31]. However, it is possible that

patients' recall may be inaccurate or incomplete, or that unintentional interviewer bias during telephone questioning may have occurred. The data presented in this article are further stratified by the duration between the initial treatment effect and the date the patient responded to the questionnaire. Intuitively, those responses that were offered very soon after the treatment would seem to be most reliable. However, those responses that were offered up to a year after treatment are not necessarily unreliable, particularly in relation to falls, which are major health-threatening events that are more likely to be remembered than more trivial matters. Despite these limitations, the answers of those interviewed 1–3 months after reversal of DPN were quite similar to those interviewed at 12–15 months. Because the data in each subgroup are remarkably similar, it would appear that the results, as a whole, are reliable. We also attempted to minimise interviewer bias by utilising eight separate interviewers in this study.

Certainly, use of randomised control groups is the ideal study design. However, when one is assessing potentially very dangerous health-care events such as falls in the elderly, it is very difficult to justify withholding available treatments or risk reduction strategies. Under these circumstances an observational approach using the patient as their own control seemed an appropriate analysis for these patients, subject of course to the limitations that are inherent in such designs. In so doing, these patients described meaningful patient-centred quality of life changes over time in response to active treatment and although glycaemic control is well known to delay microvascular complications of diabetes it will not reverse them.

Finally, the discretionary comments offered by patients at the conclusion of the interviews substantiated overall improvement in their condition. No multivariate analysis of known co-morbid risks for falls was undertaken and it is possible that some of the reported fall reductions resulted from other variables. However, recognised co-morbidities and medications associated with falls have been found not to be predictive of falls in patients with peripheral neuropathy [5]. We do agree with the widely held belief that the causes of falls are multifactoral and the best approach is a holistic one designed to reduce all applicable risk factors for the patient. Clearly, the literature recognises that peripheral neuropathy is one substantial independent risk factor for falls. In the context of this article, we investigated whether removing this one risk factor in a cohort of community-dwelling patients, who had previously exhibited this risk factor, would decrease the number of falls they reported over time. The data gathered support this salutary effect.

Conclusion

When diabetic patients have continuing access to MIRE™ in their homes following restoration of protective sensation, there is a significant reduction in the incidence of falls and fear of falling that is recognised as being closely associated with DPN. The increased activity in elderly diabetic patients may be related to improved balance and reduced pain which, based on these data, can occur with use of MIRE™ in a clinic. Reversal of DPN may have major socioeconomic benefits including the potential for significant cost savings to the Medicare system and an improved quality of life for diabetic patients.

Key points

- Restoration of sensation in the lower extremity of diabetic patients over the age of 64 reduces their fear of falling and the number of falls generally associated with loss of sensation.
- In addition, pain is diminished and quality of life is markedly improved.

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Effectiveness of Monochromatic Infrared Photo Energy and Physical Therapy for Peripheral Neuropathy: Changes in Sensation, Pain, and Balance– A Preliminary, Multi-Center Study

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ABSTRACT. *Objective:* To evaluate the effect of monochromatic infrared photo energy (MIRE™) combined with physical therapy in reducing pain, improving sensation, and increasing balance in patients with peripheral neuropathy.

Methods: Pain [VAS scale], diminished foot sensation [Semmes Weinstein Monofilament 5.07], and balance deficits [Tinetti Assessment Tool] of 272 patients, average age 69 years, were documented before and after receiving treatments at eight physical therapy clinics.

Results: Neuropathic pain, diminished foot sensation, and balance impairments at baseline were present in 93% of patients. After an average of 18 treatments, neuropathic pain decreased by 38%, lower extremity sensory impairment improved by 77%, and balance deficits decreased by 73% [$P \leq 0.006$ for all results].

Conclusions: Compared with the literature, preliminary findings suggest that MIRE™ plus manual physical therapy improves pain, balance, and sensation symptoms in patients with peripheral neuropathy, at least temporarily.

KEYWORDS. Tinetti Assessment Tool, Anodyne® Therapy System, MIRE™, microcirculation, peripheral neuropathy, falls, balance impairments, neuropathic pain

INTRODUCTION

Peripheral neuropathy [PN] defines a wide variety of symptoms due to autonomic and sensory nerve dysfunction and is estimated to affect more than 22% of all adults aged 60 to 74 (Richardson, 2002) and as many as 20 million people of all ages (Jack Miller Center for Peripheral Neuropathy, 2005). PN manifests itself as subjective paresthesias, including pain and numbness, and may result in loss of light touch and vibratory sensation as measured by the Semmes Weinstein Monofilament [SWM] and Vibratory Perception Threshold [VPT] tests, respectively.

PN results from a wide variety of causes, including traumatic injuries, chronic illness, the use of certain medications, and alcohol abuse. In addition, approximately 50% of people with diabetes mellitus have PN that is particularly debilitating and costly (Gordois et al., 2003). PN appears to be an important contributor to lower extremity ulceration [LEU] and non-traumatic amputations (Gibbons et al., 1995) and has

been reported to be the major cause of hospitalizations among people with diabetes. The annual cost of diabetic peripheral neuropathy to the US healthcare system has been growing and is estimated to be at least $37 billion (Vinik, 2002; Gordois et al., 2003). Finally, PN significantly contributes to gait and balance dysfunction, fear of falling, and falls (Richardson, 2002) and its severity can be quantified by postural instability, loss of adequate ankle strength, and diminished proprioceptive thresholds (Simoneau et al., 1994; Wallace et al., 2002; Hausdorff et al., 2001). In fact, the risk of injury from falls in elderly patients exhibiting neuropathy may exceed 50%, far more than that of the elderly population as a whole (Blaum et al., 2003).

It is well known that the substantial sensory loss associated with PN makes it very difficult for physical therapists to improve balance and reduce fall risk using conventional strategies that have proven successful in elderly patients without neuropathy. Consequently, patients with PN are taught compensatory strategies including the use of canes and walkers, and are encouraged to identify and minimize environmental hazards. However, this approach has only been able to achieve a 14-22% increase in functional activities (Richardson et al., 2001).

Although currently there is no universally effective treatment for the paresthesias associated with PN, particularly that due to chronic illnesses such as diabetes, four recent studies have demonstrated that use of monochromatic infrared photo energy therapy [MIRE™] may symptomatically improve the sensory nerve dysfunction and pain associated with diabetic or other causes of PN (Kochman et al., 2002; Leonard et al., 2004; Prendergast et al., 2004; DeLellis et al., 2005). Recently a small study in 38 patients was conducted in a hospital physical therapy geriatric inpatient department and there was a high risk of falls as well as a documented fall history in these patients with neuropathy (Kochman, 2004). After combined use of MIRE™ and physical therapy, sensation returned to the feet and lower extremities and the balance and gait abnormalities assessed by the Tinetti Screening Tool (Tinetti, 1986) improved significantly. The present study sought to determine if physical therapists in a variety of settings [hospital, out patient, and long-term care] would achieve similar results. The present report summarizes the outcomes in 272 patients with PN, following treatment with MIRE™ and adjunctive manual physical therapy, at eight physical therapy clinics in five different states.

MATERIALS AND METHODS

Patients

This summary of the clinical outcomes following combined MIRE™ and physical therapy interventions was gathered from the records of patients treated at eight physical therapy clinics, including two hospitals, two nursing homes, and four outpatient clinics. All therapists were degreed but, as might be expected, the patients in the diverse clinics (e.g., nursing homes vs. outpatient clinics) were quite different with respect to the reasons they were in a specific facility. However, all patients had PN. MIRE™ was delivered following the protocol described by Kochman (2004) for approximately 30-40 min and then several physical therapy interventions were used depending on the particular patient's needs.

As noted above, physical therapy interventions alone in neuropathy patients are unable make a significant impact on quality of life (Richardson et al., 2001). For this reason, a non-experimental, retrospective design was used in the present analysis. Furthermore, there is a strong interest by many in the health care industry in actual clinical outcomes that occur in the real world of daily practice by therapists, rather than simply in controlled, clinical studies at a university or medical center. Each facility had been using MIRE™ for at least one year and the therapists were well versed in its application. Because outpatients and inpatients have different needs and comorbid factors, we sought to determine if outcomes from the combined use of MIRE™ and physical therapy in PN would differ in different facilities. Each facility examined the records of consecutive patients with a diagnosis of PN, for whom data had been collected relative to pain, light touch, and balance deficits, before and after MIRE™ and adjunctive active physical therapy treatments. Data for a total of 272 consecutive patients form the basis of this report. Patient identifiers were removed by the staff at each facility prior to this analysis.

Measurements

Neuropathic pain was measured using the 11-point Visual Analog Scale [VAS], with a pain score of 10 being maximum pain and zero being no pain. Assessment of light touch sensation was documented objectively using the standard Semmes Weinstein Monofilament [SWM] 5.07 test. Patients were asked to respond with "Now" when they were

able to sense randomly applied pressure by this monofilament at five sites on the plantar aspect of each foot. To maximize the validity of the test results, those performing the SWM tests were given case report forms adapted from Feet Can Last a Lifetime (National Diabetes Education Program, 2005). This document recommends measuring five sites on the plantar surface of the foot and use of a "forced two choice testing method," which minimizes patient bias (Sekuler et al., 1973). Finally, the technique also involves testing random sites on the feet and avoids heavily callused or active wound sites.

Balance and gait abnormalities as well as relative fall risk were assessed using the Tinetti Assessment Tool (Tinetti, 1986). This is a widely recognized objective instrument for determining balance and gait deficiencies and assessing the risk of future falls (Tinetti et al., 1998; Tinetti & Speechley, 1989). Higher Tinetti scores (maximum 28) correlate inversely with risk of falls. Individuals with Tinetti scores under 19 are considered to be at the highest risk for falls, those with scores between 19 and 23 are considered to have a moderate risk of falling, and those with scores 24 and above are considered to be at low risk for falls.

Intervention

MIRE™ was delivered using the Anodyne® Therapy System [ATS]. The ATS is a super luminous diode-based monochromatic photon therapy modality (wavelength 890 nm) that was cleared by the FDA in 1994 for temporarily increasing local circulation and reducing pain (Burke, 2003). The ATS device was also the modality used in studies showing improved sensation and/or balance and reduced pain in patients with PN (Kochman et al., 2002; Leonard et al., 2004; Prendergast et al., 2004; DeLellis et al., 2005). The ATS device had been purchased by, and was in extensive use at, each study site for rehabilitation care plans covering a wide variety of pain and/or circulatory conditions including PN. These sites are among the over 3300 sites in the US using ATS for a variety of physical therapy challenges. The treatment protocol consisted of 30 to 60 minute treatments with the ATS, using four separate diode-containing therapy pads per limb, one on the medial and one on the lateral side of each lower extremity, and two on the plantar surface of the foot followed then by manual physical therapy depending on the assessed needs of the individual patient. Manual therapies included static and dynamic balance retraining, neuromuscular reeducation, strength training, and stretching of the Achilles tendon and hip flexors. Treatments were rendered three times per week for a minimum of six treatments [mean $\pm$ SD, 18 $\pm$ 10.2

treatments]. The number of treatments continued until the patient attained functional goals or until their progress plateaued at near normal levels for reduced pain, reduced fall risk, and/or improved sensation.

As part of the customary therapy protocols, clinical notes were maintained that described progress, on an interim basis, toward these goals. Additionally, at the conclusion of the treatment protocols, post-treatment data were evaluated to determine the degree of pain, the number of sites on the foot that remained insensitive to the SMW 5.07, and any residual balance deficits.

Data Analysis

Data were analyzed by paired 2-tailed t-test with a null hypothesis that the treatment protocol would have no effect on three endpoints: pain levels, foot sensation to the SWM 5.07, or balance. Significance was accepted when $P < 0.05$. All values are expressed as mean ± one standard deviation.

Data were first analyzed for all patients with PN and then separately for those with either diabetic peripheral neuropathy [DPN] or peripheral neuropathy from other causes [PNO]. Patients in both subgroups [DPN and PNO] may have exhibited impairment in one of the evaluated measures but not necessarily in all of them. Therefore, changes in each individual functional limitation were also evaluated.

Pain was analyzed only in those patients who exhibited a VAS score of four or more indicating moderate to severe pain that would be expected to result in some level of functional limitation. A total of 261 patients [96%] had pain VAS scores of four or greater prior to treatment (Acute Pain Management Guideline Panel, 1992). Changes in foot sensitivity to the SWM 5.07 were analyzed only among those patients who exhibited insensitivity at two or more sites on each foot (four or more sites on both feet). This allowed us to evaluate the possible efficacy of the combined use of both MIRE and physical therapy in those patients who had severe loss of protective sensation [LOPS], which is considered a localized illness of the foot (Centers for Medicare and Medicaid Services, 2001). A total of 257 patients [94%] had LOPS before treatment based on these CMS guidelines. Balance deficits as measured with the Tinetti Instrument, were analyzed only among those patients who exhibited a pretreatment Tinetti score of 23 or less. A score of 23 was selected as an indication of a balance deficit because this score is 1 point below the breakpoint between “low fall risk” and “moderate fall risk” under the

Tinetti scoring system. A total of 250 patients [92%] had Tinetti scores under 24 before treatment.

RESULTS

Patient Demographics

The mean age of the patients was 69 ± 12.3 years (mean ± 1 SD; range: 33 to 100). Among the patients, 135 (50%) were male and 137 (50%) were female. In the cohort, 128 patients (47%) had a primary diagnosis of DPN and 144 (53%) exhibited PNO. The clinical deficits in pain, foot sensation, and balance in the entire 272 patient cohort, the DPN subgroup, and the PNO subgroup are also shown in Table 1. There were no differences in the two groups with respect to the severity of sensory loss, pain, or balance deficits prior to initiating this therapy

TABLE 1. Patient Demographics (Pre-Treatment)

	PNO	DPN	Total
Patients	144 53%	128 47%	272
Male	66 46%	69 54%	135 50%
Female	78 54%	59 46%	137 50%
Age[a]	70 ± 12.1	68 ± 12.5	69 ± 12.3
Number of treatments	19 ± 11.6	17 ± 8.2	18 ± 10.2
Treatment time (in minutes)	31 ± 4.1	38 ± 12	34.2 ± 9.4
No. patients with LOPS (4 or more sites insensate out of 10)	140 97%	117 91%	257 94%
Number sites insensate (10 max)	7.2 ± 1.8	7.5 ± 1.9	7.3 ± 1.9
No. patients VAS scale > 3	138 96%	118 92%	256 94%
VAS before treatment	7.8 ± 1.2	7.7 ± 1.1	7.7 ± 1.2
Discomforting pain (VAS 4-6)	17 12%	14 11%	31 11%
Distressing pain (VAS 6.5-8)	100 69%	89 70%	189 69%
Horrible to excruciating pain (VAS 8.5-10)	22 15%	19 15%	41 15%
No. patients with balance impairment (Tinetti < 24)	138 96%	112 88%	250 92%
No. patients with moderate fall risk (Tinetti 19-23)	12 8%	18 14%	30 11%
No. patients with high fall risk (Tinetti 0-18)	126 88%	94 73%	220 81%

[a]Mean ± SD; PNO = Peripheral neuropathy other causes; DPN = Diabetic peripheral neuropathy; LOPS = Loss of protective sensation; VAS = Visual analogue scale.

protocol. Both groups responded to interventions in a similar manner. The time of treatment was similar in both groups [31 min in the PNO group and 38 min in the DPN group, P = NS].

Although every patient had to exhibit at least one functional limitation associated with their PN to qualify for a physical therapy plan of care, the prevalence of all three functional limitations was present in 89% of this patient cohort. It is clear that patients with PN are likely to have multiple functional limitations associated with PN. Interestingly, the functional impairments in these subgroups were substantially similar.

The pain intensity level at baseline of those with PNO was almost identical to that in patients with DPN [VAS = 7.8 for PNO, 7.2 for DPN]. The average number of sites insensitive to the SWM 5.07 was also virtually the same [7.2 PNO, 7.5 DPN]. The largest difference (although still relatively small) was the initial measure of balance deficit. The PNO group initially tested at 12.9 on the Tinetti Instrument and the DPN group tested at 14.4. However, both groups were well below the value of 19 and were clearly in the "high fall risk" category.

Changes in Neuropathic Pain Based on VAS Scale

Both the DPN and PNO groups obtained significant reductions in neuropathic pain based on the VAS scores. The mean improvement in VAS was 2.9 ± 2.0 in the PNO group [37%] and 3.0 ± 2.5 in the DPN group [39%], representing similar percentage reductions in pain level (see Table 2).

The severity of pain within each subgroup was also examined. The DPN group exhibited more than a 50% reduction in pain at both the discomforting pain level [VAS 4.0-6.0] and the horrible pain level [VAS 8.5-10.0] and a 35% reduction when pain was distressing [VAS 6.5-8.0] prior to treatment. The PNO subgroup only obtained a 17% reduction in their pain levels in the distressing level with progressively greater percentage pain reductions when the pain intensity was more severe at baseline. Although decreased pain was observed regardless of its initial severity, the greatest reduction in each subgroup and in the 272 patient cohort overall was noted in those patients who had horrible pain at baseline evaluation.

Figure 1 documents the VAS pain scores for all patients before and after treatment. Prior to treatment most of the patients experienced a pain level of 8 or more. The combination of MIRE™ and physical therapy treatment resulted in a significant decrease in VAS scores [P < 0.0001].

TABLE 2. Neuropathic Pain Pre- and Post-Treatment

	PNO (n = 139)	DPN (n = 118)	ALL (n = 257)
VAS pre-treatment	7.8 ± 1.2	7.7 ± 1.1	7.7 ± 1.2
VAS post-treatment	4.9[a] ± 1.8	4.7[a] ± 2.5	4.8[a] ± 2.2
VAS decreases	2.9 ± 2.0	3.0 ± 2.5	2.9 ± 2.2
% Pain reduction	37%	39%	38%
Horrible to excruciating pain (VAS 8.5-10)	PNO (n = 22)	DPN (n = 15)	ALL (n = 37)
VAS pre-treatment	9.3 ± 0.5	9.5 ± 0.5	9.4 ± 0.5
VAS post-treatment	5.3[a] ± 1.9	4.1 ± 3.6	4.8[a] ± 2.7
VAS decreases	4.0 ± 2.0	5.4 ± 3.8	4.6 ± 2.9
% Pain reduction	43%	57%	49%
Distressing pain (VAS 6.5-8)	PNO (n = 100)	DPN (n = 89)	ALL (n = 189)
VAS pre-treatment	7.9 ± 0.3	7.8 ± 0.5	7.8 ± 0.4
VAS post-treatment	5.0[a] ± 1.8	5.1[a] ± 2.0	5.0[a] ± 1.9
VAS decreases	2.9 ± 1.8	2.7 ± 2.0	2.8 ± 1.9
% Pain reduction	37%	35%	36%
Discomforting pain (VAS 4-6)	PNO (n = 17)	DPN (n = 14)	ALL (n = 31)
VAS pre-treatment	5.3 ± 0.8	5.4 ± 0.9	5.3 ± 0.9
VAS post-treatment	4.4[a] ± 1.9	2.5[b] ± 2.8	3.5[a] ± 2.5
VAS decreases	0.9 ± 2.0	2.9 ± 2.5	1.8 ± 2.4
% Pain reduction	17%	54%	34%

Values expressed as mean ± SD; [a]All post treatment measures are $P < 0.0001$ vs. Pre-treatment; [b]All post-treatment measures are $P \leq 0.006$ vs. pre-treatment.

Changes in Foot Insensitivity to the SWM 5.07

Both the DPN and PNO subgroups obtained substantial improvement in the mean number of sites sensitive to the SWM 5.07 indicating improved foot sensation [see Table 3]. The mean improvement was 5.4 ± 2.8 sites, a 72% improvement compared with baseline, in the DPN subgroup and 5.8 ± 2.6 sites, an 81% improvement compared with baseline, in the PNO subgroup [both $P < 0.0001$].

Importantly, at the conclusion of therapy, the patients with DPN had only 2.1 ± 2.9 sites [total for both feet] insensitive to the SWM 5.07. This degree of improvement indicated that most patients no longer exhibited LOPS as defined by CMS. The results were somewhat more impressive in the PNO group where the average number of sites insensitive to the SWM 5.07 was only 1.4 ± 2.1 [total for both feet] at the conclusion of

FIGURE 1. Pain before (gray bars) and after (solid bars) combined treatment with MIRE™ and physical therapy.

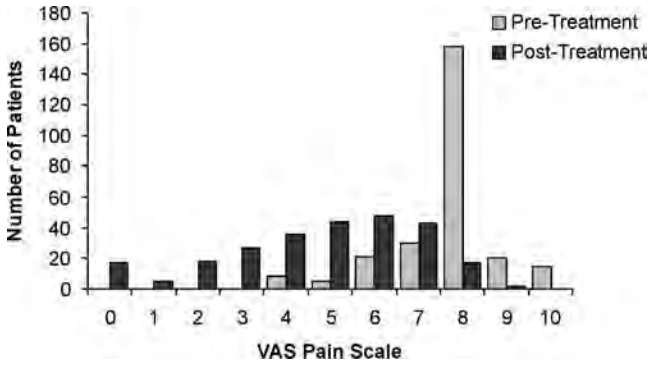


TABLE 3. Foot Sensitivity to the SWM 5.07 Pre- and Post-Treatment

	PNO (n = 140)	DPN (n = 117)	Total (n = 257)
Pre-treatment sites insensate (max 10 sites)	7.2[a] ± 1.8	7.5 ± 1.9	7.3 ± 1.9
Post-treatment sites insensate	1.4[b] ± 2.1	2.1[a] ± 2.9	1.7[a] ± 2.5
Mean decrease sites insensate	5.7[b] ± 2.6	5.4 ± 2.8	5.6 ± 2.7
% Improvement in foot sensation	81%	72%	77%

[a]Mean ± SD; [b]All post-treatment measures are P < 0.0001 vs. pre-treatment.

therapy. The absence of LOPS after therapy was a significant improvement [P < 0.0001] compared with baseline.

Figure 2 demonstrates the number of insensitive sites to the SWM 5.07 prior to and after treatment in 257 patients with LOPS as reflected by being insensitive to the SWM at four or more sites at baseline evaluation. The results clearly demonstrate that there was a significant decrease [P < 0.0001] in the number of insensate sites among the entire population.

Changes in Balance Impairment and Fall Risk Based on Tinetti Scores

Patients with either DPN or PNO demonstrated a substantial, improvement in their balance and a reduced fall risk after receiving treatment. The mean Tinetti score improvement (see Table 4) was 9.0 ± 3.8 points in the DPN subgroup and 10.5 ± 2.8 points in the PNO subgroup

FIGURE 2. Sensitivity (number of insensate sites on both feet) to the SWM 5.07 before (gray bars) and after (solid bars) treatments.

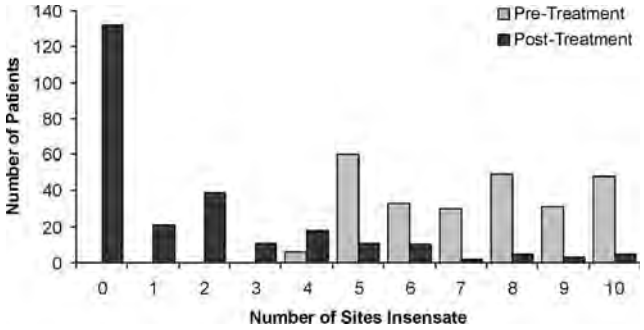


TABLE 4. Balance Impairments (Tinetti Scores) Pre- and Post-Treatment

Patients (with Tinetti < 24 at baseline)	PNO (n = 138)	DPN (n = 112)	ALL (n = 250)
Tinetti pre-treatment	12.9[a] ± 4.1	14.2 ± 4.1	13.5 ± 4.1
Tinetti post-treatment	23.4[b] ± 3.1	23.2[b] ± 3.2	23.3[b] ± 3.1
Mean increase	10.5 ± 2.8	9.0 ± 3.8	9.8 ± 3.4
% Improvement	81%	63%	73%
Moderate fall risk (19-23)	PNO (n = 12)	DPN (n = 18)	ALL (n = 30)
Tinetti pre-treatment	20.6 ± 0.9	20.9 ± 1.6	20.8 ± 1.3
Tinetti post-treatment	26.0[b] ± 1.9	24.8[b] ± 2.5	25.3[b] ± 2.3
Mean increase	5.4 ± 2.2	3.9 ± 3.0	4.5 ± 2.8
% Improvement	26%	19%	22%
High fall risk (0-18)	PNO (n = 126)	DPN (n = 94)	ALL (n = 220)
Tinetti pre-treatment	12.2 ± 3.4	13.0 ± 3.1	12.5 ± 3.3
Tinetti post-treatment	23.2[b] ± 3.1	22.9[b] ± 3.3	23.1[b] ± 3.2
Mean increase	11.0 ± 2.3	10.0 ± 3.2	10.5 ± 2.8
% Improvement	90%	76%	85%
	PNO	DPN	ALL
No. of patients with low fall risk after Tx	87	61	148
% Low fall risk after Tx	63%	54%	59%
No. of patients with moderate fall risk after Tx	38	41	79
% Moderate fall risk after Tx	28%	37%	32%
No. of patients with high fall risk after Tx	13	10	23
% of patients with high fall risk after Tx	9%	9%	9%

[a]Mean ± SD; [b]All post-treatment measures are $P < 0.0001$ vs. Pre-treatment; Tx = treatment.

representing percentage improvements of 63% and 81%, respectively [both $P < 0.0001$].

Thus, whereas both subgroups had significant increases in both raw Tinetti scores and percentage improvement, the PNO group obtained approximately a 30% higher percentage improvement than did the DPN group.

Prior to treatment, the average Tinetti score was well below the breakpoint [19 points] for high fall risk [12.9 $\pm$ 4.1 in the PNO group and 14.2 $\pm$ 4.1 in the DPN group]. Tinetti scores increased substantially in each group and overall after therapy. Importantly, at the conclusion of the treatment protocol, the average Tinetti score in both the PNO and the DPN groups was just over 23 points. This is very close to the value of 24 that, in the Tinetti scoring system, is where patients have been determined to have a low fall risk. Thus, there was a significant improvement in balance and a concomitant reduction in fall risk. The data were also analyzed with respect to the fall risk based on the initial impairment in the Tinetti scores. The greatest percentage reduction in fall risk in both the PNO and DPN subgroups occurred among those who were at high fall risk [$P < 0.0001$]. At the conclusion of the therapy interventions, only 9% of the patients [23 of 250] remained at a high risk for falls [9% or 13 of 138 patients in the PNO group and 9% or 10 of 112 in the DPN group], compared with 88% [220 of 250] at baseline evaluation [126 in the PNO group and 94 in the DPN group]. Additionally, 59% of patients [148 of 250] who were either at moderate or high risk for falls at baseline were at low risk for falls after receiving MIRE™ and physical therapy.

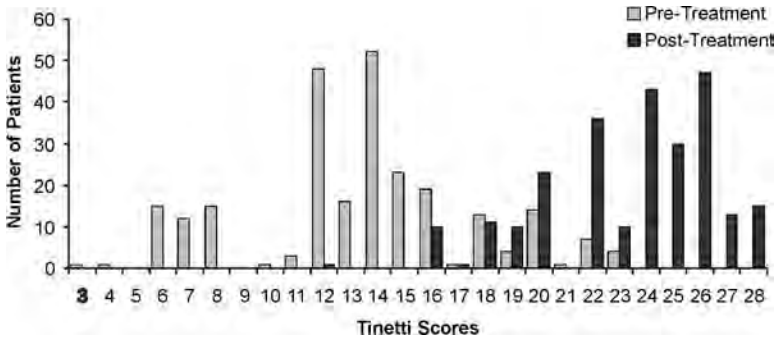
Figure 3 is a graphic representation of the dispersion of the Tinetti scores in the patient population prior to and after treatment. Prior to treatment, 50% of the patients scored in the 12 to 15 range, substantially below the high fall risk score of 19 on the Tinetti scale. After treatment, the 50% of the patients had scores from 23 to 26, indicating that most patients were now categorized as "low fall risks" [24 and above]. Thus, there was a significant decrease in fall risk in the vast majority of patients regardless of the level of their impairment prior to treatment.

DISCUSSION

It was hypothesized that the use of MIRE™ and adjunctive manual physical therapy would reduce neuropathic pain, improve foot sensation, and reduce fall risk [by improving balance] in patients with PN from diabetes or other causes. The results confirmed this hypothesis. The

analysis also demonstrates that the prevalence and extent of functional limitations [pain, foot insensitivity, and balance deficits] experienced by patients with PN are substantially similar regardless of whether the PN is due to diabetes or other causes and that the therapeutic approach employed resulted in similarly improved outcomes. Finally, the improved outcomes using the treatment protocol were significant and very similar regardless of the etiology of the PN. Because all patients received both MIRE™ and adjunctive manual physical therapy, it is impossible to attribute these improvements more so to either MIRE™ alone or the manual therapy alone. However, several inferences can be drawn from a review of the literature. First, there are no reports demonstrating that any non-surgical intervention other than MIRE™ , including manual physical therapy alone, is able to improve foot insensitivity to the SWM 5.07. Therefore, it is likely that these results occurred because physical therapists included MIRE™ as a component of treatment. Recent studies have documented the effect of MIRE™ treatment alone on foot insensitivity to the SWM 5.07 resulting from DPN and/or PNO (Kochman et al., 2002; Leonard et al., 2004; Prendergast et al., 2004; DeLellis et al., 2005). Improvements were noted after six treatments with MIRE™ alone and further improvement occurred with 10-12 treatments. It is not surprising therefore that six or more treatments [mean 18] in this cohort of patients were accompanied by improved sensation in the lower extremities. These results were unlikely to be due to a placebo effect. Leonard et al. (2004) looked closely at the possible placebo effect of MIRE on restoration of sensation by using identical units that did not emit photo energy. DPN patients on placebo devices did not improve.

FIGURE 3. Tinetti scores before (gray bars) and after (solid bars) treament.



Second, there are no published reports indicating that manual physical therapy alone is able to substantially reduce pain associated with PN. It may, in fact, be extremely difficult to engage patients with neuropathic pain in a physical therapy program that would otherwise be easily implemented in patients without pain. The patients in this analysis had significant pain at baseline. Furthermore, neuropathic pain syndromes such as those in this group of patients are not sympathetically mediated and therefore do not usually respond to sympathetic blockade through manual mobilization (The Merck Manual of Diagnosis and Therapy, 2005). Despite these problems, participation by patients in the active physical therapy treatment protocol may have been easier for the clinicians to implement because of the coincidental use of MIRE™ due to the reduction in pain and the improved sensation in the lower extremities. Accordingly, we tentatively conclude that the treatment protocol, which included MIRE™ and manual physical therapy, was associated with a substantial reduction in neuropathic pain.

Historically, physical therapy interventions designed to reduce the number of falls in elderly patients, particularly those with distal neuropathy, have resulted in minimal success (Hill-Westmoreland et al., 2002; Hageman & Thomas, 2002) although a manual physical therapy protocol without MIRE™ has been reported to have some beneficial effects on balance (Richardson et al., 2001). None of these reports included an analysis of changes in gait and balance using a Tinetti or similar test(s). Because we have been unable to locate any literature showing changes in Tinetti scores of patients with PN following treatment with manual physical therapy alone, we conclude that it was the comprehensive therapy protocol employed for the patients treated in this report that substantially increased their balance and reduced their risk of falls.

We also recognize the limitations of a post-treatment analysis, specifically that these data were based upon a review of patients' charts. There was no control arm comparing the possible effect of MIRE™ alone or physical therapy interventions alone in each patient. However, historical evidence in the published literature suggests that physical therapy alone will do little to improve quality of life issues in patients with PN and we could find no ethical justification for re-confirming in our patients, by use of another randomized control trial of physical therapy alone, what others have reported. The previous failures are probably because PN patients continue to experience neurological deficits in sensation, balance and/or pain. With the growing evidence that MIRE™ can restore sensation in patients with peripheral neuropathy (Kochman

et al., 2002; Leonard et al., 2004; Prendergast et al., 2004; DeLellis et al., 2005), it seemed reasonable to combine MIRE™ and physical therapy to determine if a combination of approaches could elicit a better outcome in patients than would physical therapy alone.

Furthermore, because the SWM is an objective test, historical controls may be appropriate since the sensory loss in DPN patients is generally thought to be progressive and irreversible (Sima & Laudio, 1996). There are no pharmacologic treatments for sensory loss associated DPN making MIRE™ an impressive therapeutic intervention for therapists. Although we did not examine the concomitant use of psychoactive drugs, pain medications, and other intrinsic or extrinsic risks for falling, there were no changes in pain medications or psychoactive drugs reported to the investigators during this short study protocol. However, the possibility does exist that this might have occurred in some patients and cannot be completely ruled out.

Lastly, the study protocol did not permit us to analyze the proportion of improvements that were attributable to physical therapy alone and those related to the increases in foot sensation alone resulting from the use of MIRE™ . Future studies should consider the use of other types of controls to determine the relative effectiveness of the combination of MIRE™ with physical therapy compared with physical therapy alone. Because patients are heterogeneous, perhaps a trial of outcomes using physical therapy alone, followed by MIRE™ and physical therapy together, would be a useful protocol design.

In conclusion, MIRE™ when used in conjunction with manual physical therapy is able to significantly reduce pain, improve foot sensation, and improve balance and gait thus reducing an objective fall risk in patients exhibiting PN, at least temporarily. Of interest, as noted in this chart review, the benefit of combined physical therapy and MIRE™ was shown in the majority of patients with neuropathy, irrespective of whether this was due primarily to diabetes or other causes and despite the fact that treatments were rendered in either an outpatient clinic, in a hospital, or in a nursing home.

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Improved foot sensitivity and pain reduction in patients with peripheral neuropathy after treatment with monochromatic infrared photo energy—MIRE

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Abstract

The medical records of 2239 patients (mean age=73 years) with established peripheral neuropathy (PN) were examined to determine whether treatment with MIRE was, in fact, associated with increased foot sensitivity to the Semmes Weinstein monofilament (SWM) 5.07 and a reduction in neuropathic pain. The PN in 1395 of these patients (62%) was due to diabetes. Prior to treatment with MIRE, of the 10 tested sites (5 on each foot), 7.1±2.9 were insensitive to the SWM 5.07, and 2078 patients (93%) exhibited loss of protective sensation defined by Medicare as a loss of sensation at two or more sites on either foot. After treatment, the number of insensate sites on both feet decreased to 2.4±2.6, an improvement of 66%. Of the 2078 (93%) patients initially presenting with loss of protective sensation, 1106 (53%) no longer had loss of protective sensation after treatment ($P<.0001$); 1563 patients (70%) also exhibited neuropathic pain in addition to sensory impairment. Prior to treatment with MIRE, pain measured on the 11-point visual analogue scale (VAS) was 7.2±2.2 points, despite the use of a variety of pain-relieving therapeutic agents. After treatment with MIRE, pain was reduced by 4.8±2.4 points, a 67% reduction. Therefore, MIRE appears to be associated with significant clinical improvement in foot sensation and, simultaneously, a reduction in neuropathic pain in a large cohort of primarily Medicare aged, community-dwelling patients, initially diagnosed with PN. The quality of life associated with these two outcomes cannot be underappreciated.

Keywords: Diabetic peripheral neuropathy; MIRE; Semmes Weinstein monofilament; Anodyne Therapy System; Monochromatic infrared photo energy

1. Introduction

Disturbance of skin sensation, characterized by pain, hyperesthesia, hypoesthesia, numbness, and/or tingling, is a common symptom of peripheral neuropathy (PN). Although there are many conditions in which PN is a comorbid factor, diabetes is the primary cause of PN in the Western world. Painful manifestations of PN have a substantial adverse effect on quality of life (Galer, Gianas, & Jensen, 2000). Foot insensitivity, particularly among patients with diabetes, is highly correlated with foot wounds and nontraumatic lower extremity amputations (LEA); indeed, PN and peripheral vascular disease are the leading causes of amputations and high mortality rates among both diabetic and nondiabetic patients (Tentolouris, Al-Sabbagh, Walker, Boulton, & Jude, 2004). The prevalence of PN is extensive. Estimates suggest that 15% of the population over 40 exhibit this condition, and in those with diabetes, the rate is 29% (Gregg et al., 2004). Of concern, although 50% of these patients showed documented insensitivity to the Semmes Weinstein Monofilament

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(SWM) 5.07 at two or more of six measured plantar sites, a significant portion were asymptomatic in the sense that they had not experienced numbness, loss of feeling, painful sensations, or tingling in their feet. Thus, they did not recognize the need for foot precautions (Gregg et al., 2004).

Historically, there have been no effective treatments for improving foot sensation diminished due to PN (Diabetic Neuropathy, 1995) other than a surgical procedure championed by Dellon and others (Dellon, 2004; Wieman & Patel, 1995; Wood & Wood, 2003). However, not all patients are acceptable candidates for this surgical procedure. With this in mind, healthcare professionals vigorously encourage lower extremity ulcer (LEU) risk-reduction strategies that currently include patient education, frequent visits to their physicians, orthotics for off-loading, and accommodative foot wear. However, despite these strategies, the incidence of LEU remains at over 8% in patients with PN and loss of protective sensation (Armstrong et al., 2004). Additionally, diabetic patients with sensory loss who were assigned to therapeutic shoes do not have a significantly lower risk of reulceration compared with controls (Reiber et al., 2002).

Because chronic neuropathic pain is also a long-term complication of diabetic PN (Ziegler, 2004) and other neuropathies and has a negative impact on quality of life (Galer et al., 2000), significant research has been devoted to therapeutic options for this condition. Unfortunately, available pharmacological and other treatments for neuropathic pain have not been totally efficacious (Davies, Crombie, Lonsdale, & Macrae, 1991). Clearly, neuropathic pain is a source of frustration to affected patients and the physicians who deal with this condition on an ongoing basis.

Several recent studies (DeLellis, Carnegie, & Burke, 2005; Kochman, 2004; Kochman, Carnegie, & Burke, 2002; Leonard, Farooqi, & Myers, 2004; Powell, Carnegie, & Burke, 2004; Prendergast, Miranda, & Sanchez, 2004) show that, at least, temporary increases in foot sensitivity, documented using either the SWM 5.07 or the Neurometer CPT sNCT, occur following the application of monochromatic near infrared photo energy (MIRE) to the feet of symptomatic diabetic patients with impaired foot sensation associated with PN. Another study showed that improvement in foot sensation resulting from MIRE treatments was associated with a substantial reduction in the incidence of new LEU among a Medicare aged population (Powell et al., 2004). Moreover, we recently reported improved foot sensation after MIRE in 1047 patients (790 with diabetes) for whom sensory data had been collected in the routine course of medical treatment (DeLellis et al., 2005).

Table 1
Patient demographics

	Number	Percent (%)
Patients with peripheral neuropathy	2239	
Male	1069	48
Female	1170	52
Diabetic	1395	62
Nondiabetic	844	38
Mean age±1 S.D.	73±8.4 (range 29–100)	
Mean number of sites insensate (10 maximum)	7.1±2.9	

Table 2
Foot insensitivity to the SWM 5.07 pre- and posttreatment

	Current study		Prior study (DeLellis et al., 2005)	
Total number of patients	2239		1047	
Pretreatment sites insensate (max 10)	7.1±2.9[a]		7.9±2.4[a]	
Posttreatment sites insensate	2.4±2.6*		2.3±2.4*	
Mean decrease sites insensate	4.7±2.8*		5.6±2.7*	
Pretreatment patients with LOPS	2078	93%	1033	99.6%
Posttreatment patients regaining protective sensation	1106	53%	580	56.1%
Posttreatment total number of patients with LOPS	972	47%	453	43.9%
Pretreatment number of patients with all 10 sites insensate	770	34%	452	43%
Posttreatment sites insensate	3.8±3.0*		3.1±2.7*	
Mean decrease sites insensate	6.2±3.0*		6.9±2.7*	

LOPS: loss of protective sensation.
[a] Mean±S.D.
* $P<.0001$.

The present results demonstrate improved foot sensation as well as a reduction in neuropathic pain after MIRE treatments in 2239 community-dwelling patients with PN (1395; 62% with diabetes). The improvements in foot sensitivity to the SWM 5.07 also compare favorably with those we reported previously (DeLellis et al., 2005).

2. Research and design methods

The insurance claims of a durable medical equipment supplier (DME) offering Anodyne Therapy System (ATS; Anodyne Therapy, Tampa, FL), an item of durable medical equipment delivering MIRE, were reviewed to obtain a list of patients who had been treated with MIRE in physicians'

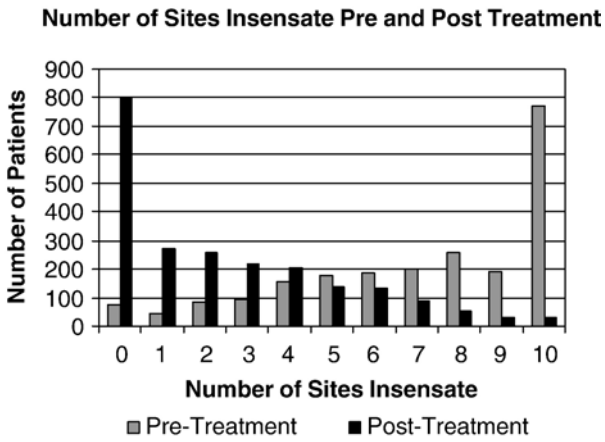

Fig. 1. Number of patients with insensate sites before (gray bars) and after (black bars) MIRE treatment.

Table 3
Foot insensitivity to the SWM 5.07 pre and posttreatment (diabetic patients compared with nondiabetic patients)

	Current study				Prior study (DeLellis et al., 2005)			
	Pre	Post	Improvement	*P* value	Pre	Post	Improvement	*P* value
All patients	7.2±2.9	2.4±2.6	4.7±2.8	<.0001	7.9±2.4	2.3±2.4	5.6±2.6	<.0001
Diabetics	7.3±2.8	2.5±2.6	4.8±2.8	<.0001	8.0±2.4	2.4±2.4	5.6±2.7	<.0001
Nondiabetics	7.0±3.1	2.3±2.6	4.6±2.8	<.0001	7.9±2.4	2.3±2.4	5.5±2.6	<.0001

The correlation of the improvement between both studies is .98186.

offices and therapy clinics throughout the United States. The ATS delivers MIRE through therapy pads, each containing 60 superluminous diodes (890 nm near-infrared wavelength), which are attached to a control unit, which pulses the MIRE at 292 times/s (Burke, 2003). The ATS was cleared by the FDA for use in increasing circulation and reducing pain. Prior to providing the ATS to patients for use at home, the supplier had obtained signed physician orders and therapists' clinical notes that documented the results of MIRE treatment in a clinical setting. Collectively, the data supported a diagnosis of PN in all patients; and, in all instances, the clinical notes included SWM evaluations of foot sensitivity both immediately before and shortly after a course of treatment with MIRE. Additionally, the physician orders and clinical notes also provided data regarding the severity of neuropathic pain prior to and after MIRE treatments. Charts specified the pre- and posttreatment pain on an 11-point visual analogue scale (VAS).

We used a searchable database containing a record of all claims filed, including ICD-9 coding of the underlying conditions for which the ATS had been ordered by referring physicians. The database, excluding any patient identifiers, was sorted by the DME supplier to obtain a list of all patients who had a diagnosis of PN based on ICD-9 code 357 or 782. The list was then stratified to obtain a list of those with Type 1 or 2 diabetes using ICD-9 codes 250.61 and 250.62, respectively. The period of inquiry was January 26, 2004, to November 30, 2004. In total, 2812 patients satisfied these criteria. Most patient records contained bilateral foot sensitivity data for the SWM 5.07 (at 10 sites; 5 on each foot) before and after MIRE treatment. Although all records contained data relative to improvement in foot sensation, some were not included in this analysis because (1) the SWM measurements were done at less than or more than 10 sites bilaterally, (2) the healthcare professionals used SWM other than the 5.07 SWM, or (3) they documented changes with other sensory testing devices, including the Pressure Specified Sensory Device (PSSD) or the Neurometer sNCT. Thus, 2239 patient records fulfilled the criteria for analysis in this report.

2.1. Statistics

The results were analyzed by paired two-tailed *t* test with a null hypothesis that there would be no change in sensitivity to the SWM 5.07 or neuropathic pain (either an increase or a decrease) following the use of MIRE. Significance was accepted if $P<.05$. Data are expressed as mean±1 S.D.

3. Results

The mean age of the study population (1069 male; 48%) was 73±8.4 years (range: 29–100; Table 1). One thousand three-hundred ninety-five patients (62%) were diagnosed with diabetic PN, and 844 patients were diagnosed with PN associated with other etiologies (PNO). The mean number of sites insensitive to the SWM 5.07 (bilaterally; maximum 10 sites for both feet) was 7.1±2.9 before treatment and 2.4±2.6 after treatment ($P<.0001$), an improvement of 66% in foot sensation (Table 2). Prior to treatment, 2078 patients (93%) exhibited loss of protective sensation as determined by foot insensitivity to the SWM 5.07 at two or more sites on either foot. At the conclusion of the MIRE treatments in the clinic, 53% of these patients no longer exhibited loss of protective sensation ($P<.0001$; Table 2).

Fig. 1 shows the number of insensate sites pre- and posttreatment in this group of patients. Prior to treatment with MIRE, most of the patients exhibited a loss sensation at 8 to 10 sites, and 73% of all patients had documented loss of sensation at 6 or more sites. After treatment, more than 60% of the patients were insensate at two sites or less, and more than 79% were insensate at four sites or less. The change in the distribution pattern of insensitivity to the SWM 5.07 graphically demonstrates the significance of the MIRE treatment effect in elderly outpatients with PN.

We also examined the data to determine whether there was a difference in the sensory responsiveness to MIRE in patients with diabetic PN as compared with those with PNO (Table 3). Both diabetic PN and PNO patients were similarly impaired prior to receiving MIRE treatment, and each group achieved the same clinical improvement in sensation ($P<.0001$).

We compared the foot sensitivity data that we previously collected reported on 1047 patients (DeLellis et al., 2005) with PN to determine the degree of correlation between the

Table 4
Patients reporting significant pain pre- and posttreatment

	Pre	Post	Improvement	Percent improvement (%)
All patients	1563	33	1530	98
Diabetic	979	23	956	98
Nondiabetic	584	10	574	98

Table 5
Changes in pain on the 11-point VAS

	Pre	Post	Improvement	*P* value	Percent improvement (%)
All patients	7.2±2.2	2.4±2.1	4.8±2.4	<.0001	67
Diabetic	7.1±2.2	2.4±2.2	4.7±2.5	<.0001	66
Nondiabetic	7.3±2.1	2.5±2.1	4.8±2.3	<.0001	66

results of that study and of the present study. The correlation of the sensory improvement values between the two studies was .98186; clearly, the results of the two studies are virtually identical (Tables 2 and 3).

Interestingly, although the patients exhibited severe sensory impairment as measured by the SWM 5.07 (mean=7.1±2.9 of 10 sites insensitive), 1563 patients or 70% also exhibited neuropathic pain (Table 4). Physician notes (verified by analysis of clinical records) showed that 98% of patients initially reporting neuropathic pain obtained substantial reduction in their pain after treatment. Mean pain as reported on the 10-point VAS was 7.2±2.2 immediately prior to MIRE treatment. After MIRE treatment, the mean pain level was reported to be 2.4±2.1, a mean reduction of 4.8 points, or 67% (Table 5). From a descriptive standpoint, the mean pain level was reduced from "distressing" to "mild." As is the case for changes in foot sensitivity after MIRE (Table 2), there was no significant difference between the initial level of pain or in pain reduction between the diabetic PN and PNO patients (Table 5).

The clinical records of the patients with PNO were quite detailed and showed that the pretreatment pain continued to be a complaint of these patients despite the fact that more than 62% were taking one or more prescription medications (anticonvulsants, antidepressants, and/or opiates) in an unsuccessful effort to reduce their neuropathic pain. Of the remaining patients, 13% had continued to experience significant levels of neuropathic pain despite the use of topical analgesics (e.g., capsaicin cream, Lidocaine patches, and Biofreeze), physical therapy, nerve blocks, and over-the-counter pain medications. Additionally, the duration of the PNO was significant, with a mean duration of 70 months (range, 0.5 to 1020 months; Table 6).

Table 6
Descriptive characteristics of nondiabetic patients

Total	844	
Duration (months)	mean=70; range, 0.5 to 1020	
Etiology		
Idiopathic neuropathy	558	(66%)
Inflammatory and toxic neuropathies	36	(4%)
Mononeuritis	65	(8%)
All other	185	(22%)
Total reporting ineffective prescription drugs[a]	521	(83%)
Total reporting ineffective other treatments[b]	110	(17%)

[a] One or more antidepressants, anticonvulsants, opioids.
[b] More than one of the following: topical analgesics, over-the-counter analgesics, physical therapy, and nerve block injections.

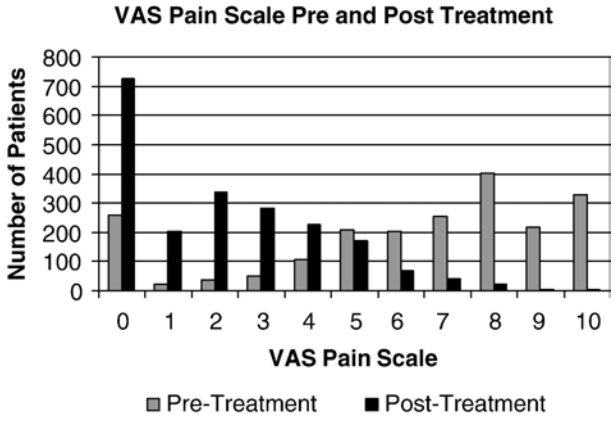

Fig. 2. Number of patients with pain levels on VAS scale before (gray bars) and after (black bars) MIRE treatment.

Fig. 2 shows the 11-point VAS reported pre- and posttreatment in this group of patients. After treatment with MIRE, more than half of the patients initially reporting high degrees of neuropathic pain reported pain levels of two or less. Additionally, 30% of patients initially reporting pain reported no pain at all after MIRE treatments. The change in the distribution pattern of pain intensity graphically demonstrates the significance of the MIRE treatment effect in this patient population.

4. Discussion

Until recently, sensory impairments associated with PN, particularly due to diabetes, were thought to be progressive and irreversible. Several groups have employed a surgical technique, tarsal tunnel decompression surgery, with very favorable outcomes in selected patients with neuropathy (Dellon, 2004; Wieman & Patel, 1995; Wood & Wood, 2003). The present results confirm a recent report in a similarly large group of patients (1047) that improvement can occur in a very real world study population (i.e., community-dwelling patients with PN) treated in routine clinical practice with MIRE (DeLellis et al., 2005). These data support other published studies relative to the effectiveness of MIRE treatments for PN (Kochman, 2004; Kochman, Carnegie, & Burke, 2002; Leonard et al., 2004; Prendergast et al., 2004; Powell et al., 2004).

More than half of the patients who were initially diagnosed with loss of protective sensation (53%) obtained at least a temporary return of protective sensation, which compares favorably with the results that we reported previously in 1047 patients (56%; DeLellis et al., 2005). Even those patients with the most severe sensory dysfunction (all 10 sites insensitive to the SWM 5.07) obtained significant sensory improvement (6.2±3.0 sites were sensed after MIRE). Again, this result compares favorably with previous results that demonstrated 6.9±2.7 sites sensed after

MIRE in patients who were initially totally insensate to the SWM 5.07 (DeLellis et al., 2005). This result occurred irrespective of the etiology of the PN because there was no significant difference in the response of the patients with diabetic PN as compared with those with PNO. Thus, the results of this analysis demonstrate that sensory loss associated with PN, even when it has advanced to and beyond simply the loss of protective sensation, is not necessarily irreversible.

These data also demonstrate that neuropathic pain is closely associated with impaired sensation to the SWM 5.07 because 70% of the patients exhibited both manifestations of PN. Ninety-eight percent of patients reported having a "significant reduction in pain" after MIRE, as verified through the review of the clinical notes. We know of no other intervention that is as successful for patients with PN.

Of importance, the etiology of the PN was not a determining factor of whether the patients responded to treatment. There was no significant difference in the response of the diabetic PN and PNO patients, either in terms of pain reduction or increased sensation to the SWM 5.07. The clinical history for the PNO patients showed that the mean duration of their pain was 70 months and that, prior to treatment with MIRE, 62% of the patients continued to exhibit clinically significant symptomatic pain despite taking anticonvulsants, antidepressants, and/or opiate analgesics. These data on the relative ineffectiveness of medications for neuropathic pain are not surprising because a recent survey of physicians, experienced in treating neuropathic pain, noted that only a minority would rate the results of these medications as either excellent or good (Davies et al., 1991).

These observations and the conclusions derived must be analyzed in the context of certain limitations in our design. For example, there was no control group against which the results of this study were measured. However, when a disease such as diabetic PN is known to be progressive and irreversible, use of historical controls from published literature may be appropriate (Sima & Laudadio, 1996). In the case of diabetic PN, there have been no reports of either spontaneous reversal of this condition or efficacy of any nonsurgical intervention (Diabetic Neuropathy, 1995; Prendergast et al., 2004). In fact, two published randomized control trials have shown that 4 weeks of either thrice or biweekly sham photo energy treatment did not result in any improvement in the ability to detect the SWM 5.07 by patients with diabetic PN (Leonard et al., 2004; Zinman et al., 2004). Additionally, the present data were obtained from the records of patients who all exhibited some improvement in their neuropathic symptoms. Therefore, although we cannot generalize these results to all patients with PN, we can conclude that these 2239 patients, similarly to the 1047 patients on whom we reported previously, obtained objective improvement in foot sensation to the SWM 5.07 after treatment with MIRE.

Furthermore, we confirm that insensitivity to the SWM 5.07 is often associated with neuropathic pain, and in the group of patients that were treated with MIRE, improved foot sensation resulting from MIRE treatment was paralleled by significant reductions in neuropathic pain. Importantly, in the PNO patients, significant pain reductions were apparent despite a long history of chronic pain unrelieved by conventional prescription or OTC medications and other interventions.

We cannot totally discount physician or therapist bias, because the SWM 5.07, while broadly accepted and objective, is only a patient-blinded test. Additionally, all of the patients knew that they were receiving active treatment. However, it is exceedingly unlikely that the more than 1000 evaluators in testing more than 2239 patients systematically misinterpreted the sensitivity to the SWM before and after MIRE treatment. Similarly, the effectiveness of MIRE treatments in improving sensitivity to the SWM 5.07, as reported in a recent double-blinded, placebo-controlled RCT, lessens the likelihood that the present results were due to evaluator bias (Leonard et al., 2004). Other testing modalities, namely, PSSD (Aszmann & Dellon, 1998) and the Neurometer (Pitei, Watkins, Stevens, & Edmonds, 1994), are currently being used to detect discrete changes in skin sensation impaired due to PN that cannot be determined with the SWM 5.07. Nevertheless, the SWM 5.07 is the most commonly used test to determine loss of protective sensation resulting from PN. It is highly sensitive (between 85% and 100%) and specific (between 34% and 100%) based on the number of sites tested and the testing methodology (Mayfield & Sugarman, 2000). Additionally, SWM data have been correlated with abnormal nerve conduction velocity outcomes, especially with more severe nerve impairment (Perkins, Olaleye, Zinman, & Brill, 2001). Like all tests in which the patient is an active participant, the accuracy of the SWM is dependent upon communication from an alert, cooperative, and responsive patient (Mayfield & Sugarman, 2000). To maximize the validity of the test results, those performing the SWM tests were given case report forms adapted from Feet Can Last a Lifetime (Feet Can Last a Lifetime, 2005). This document recommends measuring five sites on the plantar surface of the foot and the use of a "forced two choice testing method," which minimizes patient bias (Sekuler, Nash, & Armstrong, 1973). Finally, the technique also involves random testing sites on the feet and avoids heavily callused or active wound sites.

It is obvious that changes in pain are difficult to objectively measure and are subject possibly to placebo effect. The 11-point VAS has been widely validated (Flandry, Hunt, Terry, & Hughston, 1991) and is not subject to evaluator bias because it is reported by the patient. The extent of the reduction in reported pain by the patients in this study (67%) substantially exceeds the reported minimal level of detectable change (1.3 to 1.6 points on the VAS), which is considered clinically relevant (Gallagher, Bijur, Latimer, & Silver, 2002). Moreover, the VAS pain reduction exceeded 3.0, which has been reported to be a clinically important difference in pain severity corresponding to

patient's perception of adequate analgesic control (Lee, Hobden, Stiell & Wells, 2003). Zinman et al. (2004) examined the placebo effect of 12 sham treatments with low-intensity laser therapy delivered over 6 weeks and noted an approximately 20% reduction in pain (6.9 ± 1.7 to 5.4 ± 1.9). The patients in the present study had a similar level of initial pain (7.2 ± 2.2), but they reported more than three times the pain relief (67%) reported by the sham treated patients in the Zinman et al. study, making it very unlikely that the present results are due to a placebo effect. Lastly, the large number of patients (1563) with neuropathic pain whose pain decreased in this study would also tend to discount a placebo effect.

5. Conclusion

MIRE treatments are associated with a substantially improved foot sensation, assessed by the SWM 5.07, and a robust reduction in neuropathic pain that had been previously unresponsive to other interventions (both $P<.0001$) in a cohort of 2239 patients initially diagnosed with PN. The improvements in foot sensation to the SWM 5.07 are remarkably similar (correlation=.98186) to our previous analysis of 1047 patients (DeLellis et al., 2005). Overall, the magnitude and consistency of these results and those from other studies using MIRE (Kochman, 2004; Kochman et al., 2002; Leonard et al., 2004; Prendergast et al., 2004; Powell et al., 2004) show that sensory disturbances associated with PN are not necessarily progressive and irreversible and that this condition can be effectively treated noninvasively with a high degree of patient safety.

This reported advancement in the treatment of sensory disturbances associated with PN has enormous potential to affect health care in other ways. For example, it would seem likely that a secondary outcome after the restoration of sensation would be a reduction in the incidence of LEU, consequent amputations, and high morbidity, particularly among patients with diabetic PN. One study reported a 1.5% annual incidence of LEU after symptomatic improvement in foot sensation to the SWM 5.07 through the use of MIRE (Powell et al., 2004). This represents more than an 80% reduction in the 35-week incidence rate (8%) recently reported by Armstrong et al. (2004) in patients with diabetic PN who had been prescribed accommodative footwear and were under the ongoing care of physicians. Additionally, at least where MIRE is used in conjunction with appropriate physical therapy, there is a significant improvement in balance and a substantial reduction in the number of falls in elderly patients (Kochman, 2004). The improved sensation during MIRE in patients who have a significant fall history may allow physical therapy interventions to be more effective. Because of the high reported costs of PN and its devastating sequelae (Gordois, Scuffham, Shearer, Oglesby, & Tobian, 2003; Harrington, Zagari, Corea, & Klitenic, 2000; Hogan, Dall, & Nikolov, 2003; Shearer, Scuffham, Gordois, & Oglesby, 2003), the use of MIRE in patients can be expected to improve their quality of life and simultaneously offer significant cost savings to the U.S. and international healthcare systems.

Acknowledgments

We extend our appreciation to the more than 1000 physicians and therapists who first documented PN in their patients and carefully recorded clinical changes in foot sensation and pain after treatment with MIRE. In addition, we extend our appreciation to the staff of the supplier who worked with us to access their database and identify the applicable patient records. We also thank Amy Spirides for her assistance with the statistics and figures.

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Infrared Photo Energy May Reduce Neuropathic Pain

Near infrared light therapy, together with physical therapy, may be able to reduce pain in neuropathy patients and possibly reduce medication dosage levels of those undergoing drug therapy.

Diabetic neuropathy is a common health problem today which often poses a variety of clinical challenges. In this article, Dr. Thomas J. Burke reports on the results of a study utilizing phototherapy (non-coherent light therapy) on patients with neuropathies. This is an exciting paper and demonstrates the potential value of light therapy in these clinical conditions. There is a rapidly increasing body of evidence that is demonstrating the clinical value of using non laser light therapy for a wide variety of painful conditions.

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By Thomas J. Burke, PhD

In a recent issue of *Practical Pain Management*, two papers discussed treatment of pain patients using FDA cleared alternative modalities referred to generically as light therapy.[1,2] This paper describes the effects of light therapy on the pain accompanying neuropathy. Pain is a common complaint of patients with peripheral neuropathy (PN) due to either diabetes or other causes and it often interferes with quality of life, irrespective of pharmaceutical intervention.[3] For example, painful PN may be a complication from 1) chemotherapy drugs, 2) metabolic diseases such as hypothyroidism, 3) abuse of alcohol, 4) environmental toxins or drugs, 5) certain viral infections, 7) scar tissue formation following surgery, or 6) it may be idiopathic.[4] There are only a few FDA approved drugs for the pain of PN. These drugs do not modify blood flow and, therefore, they do not correct microcirculatory defects that can, in some cases, contribute to ischemic, neuropathic pain. Some of the approved drugs have significant side effects that compromise quality of life.[5] Beyond pharmacology, there has been some success—in carefully selected patients—in effecting significant neuropathic pain relief with surgical intervention to decrease nerve compression.[6]

An alternative to drugs or surgery— monochromatic infrared energy (MIRE™) along with concurrent physical therapy—has been reported to provide significant pain relief to patients presenting with neuropathic pain due to either diabetes or other etiologies.[7-10] This report documents the reduction in neuropathic pain achieved with use of MIRE in 493 consecutive, mostly elderly, patients treated in health care facilities from the beginning of May 2006 to the end of June 2006. These patients also detailed their use (or lack thereof) of various drugs for neuropathic pain relief prior to and during MIRE treatment.

Materials and Methods

The medical history and clinical notes related to pain were included as part of insurance claims made by a durable medical equipment (DME) supplier offering the Anodyne® Therapy System (ATS; Anodyne Therapy LLC, Tampa, FL) that delivers MIRE at 890 nanometers from gallium aluminum arsenide diodes. The ATS has FDA 510k clearance for temporarily increasing circulation and reducing pain, stiffness, and muscle spasm.[11]

The medical records and clinic notes provided by the healthcare professionals included:

- a physician diagnosis of peripheral neuropathy associated with diabetes (diabetic peripheral neuropathy; DPN) or other etiologies (peripheral neuropathy-other; PNO),
- the level of pre-treatment neuropathic pain measured on an 11 point numeric pain rating scale (NPRS; 10 equating to maximum pain and zero (0) equating to no pain), and
- pain levels measured after MIRE treatment.

456 separate physicians attested to the accuracy of the medical data that they supplied to justify these insurance claims. MIRE was administered as part of a comprehensive care plan that also included individualized physical therapy for various gait and balance problems that occur quite frequently in patients with PN.[12] Shurman and colleagues recommend physical therapy, exercise and integrated techniques in their powerful tool, the Share The Risk Model, for managing patients with pain.[13] However, it is often difficult for patients to begin or complete a therapy program if they are in constant, unremitting pain.

Patients were told to anticipate being treated with MIRE approximately 12 times, 30 min. each time, 3 times per week, for their pain. After completing outpatient therapy, 493 out of 550 patients agreed to provide answers to a health questionnaire. This was done under HIPPA protection assurances by the DME.

Table 1. Patient Demographics

Total Patients with PN	493	
Male	214	43%
Female	279	57%
Diabetic (DPN)	248	50%
Non-Diabetic	245	50%
Age (years)[a]	72 ± 8.4	Range (44-94)
Pre-Treatment Pain (10 max)[a]	6.9 ± 2.2	

a = mean ± SD
PN = peripheral neuropathy
DPN = diabetic peripheral neuropathy
PNO = peripheral neuropathy from other causes

Table 2. Changes in pain in response to MIRE treatment in DPN and PNO Patients

	All Patients	DPN	PNO
Number of Patients	493	248	245
Pre-Treatment Pain (10 max)[a]	6.9 ± 2.2	6.9 ± 2.2	6.9 ± 2.1
Post-Treatment Pain	2.5 ± 2.1[b]	2.5 ± 2.4[b]	2.5 ± 2.0[b]
Mean Decrease in Pain	4.4 ± 2.3[b]	4.4 ± 2.4[b]	4.4 ± 2.1[b]

a = mean ± SD
b = p<0.0001
DPN = diabetic peripheral neuropathy
PNO = peripheral neuropathy from other causes

Furthermore, patients had signed HIPPA and informed consent documents in both the physician and therapist's office. Patient identifiers were removed prior to the analysis of the data. Patients answered the following questions: 1) the duration of the neuropathic pain, 2) which medications (if any) they were using prior to initiating MIRE, and 3) whether they had increased, decreased or changed medications or dosage during MIRE treatment.

The answers to the questionnaire were gathered over a 7-week period during the late spring of 2006. Neuropathic pain intensity—before and after MIRE—was determined separately for patients collected into four groups, as follows:

Group 1: Patients not utilizing medications for pain prior to and during MIRE treatments (n=129)

Group 2: Patients utilizing drug therapy prior to MIRE and were able to reduce their dosage by the completion of MIRE treatments (n=187)

Group 3: Patients utilizing drug therapy prior to MIRE and did not alter this use during MIRE treatments (n=151)

Group 4: Patients utilizing one or more drugs prior to MIRE and either changed dosage or switched to a new medication, or both, prior to the conclusion of MIRE therapy (n=26).

Statistics

The pain outcome among the four treatment groups was analyzed by one-way ANOVA to test the null hypothesis that decreases in neuropathic pain would depend on pharmacologic interventions during the course of MIRE treatments. All values are reported as mean ± one standard deviation (SD). Significance was accepted if $P<0.05$.

Results

Mean age of the respondents (214 male, 279 female) was 72 years (see Table 1). 248 patients were diagnosed with DPN and 245 patients were diagnosed with PN associated with other etiologies (PNO). Mean pre-treatment neuropathic pain reported on an 11-point NPRS was 6.9 ± 2.2 with no difference between the DPN and PNO groups (see Table 2). Post-treatment pain averaged 2.5 ± 2.3, a 64% reduction; there was no significant difference in the decreased pain between the DPN and PNO groups (see Table 2). The average number of PT visits during which MIRE was also given was 15±8. At the initiation of MIRE therapy, 129 patients (26%) were not taking medications for their neuropathic pain, whereas 364 patients (74%) were taking one or more medications. As one would expect, based on the medical literature for neuropathic pain, drugs included anticonvulsants, antidepressants, and opiates. In 263 out of 364 patients (72%), more than one drug was being consumed. The most frequently used medication was the anticonvulsant gabapentin, with 197 patients (54%) using this pharmacologic agent.

Of the 364 patients who were taking medications for their neuropathic pain at initiation of MIRE therapy, 187 (51%) reported that they had reduced the use of medications during MIRE therapy, 151 (41%) reported that their use of medications was unchanged throughout therapy, and 26 (7%) reported either a change in medication, an increase in the dosage of one or more of the initial medications, or both, during MIRE therapy.

There were no significant differences in the pre-treatment pain levels, the post-treatment pain levels, or the extent of pain relief among these four groups, nor were there differences in the number of MIRE treatments given (Table 3). Questionnaire responses indicated that patients had experienced neuropathic pain, on average, for at least 3.5 – 4.5 years (Table 3). The actual duration of neuropathic pain may have been much longer because the maximum duration of pain entered as data for any one patient was input as 99 months even if it was longer. Those patients with 99 (or more months of neuropathic pain) made up the following percentages of each group:

Group 1: 20 of 129 patients (16%)
Group 2: 40 of 187 patients (21%)
Group 3: 44 of 151 patients (29%)
Group 4: 9 of 26 patients (35%)

Discussion

These data demonstrate that using MIRE in an outpatient setting is associated with a significant and strikingly similar decrease in neuropathic pain intensity in both diabetic and non-diabetic patients.

Table 3. Pain Response to MIRE is independent of medication usage.

	No Meds during MIRE	Decreased Meds	No Change in Meds	Changed Meds
	Group 1	Group 2	Group 3	Group 4
Patients (n)	129	187	151	26
Male	66	72	63	13
Female	63	115	88	13
Age (Range)	74(53-94)	72(44-90)	73(46-93)	69(54-94)
Duration of Neuropathic Pain (Months)[a]	41.5 ± 31.4	49.9 ± 32.9	54.3 ± 35.3	54.7 ± 38.8
Initial Pain[a]	6.7 ± 2.4	7.2 ± 1.9	6.7 ± 2.3	7.3 ± 1.9
Post Pain[a]	2.4 ± 2.2[b]	2.5 ± 2.2[b]	2.6 ± 2.0[b]	2.6 ± 1.9[b]
Mean Pain Decrease[a]	4.3 ± 2.5[b]	4.7 ± 2.1[b]	4.2 ± 2.3[b]	4.7 ± 2.4[b]
Number of Treatments[a]	15 ± 9.2	15 ± 8.2	16 ± 9.1	19 ± 8.9

a = mean ± SD. b = P<0.0001 vs. initial pain. Meds = medications. (n) = number of patients. Changed meds indicates either a different dose or a different medication, or both.

These outcomes are consistent with a growing body of clinical evidence showing MIRE is able to significantly decrease pain in diabetic and non-diabetic neuropathy patients.[7-10]

Perhaps more important, the decrease in pain intensity in response to MIRE combined with therapy was independent of concomitant use of medications that are typically used for neuropathic pain. Patients who were not taking drugs for their pain responded exactly like those patients who were taking medications at the initiation of the therapy. For those who were already taking drugs, the reduction in symptomatic pain was not related to either a continuation of current drug usage, to a reduction in drug use or to changes in either the dosage or class of medications consumed throughout the period of treatment. Indeed, 51% of patients achieved significant neuropathic pain reduction and were concomitantly able to decrease the dosage of medication(s) they had been taking at the initiation of MIRE therapy. The similar degree of pain mitigation was not due a difference in the number of treatments, age or gender, or the length of time the patients had been aware of neuropathic pain severe enough to cause them to seek medical attention.

Clearly, pharmacologic agents have been found to be effective in reducing pain in both diabetic and non-diabetic patients.[14-17] However, as is the case with virtually all drugs, side effects may limit the patient tolerance. Side effects also become more evident with the use of higher drug doses that are often necessary when low doses are no longer effective or when patients report a waning effect. High drug doses often relieve pain but the quality of life may be adversely affected. The answers to the questionnaire revealed that a few patients were using some of the newer medications that had been approved recently by the FDA for the reduction of neuropathic pain. However the vast majority of patients were continuing to take gabapentin and/or antidepressants, which have been clinical mainstays for many years for the treatment of neuropathic pain. Therefore, the results of this post-marketing survey may not apply to patients who have begun to use newer drugs. MIRE has not been reported to be associated with any systemic side effects. There have been a few reports of superficial burns when treatment guidelines were not followed.

Mechanism of Action

While the mechanism of action underlying neuropathic pain relief associated with MIRE is not well understood, it may be due, in part, to a combination of topical heat and an increased local release of nitric oxide that has been reported using this wavelength (890nm) of near infrared photo energy.[18,19] The source of released nitric oxide may be endothelial cells or red blood cells, or both.[20,21] Nitric oxide production is compromised in both type 1 and type 2 diabetic patients.[22-24] If near infrared light is able to favorably alter local nitric oxide availability in the diabetic patient, this may improve microcirculation via an alteration of cGMP-mediated vasodilation at the site of treatment.[25] Better blood flow may, in part, explain the symptomatic decrease in pain these patients.

Nitric oxide also appears to be able to mitigate pain via a mechanism similar to morphine,[26] namely via nitric oxide mediated production of cGMP and phosphorylation of ATP-dependent potassium channel activity.[27] There may be a significant analgesic effect of MIRE if local concentrations of nitric oxide are increased. Nitric oxide was not measured in any patient during MIRE treatments.

Study Limitations

There are, of course, limitations to our conclusions. First, information about the use and types of medications is based solely upon patient response to a health questionnaire administered just after the conclusion of outpatient MIRE therapy. However, since patients self-administer medications for neuropathic pain based on perceived pain levels or physician prescription, we believe they were competent to accurately comment on the use of medications during the fairly brief period of MIRE therapy (6-7 weeks). Additionally, the health questionnaire was very specif-

ic. Patients were required to name the actual medications they were taking for neuropathic pain; this increased the likelihood of an accurate response.

Second, we cannot ascertain with absolute certainty whether the decrease in pain intensity in this group of patients was not due to a "placebo effect" since there was no control group using either placebo MIRE or no treatment at all. However, these patients experienced a mean reduction of 64% in their pain intensity during MIRE treatments, which is much greater than either any placebo effect in response to infrared therapy (less than a 20% decrease in pain) for neuropathic pain[28] or the pain reductions documented with placebo treatment during clinical trials of duloxetine hydrochloride (Cymbalta®) and pregabalin (Lyrica®), which have been approved by the FDA for the management of neuropathic pain.[29,30] Furthermore, the magnitude of pain reduction among the present group of patients is consistent with other published reports on the effectiveness of MIRE for neuropathic pain.[7-10]

While our analysis permits us to conclude that the decrease in pain was not dependent on the concomitant use of medications (i.e., Group 1), we cannot exclude other possible variables that might have affected these outcomes. All patients received MIRE adjunctively as part of a plan of care that also included skilled therapies, if necessary, to improve balance and gait that are often complications of neuropathic pain.[31] However, we can find no published information indicating that balance and gait related physical therapy interventions, in and of themselves, are effective for the reduction of neuropathic pain. Moreover, in each of the medical records, the 456 attending physicians certified that, in their medical judgment, the reductions in neuropathic pain were in direct response to the MIRE treatments. Finally, many patients—either those using no medications for their pain or those who were taking one or more pain relieving drugs—responded equally well to MIRE despite, in some cases, having experienced neuropathic pain for over 99 months. This suggests that the duration of neuropathy may not be a complicating factor in the effect of MIRE plus physical therapy to diminish neuropathic pain.

Conclusion

Based on these data, MIRE—administered as part of a care plan prescribed by physicians—is associated with a substantial reduction in neuropathic pain. Use of MIRE may be an alternative for physicians to consider for patients with neuropathy, especially those who have obtained an unsatisfactory level of neuropathic pain relief while using various oral medications. MIRE might also be an alternative first line treatment in some patients with significant neuropathic pain who have not yet begun drug therapy. ■

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Anodyne therapy for recalcitrant diabetic foot ulcers: a report of four cases

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ABSTRACT

Four patients with diabetic foot ulcers that failed to heal after one month of treatment underwent anodyne therapy. Each therapy session lasted half an hour and was conducted 3 times a week for patients at home or daily for patients in hospital, for one to 2 months. The wound sizes and depths were graded according to the Wagner classification. Pictures were taken to evaluate the effects of anodyne therapy. All 4 patients had good healing of their foot ulcers. Anodyne therapy augments the effects of conservative treatment. Proper wound care and appropriate antibiotic coverage remain the basis of treatment.

Key words: *diabetic angiopathies; diabetic foot; diabetes mellitus; wound healing*

INTRODUCTION

Diabetes mellitus involved 8.2% of the Singaporeans aged 18 to 69 in 2004.[1] Foot ulcers take a longer time to heal in diabetics because of pathogenic abnormalities: intrinsic defects in blood supply, angiogenesis, and extrinsic factors of infection and trauma causing delayed healing.[2] Diabetic patients lack bioavailable nitric oxide (NO) resulting in poor blood supply in the foot.[3,4] Monochromatic infrared energy or anodyne therapy has been used to promote healing in diabetic foot ulcers, because it increases NO concentration in the bloodstream and dilates blood vessels in the foot.[5]

CASE REPORTS

Four patients with ulcers that failed to heal after one month of treatment underwent anodyne therapy. Their

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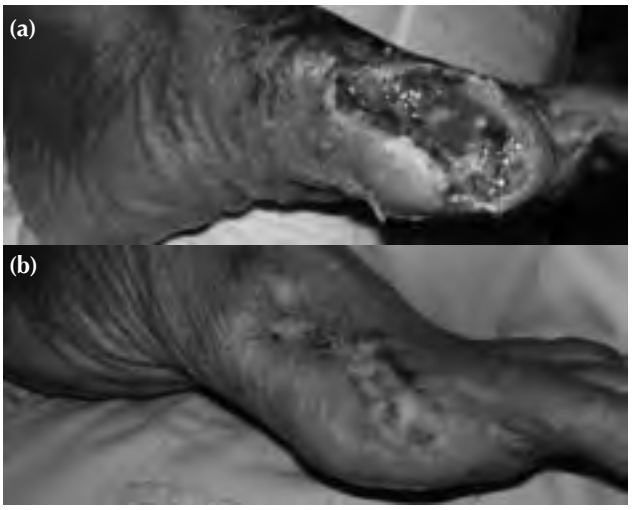

Figure 1 Patient 1: **(a)** grade-2 surgical ulcer measuring 5.5x3.5 cm, **(b)** completely healed ulcer at day 43.

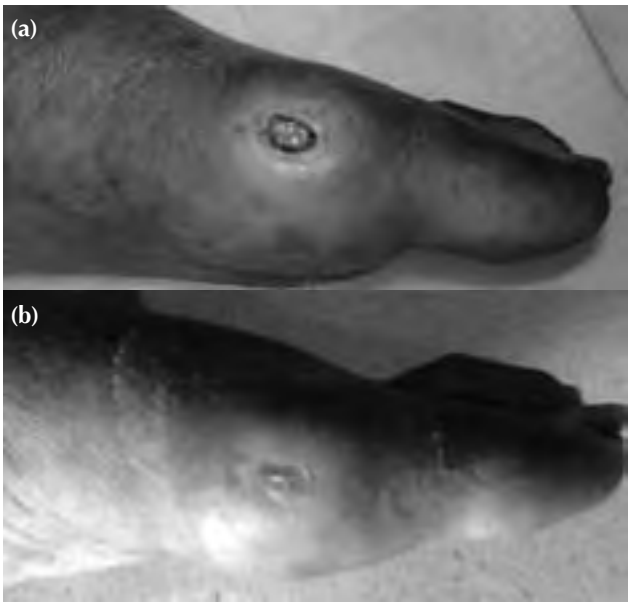

Figure 2 Patient 2: **(a)** grade-2 ulcer (capsule of metatarsophalangeal joint exposed) measuring 1.5 cm in diameter, **(b)** completely healed ulcer at day 34.

wounds were covered with clear plastic (Tagaderm), and anodyne therapy system pads were placed over the plastic to prevent contamination, and on the lateral and medial aspects of the ipsilateral calf. Each therapy session lasted half an hour and was conducted 3 times a week (Monday, Wednesday, Friday) for patients at home or daily for patients in hospital, for one to 2 months. Wounds were cleaned and dressed after each session to minimise disturbances to the wound. No adverse symptoms or events were noted in any patients during therapy. Patients were assessed for peripheral neuropathies, pedal pulses, and wound size before and after therapy. Pictures were taken at each session to evaluate the effects of anodyne therapy on wound healing. Wound sizes and depths were graded according to the Wagner classfication.[6]

Case 1

In February 2006, a 54-year-old woman with a 2-year history of diabetes presented with gangrene of the left big toe. She had no neuropathy, and both dorsalis pedis and posterior tibialis pulses were palpable. She underwent ray amputation and wound debridement. Anodyne therapy was performed for the grade-2 surgical ulcer measuring 5.5x3.5 cm thrice weekly at her home. After each session, the wound was cleaned with 5% chlorhexidine solution and dressed with tulle gras. The wound healed 43 days later (Fig. 1).

Case 2

In September 2005, a 73-year-old man with a 20-year history of diabetes sustained a fracture of his left fourth and fifth metatarsals after a fall. He was treated with a below-knee plaster cast. A small ulcer over the medial aspect of his left big toe was detected 2 weeks later. Both dorsalis pedis and posterior tibialis pulses were not palpable, and he had bilateral glove and stocking neuropathy up to his ankle. The ulcer was grade 2 (the metatarsophalangeal joint capsule was exposed), measuring 1.5 cm in diameter and was treated with dressings for 5 months without success. He underwent anodyne therapy thrice weekly at his home. After each session, the wound was cleaned with 5% chlorhexidine solution and dressed with polymem. The ulcer healed 34 days later (Fig. 2).

Case 3

In February 2006, a 68-year-old man with a 4-year history of diabetes presented with gangrene of the left fifth toe. Both dorsalis pedis and posterior tibialis pulses were palpable. He underwent ray amputation, followed by anodyne therapy thrice weekly at his home. The surgical ulcer was grade 2 in depth and measured 5x3.5 cm. After each session, the wound was cleaned with 5% chlorhexidine solution and dressed with duoderm gel. 45 days later, the wound shrank and measured 3x2 cm. Anodyne therapy was stopped and daily duoderm gel dressings continued. The wound healed completely after a further 21 days (Fig. 3).

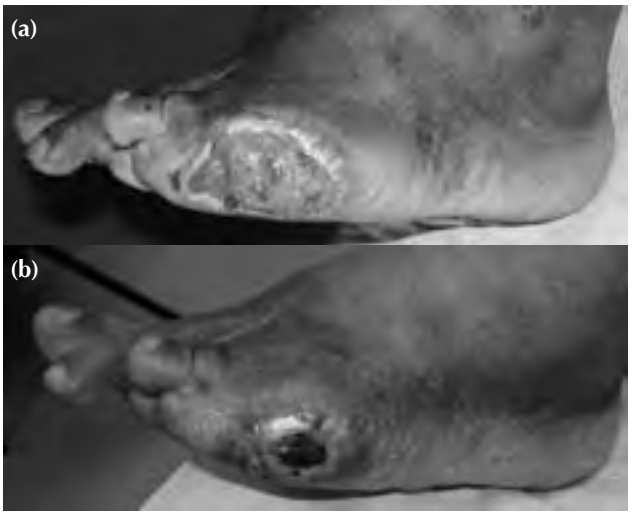

Figure 3 Patient 3: **(a)** grade-2 ulcer measuring 5x3.5 cm, **(b)** shrunken ulcer with clean granulating bed measuring 3x2 cm at day 45.

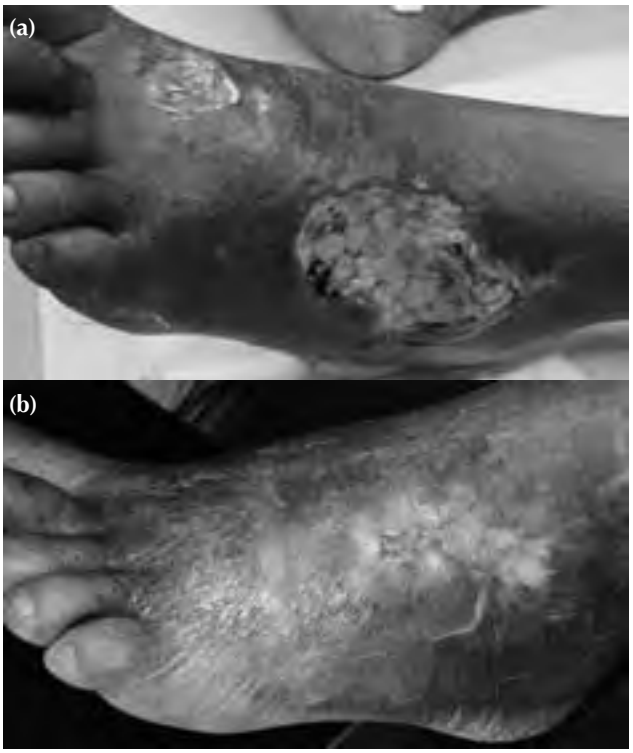

Figure 4 Patient 4: **(a)** grade-1 ulcers measuring 2.5x2 cm and 6x4.5 cm, **(b)** both ulcers healed completely at day 52.

Case 4

In January 2006, an 85-year-old woman with a 15-year history of diabetes presented with 2 superficial ulcers over the dorsum of her left foot. Both dorsalis pedis and posterior tibialis pulses were palpable, and the patient had no neuropathy. She underwent debridement and anodyne therapy. The ulcer on the medial side measured 2.5x2 cm and that on the lateral side near the lateral malleolus measured 6x4.5 cm. Both ulcers were grade 1. After each session, her wound was cleaned with 5% chlorhexidine solution and dressed with tulle gras. Both wounds healed 52 days later (Fig. 4).

DISCUSSION

NO is an endogenous vasodilator produced by endothelial NO synthetase during the oxidation of L-arginine to L-citrulline and NO.[3] Patients with diabetes often lack bioavailable NO due to reduced production of NO by NO synthetase and inactivation of NO by reactive oxygen species produced by glycated proteins or from vascular endothelium.[3,4] A small proportion of NO released into the vascular lumen is also transported in blood in the form of S-Nitrosothiol attached to haemoglobin.[4,7] In diabetic patients with elevated levels of glycated red blood cells, an increase in NO binding to red blood cells decreases delivery of vasoactive NO to hypoxic tissues.[4]

Monochromatic infrared energy (MIRE) treatment may increase local and systemic levels of NO in diabetic patients. NO has been found to be liberated from haemoglobin on exposure to various wavelengths of energy.[8] Plasma NO in non-diabetic subjects increased after MIRE application to the skin for 30 minutes.[5] The exact mechanism is still unknown. Far infrared therapy (FIR) in a rat model stimulated skin blood flow, which was maintained for a period afterward. This increase in circulation was mainly due to an increase in NO synthetase activity, rather than a hyperthermic effect, as this post-FIR enhancement of skin blood flow can be inhibited by NG-nitro-L-arginine methyl ester, an inhibitor of NO synthetase activity.[9,10] The foot circulation increased in diabetic patients with microangiopathy after treatment with visible red monochromatic energy, and this was sustained even after the treatment discontinued.[11] Hence, anodyne therapy is useful for patients with diabetic foot ulcers and poor blood supply; it has successfully healed wounds that have become stagnant or deteriorated.[5,12,13]

Our study lacks controls not receiving anodyne therapy nor wound dressings to compare with our subjects. Anodyne therapy is labour intensive. A thrice-weekly home visit is difficult to implement and limits the number of treated patients. A viable alternative is to provide patients with home therapy units. The patients could first be educated about its use and then perform the therapy sessions themselves. This is already practised in the United States where patients may rent-to-own an anodyne therapy system. Another option would be to establish anodyne therapy centres in local hospitals and polyclinics similar to those in the United States, where patients receive such therapy regularly.

CONCLUSION

Anodyne therapy enhances the healing of ischaemic foot ulcers in diabetic patients. Proper wound care and use of appropriate antibiotics remain the basis of treatment, as anodyne therapy augments, but is not a substitute for, conservative treatment.

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CASE REPORT Open Access

Use of near-infrared light to reduce symptoms associated with restless legs syndrome in a woman: a case report

Ulrike H Mitchell

Abstract

Introduction: We describe a potential new treatment option for patients suffering from restless legs syndrome. Contemporary treatment for restless legs syndrome consists mostly of dopaminergic drugs that leave some patients feeling nauseated and dizzy. A non-invasive, drug-free option would open new doors for patients suffering from restless legs syndrome.

Case presentation: A 69-year-old Caucasian woman met International Restless Legs Syndrome Study Group criteria for the diagnosis of restless legs syndrome. She had been afflicted with restless legs syndrome for over 30 years and tried many of the available pharmaceutical remedies without success. For this study she received 30-minute treatment sessions with near-infrared light, three times a week for four weeks. The restless legs syndrome rating scale was used to track symptom changes; at baseline she scored "27" on the 0 to 40 point scale, which is considered to be "severe". Our patient was almost symptom free at week two, indicated by a score of "2" on the rating scale. By week four she was completely symptom free. The symptoms slowly returned during week three post treatment.

Conclusions: The findings suggest that near-infrared light may be a feasible method for treating patients suffering from restless legs syndrome. Undesirable side-effects from medication are non-existent. This study might revive the neglected vascular mechanism theory behind restless legs syndrome and encourage further research into this area.

Introduction

Restless legs syndrome (RLS) is a chronic sensorimotor disorder, characterized by a strong urge to move, accompanied or caused by uncomfortable or even distressing paresthesia of the legs, described as a creeping, tugging, "pulling" feeling. The symptoms often become worse throughout the day, leading to sleep disturbances or deprivation and, consequently, to impairment of alertness and daytime functions [1]. The symptoms are usually lessened by movement [2].

The diagnosis of RLS is clinical and based on a patient's description of the symptoms. In an attempt to standardize diagnostic procedures, the International Restless Legs Syndrome Study Group (IRLSSG) identified four criteria to substantiate the diagnosis of RLS [3]. To meet the criteria the patients had to answer the four questions affirmatively. The questions explore whether the subjects have an urge to move their legs, whether the symptoms begin or worsen during periods of inactivity, whether the urge to move is at least partially relieved by movement, and whether this urge to move is worse in the evening or night [3]. The IRLSSG also defined three supportive features. While they are not essential to the diagnosis of RLS, their presence can help resolve diagnostic uncertainty; they are: family history, presence of periodic limb movement and the response to dopaminergic treatment [3].

The IRLSSG developed the International Restless Legs Scale (IRLS) for measuring severity of the symptoms and their impact on a person's life [3]. The scale evaluates and reflects subjective assessment of the primary features, intensity, and frequency of the disorder and associated sleep problems as well as the impact of the symptoms on a patient's mood and daily functioning [4]. The 10-question scale has five response options with an

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associated score from "0" (no impact or symptoms) to "4" (severe), yielding a maximum score of 40. Hoegl and Gschliesser [5] reviewed several assessment tools used for RLS patients. They strongly support the use of the IRLS as the gold standard for assessing disorder severity. They also recommend it as a tool to follow changes in a subject's status and suitable for repeated measurements.

The pathophysiology of RLS is not fully clear. RLS can be classified into primary or secondary forms, delineating genetic and idiopathic contributions or involvement of other underlying pathologies respectively. Secondary RLS is usually dealt with by treating the underlying causes or associated medical conditions. For primary RLS dopaminergic medications are considered first line treatment for their effectiveness and usual rapid and dramatic improvement of the symptoms [6]. Other drugs, such as opioids (methadone, hydrocodone), GABA analogue (gabapentin, pregabalin), and benzodiazepines (clonazepam) are also used to treat moderate to severe RLS [6,7]. Until May 2005 there were no FDA-approved drugs on the market for the treatment of RLS. Now ropinirole and pramipexole, both dopamine agonists, are available. Unfortunately these drugs can cause insomnia, nausea, dyspepsia, and dizziness [8]. Since the drugs only provide symptomatic relief and are not considered a cure, the benefit of the treatment should justify any potential side effects and costs [6]. Non-pharmacological treatment of RLS includes improving sleep quality by controlling sleep times, reducing caffeine and alcohol consumption, and maintaining a daily moderate exercise program [9]. The efficacy of these options has not been well documented and is limited.

Promising alternative treatment choices are welcomed options. One of them might already be on the market, but is currently used for other disorders: near-infrared light (NIR). It is utilized for patients with neuropathy to increase sensation and decrease pain. NIR has a wavelength of 880 nm to 890 nm and is emitted through diodes [10]. For this case report Anodyne was used, but there are other similar devices available for healthcare providers. Anodyne is FDA approved for increasing circulation and reducing pain, and it has been successfully used in wound management [11]. Researchers hypothesize that the success of NIR treatment lies in its ability to increase bioavailability of nitric oxide (NO) in the lumen. In 1992 NO was hailed as the molecule of the year for its significant role in vasoregulation, neurotransmission, signal transduction, anti-microbial defense, and digestion [12]. It is produced by the enzyme nitric oxide synthase (NOS-3), which is activated by, among other factors, shearing forces generated by blood flow that act on the vascular endothelium [13]. Nitric oxide is also found tightly bound to the hemoglobin contained in erythrocytes. It has been suggested that NO can be released from this bond through intensive illumination [14]. Once generated, NO initiates a cascade of events, leading to vasodilation and increased blood flow.

After being treated for neuropathy for 30 minutes with NIR, three times a week for four weeks, three patients reported that, while their neuropathy was better, they were more excited that their RLS symptoms had either decreased or been eliminated. These findings prompted this investigation into the effectiveness of NIR therapy for the treatment of symptoms associated with RLS.

Rationale

Treatment with NIR has been shown to increase blood flow, possibly due to its ability to generate NO in the endothelium. Nitric oxide has also been linked to improved neurotransmission. It is thus conceivable that tissue treated with NIR could impact RLS, a neurological disease, and decrease the symptoms associated with it.

This case report was part of a randomized, controlled study (not yet published), which was approved by the institutional review board at Brigham Young University, Provo, Utah.

The purpose of this report is, therefore, to describe an investigation that was conducted on the effectiveness of using NIR to decrease symptoms associated with RLS. Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Case presentation

A respondent to a newspaper advertisement with symptoms of RLS, was recruited for this case report. During the evaluation she was asked about her symptoms–RLS can only be diagnosed based on subjective findings–and she met the four IRLSSG criteria [3].

Our patient was a 69-year-old Caucasian woman (1.63 m, 63.5 kg) who described her general health status as "good". Her activity level was "reasonably active"; she walked in the mornings and did some occasional yoga. She did not complain of any mobility decreases and enjoyed good flexibility. Her sleep pattern was disturbed, mostly because of her RLS symptoms. Her urge to move her legs was especially strong every evening. She had difficulty falling asleep and could only do so after taking zolpidem 10 mg (Ambien). She also reported having been diagnosed with depression and had taken 20 mg fluoxetine (Prozac) daily for almost 25 years. Our patient never made a connection or noticed a correlation between the antidepressant and RLS symptoms. She complained of constant tiredness and fatigue, due to restless sleep. Our patient was not aware of any other

family member before her suffering from RLS. Her father had "circulation problems" in his legs, but details are unknown. However, both of her daughters, aged 43 and 39, reported symptoms of RLS. Neither of them was taking medication for RLS. Our patient's chief complaints were painful sensations in her legs and hips, triggering an urge to move the legs, as well as sleep disturbance. Her social life suffered due to her inability to sit still when going to the movies or the theater or when flying in a plane. She remembered having suffered from RLS before she knew her symptoms had a name–that was about 30 years ago. Since then the symptoms had become more pronounced. For many years she did not receive treatment for the symptoms, because doctors did not recognize her condition–until four years ago, when her family doctor diagnosed her with RLS. At that time she was given muscle relaxants (names not known), but they did not change her symptoms. Consequently, she was given a benzodiazepine (Clonazepam) combined with a sedative (zolpidem). Although her sleep improved, the symptoms associated with RLS remained. When ropinirole became available on the market as one of two FDA approved drugs for RLS, she tried the Starter Kit, where the pills with increasing strength were marked each day they needed to be taken. After less than two weeks she discontinued taking the drug because it made her feel "horrible". Our patient does not remember having had a positive response from the drug, just side effects. The side effects included nausea, balance problems, impaired thinking ability, and, worst of all, remaining RLS symptoms. Our patient was not aware of ever having periodic limb movements, in sleep or at rest.

She responded to the newspaper advertisement for this study because she hoped that some treatment would be available for her. She gave written informed consent to take part in this trial.

Vital signs: blood pressure is 120/78 with a pulse rate of 68. Sensation in lower extremities including feet was intact as measured with Semmes-Weinstein monofilament. The patient was non-diabetic.

Pathologies such as hypertension, arthritis, gastroesophageal reflux disease, depression, anxiety, and diabetes, as well as several lifestyle factors such as increased body mass index, lower income and being unemployed, smoking, lack of exercise, less than six hours of sleep, and low alcohol consumption are linked to this disorder [15]. With the exception of depression, our patient had none of the above.

Our patient exhibited normal range of motion in upper and lower extremities and trunk. Strength was graded 5/5 in all major muscle groups.

The history, systems review, and other examination findings seemed to corroborate her diagnosis of RLS; the differential diagnosis of neuropathy could be excluded.

Based on anecdotal evidence of NIR reducing symptoms associated with RLS, our patient received twelve 30-minute NIR treatment sessions. This is the same protocol that is used nationwide for neuropathy treatment.

The treatments were administered three times a week for four weeks. No other treatment was given, and our patient was asked not to change anything in her daily routine. She lay comfortably on a treatment bench in a quiet room at 21°C (+1°). For comfort, the knees were supported by a five-inch bolster. The lower leg skin area was covered with plastic wrap, which acted as a barrier between skin and diodes to ensure compliance with infection control procedures. Eight flexible monochromatic near-infrared photo energy diodes (60 on each pad) were placed on the lower legs. During each treatment the output was adjusted to the highest level of intensity. After a 30-minute supervised treatment period with NIR, the diodes and plastic wrap were removed. During the Anodyne treatment our patient received an 890 nm wavelength light, pulsed at 292 times/s, with a power output of 600 mW/cm^2. Our patient was asked to fill out a validated RLS self-rating scale[4] in the week before treatment, at the end of each treatment week, one week after and three weeks after cessation of treatment. It was determined that treatment with NIR therapy was deemed to be successful if the patient improved by 10 points on the scale after four weeks of treatment.

Our patient scored a "27" (out of "40") at her first visit, "14" after her first treatment week, "2" after her second week, and "1" after her third week. Weeks four and five were scored a "0" (no symptoms) (Figure 1). The symptoms associated with RLS decreased from "severe" (27/40 possible points on IRLS) to "no symptoms" (0/40 possible points on IRLS) after four weeks of treatment. Our patient stated that she felt marked improvement in every aspect of living. In her own words, –It has changed my "life". Our patient reported that the symptoms returned slowly during week seven and were at a "15" by the end of week eight (four weeks post treatment).

Discussion

The pathophysiology of RLS is not clear. In the 1940s and 1950s it was hypothesized that decreased blood flow was responsible for the symptoms associated with RLS [16]. Ekbom [2] believed that vasodilators given to RLS sufferers would decrease the symptoms. Today it is widely accepted that the central nervous system is involved in RLS, but the original hypothesis of a vascular association still exists. One study reports that increased vascular blood flow with enhanced external

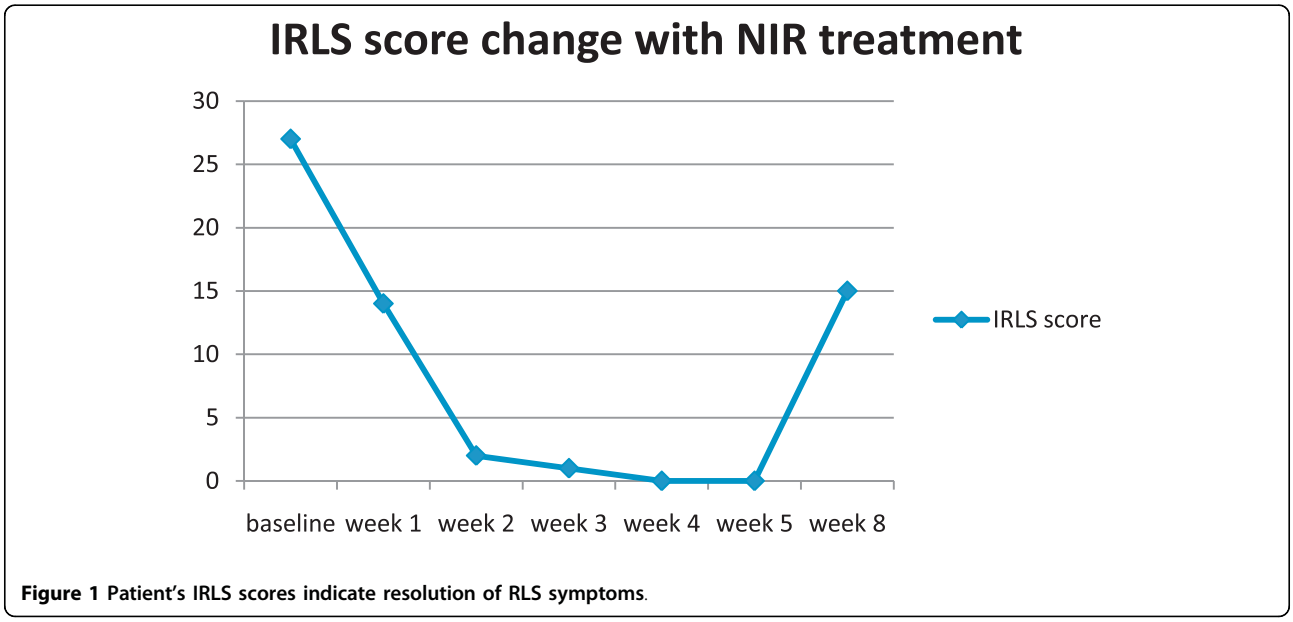

Figure 1 Patient's IRLS scores indicate resolution of RLS symptoms.

counter pulsation significantly decreased RLS symptoms in six patients [16]. Another study [17] showed a high prevalence (36%) of RLS in patients presenting with chronic venous disorder. The author of this case report theorizes that the symptoms associated with RLS could stem from a feedback mechanism where decreased tissue perfusion in the legs signals to the brain the need to move. Activity, such as movement or walking, increases blood flow to the muscle and tissue [18]. The proposed mechanism of NIR therapy is its ability to generate NO in the endothelium [19] and even in the lumen directly by dissociating NO from hemoglobin contained in erythrocytes [14,20]. Nitric oxide is able to initiate and sustain vasodilation [21,22] and, as a neurotransmitter itself, has influence on neurotransmission [22]. Phototherapy, which includes NIR, has been known to decrease pain by changing cell membrane permeability. This leads to enhanced synthesis of endorphins, increased nerve cell potential and hence to pain relief [23]. NIR consequently can affect three factors associated with RLS: vasodilation [16], neurotransmission [24] and pain relief [25]. It is thus conceivable that NIR could positively impact this pathology. Recent findings could validate this hypothesis as well as function as the missing link between theory and fact. A German study [26] discovered significant evidence for an association of RLS with sequence variations in the NOS1 gene, pointing to a possible involvement of the NO/arginine pathway in RLS disease susceptibility and in the etiology of RLS.

Other factors may have contributed to our patient's improvement. As in the study by Ferini-Strambi *et al.* [7], where IRLS scores decreased in medicated and non-medicated RLS patients after taking part in weekly group sessions, the social interaction between therapist and subject could have contributed to her improvement. However, the therapist/subject interaction in this case report was kept within the limits of a typical therapist/patient relationship and was not intended or designed to have a "support group" character.

A recent meta-analysis [27] assessing the placebo effect in RLS treatment studies found a substantial placebo response associated with RLS treatment. This response was greater for the IRLS compared to other scales, possibly related to its multidimensional assessment character. On average, more than one-third of RLS subjects experienced a major improvement of RLS symptoms while receiving placebo treatment. The author proposes that the reason for this might be related to the unique responsiveness of RLS to dopaminergic agents and opioids - both systems implicated in the placebo response. The question of whether our patient's improvement was likely due to a pure placebo effect can only be answered by conducting a randomized controlled trial.

Conclusions

This case report shows how NIR helped one patient suffering from RLS symptoms to eliminate her symptoms and suggests that this protocol might be a potential treatment option for other, similar patients. One patient received 30-minute NIR treatment sessions, three times a week for four weeks. This regimen was taken from a protocol used in home health to treat patients with neuropathy. If treatment with NIR could be used to alleviate RLS symptoms, the patients would be able to benefit greatly from this non-invasive option.

This report adds to existing studies as it suggests a different, non-drug-related treatment option to patients who would otherwise have to take dopaminergic or other drugs. The mechanisms with which NIR can alleviate RLS symptoms are not clear. One supposition can be made: light has been shown to generate NO in the endothelium, which through a cascade of events leads to vasodilation. Vasodilation is also the result of exercise [18], one of the few non-drug related treatment options that decreases RLS symptoms. While no direct relationship between NO and RLS symptoms can be shown, it is plausible that this radical, generated in the lumen of blood vessels, might have similar benefits to the patients as exercise. Further research into this hypothesis is suggested.

It is of course too early to suggest that treatment with NIR is the best treatment option for patients suffering from RLS; a randomized clinical trial would shed more light on the usefulness of this treatment.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The author declares that they have no competing interests.

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RESEARCH REPORT

Restless legs syndrome and near-infrared light: An alternative treatment option

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ABSTRACT

There are few treatment options in managing restless legs syndrome (RLS); the most frequently used are dopaminergic drugs and movement. New treatment options are highly sought after. This study evaluated the effectiveness of monochromatic near-infrared light treatment in decreasing symptoms associated with RLS. The design used was 2×6 repeated-measures design with two groups (treatment and control) and six repeated measures (baseline, weeks 1–4, and posttreatment). Data collection took place in the university modalities laboratory. Thirty-four volunteers with symptoms of RLS were randomly assigned to a treatment or control group. Over a 4-week period subjects underwent twelve 30-min treatments to their lower legs with near-infrared light. The International RLS rating scale (IRLS) was used to assess and track patient symptoms. There was a steady decrease in symptoms associated with RLS over the 4 weeks in the treatment group. After 4 weeks of treatment the treatment group had a significantly greater improvement in restless legs syndrome symptoms than the control group ($p<0.001$); improvement was still significant after 4 weeks posttreatment compared to baseline ($p<0.001$). Treatment with near-infrared light does decrease symptoms associated with RLS as demonstrated in lower IRLS scores. This new noninvasive method of treating RLS might become a valuable new management option. More research is needed to determine the mechanism(s) behind infrared light treatment and RLS.

INTRODUCTION

Restless legs syndrome (RLS) has troubled many people over the centuries (Ekbom, 1960). It is characterized by a strong urge to move, accompanied or caused by uncomfortable, or even distressing paresthesia of the legs, described as a "creeping, tugging, pulling" feeling (Ekbom, 1960). The symptoms often become worse as the day progresses, leading to sleep disturbances or sleep deprivation that further results in impairment of alertness and daytime functions (Kushida, Allen, and Atkinson, 2004).

Ekbom (1960), who first described and defined this disease in modern days, reported that 24% of people with low serum iron levels (levels<60 μg/L) exhibit RLS symptoms and that these symptoms decreased when treated with iron injections. More recent research corroborated the association of low serum ferritin levels (<50 μg/L) with RLS (Lee, Zaffke, and Baratte-Beebe, 2001; Sun et al, 1998; Thorpy, 2005). Other pathologies, such as diabetes mellitus, end stage renal disease, vitamin B_{12} deficiency, folate deficiency (Lee, Zaffke, and Baratte-Beebe, 2001), or Parkinson's disease (Appiah-Kubi, Pal, and Chaudhuri, 2002), have been connected to RLS.

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In the 1940s and 1950s it was hypothesized that decreased blood flow led to the symptoms associated with RLS (Rajaram et al, 2005). Ekbom (1960) believed that vasodilators given to RLS sufferers would decrease the symptoms. The vascular hypothesis was later neglected until 2005, when increased vascular blood flow with enhanced external counter pulsation (EECP) was shown to significantly decrease RLS symptoms in six patients (Rajaram et al, 2005). Another study (McDonagh, King, and Guptan, 2007) showed a high prevalence (36%) of RLS in patients presenting with chronic venous disorder. This might be another piece of evidence that RLS is at least in part associated with vascular changes.

There are few options in managing RLS. Dopaminergic agents, such as levodopa and dopamine agonists are the best-studied drugs to date (Oertel et al, 2007) and are now considered the treatment of choice for RLS (Ferini-Strambi et al, 2008). Until May 2005 there were no FDA-approved drugs for the treatment of RLS on the market. Now ropinirole hydrochloride and pramipexole, both dopamine agonists, are available. Unfortunately, these drugs can have side effects, such as nausea, vomiting, dizziness, and somnolence (Ferini-Strambi et al, 2008). Recent research (Ondo, 2009) questions dopamine deficiency as being the reason for RLS.

Nonpharmacological treatment choices for RLS are welcomed options. Because the symptoms are usually lessened by movement (Ekbom, 1960), walking is considered as a management alternative (Oertel et al, 2007), but it loses its attraction when the patient wants to go to sleep. It was recently shown in a randomized controlled trial that a 3-day per week exercise program of aerobic and lower-body resistance training significantly decreased RLS symptom severity (Aukerman et al, 2006). No explanations of the mechanism behind the success of exercise were given, but it is conceivable that the increase in blood flow that results from activity played a role (Clifford and Hellsten, 2004). Other than regular exercise (Aukerman et al, 2006), nonpharmacological treatment choices for RLS include improving sleep quality by controlling sleep times and by reducing caffeine and alcohol consumption (Aukerman et al, 2006; Ferini-Strambi et al, 2008; Oertel et al, 2007; Thorpy, 2005). The success of the latter choices is not well documented. There is a need for other alternative treatments.

Based on anecdotal evidence of clinical success, this study examined another drug-free option; a device that delivers monochromatic near-infrared light (NIR). The Anodyne® therapy system is a noninvasive, drug-free device that delivers light with a wavelength of 890 nm through diodes (Anodyne Therapy, 2007). The proposed mechanism of infra-red light therapy is its ability to generate nitric oxide in the endothelium (Matsunaga and Furchgott, 1989). Nitric oxide is able to initiate and maintain vasodilation (Ignarro, Buga, Wood, and Byrns, 1987; Moncada, Palmer, and Higgs, 1991), and it has influence on neurotransmission (because it is a neurotransmitter itself) (Moncada, Palmer, and Higgs, 1991). Phototherapy, which includes NIR, elicits changes in cell membrane permeability, leading to enhanced synthesis of endorphins, increased nerve cell potential and hence pain relief (Hawkins and Abrahamse, 2007). The following three factors have been associated with RLS: 1) vasodilation (Rajaram et al, 2005); 2) neurotransmission (Trenkwalder and Paulus, 2004); and 3) pain relief (Winkelmann et al, 2000). Therefore, it is conceivable that NIR could positively impact this pathology. The primary purpose of this randomized single blind clinical trial was to investigate the effectiveness of monochromatic near-infrared light energy in decreasing symptoms associated with RLS compared to a sham treatment. Our secondary post hoc analyses examined the relationships between familial and non-familial RLS and their symptom resolution as well as serum ferritin levels and symptom changes.

METHODS

Experimental design

This is a 2×6 repeated-measures design with two groups (treatment and control) and six repeated measures (baseline, weeks 1–4, and posttreatment) over time. An analysis for necessary sample size, taking into account the variability associated with the RLS scale (Ferini-Strambi et al, 2008) and a self-determined clinical significant change in RLS score of 10 points (representing a 25% change), yielded a sample size of 34 subjects, 17 each in the treatment and control groups.

Subjects

From January 2009 through August 2009, 34 volunteers with symptoms of RLS were recruited for this study. The recruitment approaches were newspaper advertisements and flyers.

Inclusion criteria

Subjects had to meet the four minimal criteria established by the International Restless Legs Syndrome Study Group for the diagnosis of RLS (Allen et al, 2003) to be admitted to the study. Subjects did so by answering affirmatively to questions on whether

1) they have an urge to move their legs, 2) symptoms begin or worsen during periods of inactivity, 3) the urge to move was at least partially relieved by movement, and 4) this urge to move was worse in the evening or night (Allen et al, 2003). Other investigations (Aukerman et al, 2006; Clavadetscher, Gugger, and Bassetti, 2004; McDonagh, King, and Guptan, 2007; Minai et al, 2007; Rajaram et al, 2005) used these criteria to identify subjects for their studies. The subjects had to score at least 11 points on the International RLS rating scale (IRLS) (The International Restless Legs Syndrome Study Group, 2003). This threshold was chosen because 11–20 points is considered to represent a "moderate" severity level of this pathology (The International Restless Legs Syndrome Study Group, 2003). The subjects had to have good skin integrity and no obvious signs of impaired circulation, as verified by visual inspection.

Exclusion criteria

The following subjects were excluded from the study: subjects who were not able to read the English informed consent form and RLS questionnaire; subjects who exhibited decreased sensation of the sole and dorsum of the feet, as tested by light manual touch; and subjects who were not able to come to the university campus the assigned number of times.

One subject from the control group decided not to continue the study after four treatments. He started having problems with focusing his eyes and his optometrist recommended discontinuance. This person was replaced. The demographic characteristics of subjects in the treatment and control groups are found in Table 1.

Instrumentation

The devices used in this study were Anodyne® Therapy System 480 (Anodyne Therapy, Tampa, FL). The device consists of a base power unit and 8 therapy pads, each containing 60 gallium aluminum arsenide diodes. The area of Anodyne LEDs per therapy pads is 22.5 cm^2, yielding a total treatment area of 180 cm^2. The Anodyne® therapy system delivers pulsed light at 292 Hz with a wavelength of 890 nm through the diodes (Anodyne Therapy, 2007). The active unit provided 62.4 Joules/cm^2 of energy density. For this study the treatment unit output was preset at 10 bars (maximum output) by the manufacturer. No adjustments could be made by the investigators. The manufacturer disabled the control unit so that no light or other energy was emitted, but the panel showed the same 10 illuminated bars as the treatment unit.

TABLE 1 Demographics of the two groups

	Treatment mean (SD)	Control mean (SD)
Age (yr)	54.4 (14.3)	55.5 (17.1)
How long symptoms (yr)	17.6 (19.3)	12.7 (13.3)
IRLS baseline score	24.5 (5.3)	23.6 (6.9)
	n (%)	*n* (%)
Female	12 (71)	8 (47)
Positive family history	9 (53)	12 (71)
Ferritin<50 ng/mL	9 (53)	9 (53)

The tool that allowed us to track improvement of the patients' symptoms was a validated RLS rating scale (IRLS) (The International Restless Legs Syndrome Study Group, 2003). This 10-question survey evaluated different facets of the disorder: 1) subjective assessment of the primary features (questions 1, 2, 3, 6); 2) intensity and frequency (questions 7, 8); 3) associated sleep problems (questions 4, 5); and 4) the impact of patient's symptoms on mood and daily functioning (questions 9, 10) (The International Restless Legs Syndrome Study Group, 2003). The 10-question scale has 5 response options with an associated score from 0 (no impact or symptoms) to 4 (severe), yielding a maximum score of 40. Hoegl and Gschliesser (2007) reviewed several assessment tools used for patients with restless legs syndrome. They strongly support the use of the IRLS rating scale as the gold standard for assessing the severity of the disorder. Other studies have used the IRLS exclusively to track changes associated with RLS symptoms (Aukerman et al, 2006; Clavadetscher, Gugger, and Bassetti, 2004; Minai et al, 2007).

Procedures

The study was approved by the university institutional review board. The patients read and signed an informed consent and were randomly assigned to the treatment or control group by drawing a number "1" or "2" out of a bag. The subjects indicated their RLS-relevant medication intake. For our secondary study purposes we conducted post hoc analyses. First, we classified the subjects into "familial" "and nonfamilial" RLS (Kimura and Winkelmann, 2007). This was done by interview. A person was classified as having "familial RLS" if at least one immediate family member had symptoms of RLS and "nonfamilial RLS" if no immediate family member had symptoms of RLS, or when it was unknown. Second, we grouped the subjects into "low ferritin" (<50 μg/L) and "normal ferritin" (≥50 μg/L) levels. Their blood was

drawn at a local hospital, at no cost to the subjects, before the first treatment and serum ferritin levels were obtained. The subjects' specific treatment days and times were established; the anticipated routine was Mondays, Wednesdays, and Fridays, preferably always at the same time. If the patient was not able to keep an appointment, it was made up on any of the other weekdays.

All subjects independently completed the IRLS on six occasions: 1 week prior to treatment (baseline); at the end of each week of treatment (weeks 1–4); and 1 week after cessation of treatment (post 1). In addition to these 6 weeks of data collection, the near-infrared treatment group was also asked to complete the IRLS at 4 weeks posttreatment (post 4). No data were collected 4 weeks after cessation of treatment from the control group. When subjects had questions concerning the IRLS, the primary investigator provided clarification.

The treatment group underwent 12 treatments with near-infrared light. The control group received 12 sham treatments, where no actual light was administered. The treatment frequency for both groups was three times a week for 4 weeks. No other treatment was given. The subjects were encouraged to maintain their level of medication and to make changes only after confirming with their doctor. At the end of each week the subjects were asked about any changes of medication in the preceding week.

Each subject sat comfortably in a quiet room at 21°C (±1°). The skin of the treatment area was covered with plastic wrap as a barrier between the skin and the diodes to ensure compliance with infection control procedures. Eight flexible monochromatic near-infrared photo energy diodes (60 on each pad) were placed on the lower legs and fastened with a strap. The energy setting was at 10 bars for every patient, as recommended by the Anodyne Therapy, LLC (Anodyne Therapy, 2005). After a 30-minute supervised treatment period with the Anodyne® system, the diodes and plastic wrap were removed.

Data analysis

To ascertain initial comparability in RLS severity, the baseline IRLS scores from the treatment and control groups were compared by using a two-sample t-test. The effect of 4 weeks of NIR treatment on severity of RLS symptoms was assessed by using ANCOVA. The outcome was the difference in baseline and week 4 IRLS scores; therefore, negative differences indicated a decline in severity and positive differences indicated an increase in severity. The analysis was controlled for gender. Finally, to explore at what point in time a discernible and significant difference in symptom amelioration between the treatment and control groups might occur, a series of two-sample t-tests were performed, with the outcomes being the differences in baseline and the 4 weeks of treatment. Because the intent of this latter analysis was simply exploratory, no Bonferroni correction was made to the significance level of these tests to maximize the power of the tests to detect potential differences.

RESULTS

Demographics for both treatment and control groups are presented in Table 1. RLS related drug intake was similar in both groups (Table 2). At baseline, the treatment and control groups were not significantly different in severity of RLS symptoms ($p=0.68$); however, after 4 weeks of near-infrared light treatment and after controlling for gender, the treatment group had significantly greater improvement in symptoms than the control group ($p<0.001$) (Table 3). There was no baseline by treatment interaction, indicating that the treatment effect was similar for all patients, regardless of the initial severity of their symptoms. After 1 week posttreatment, the treatment group continued to be significantly better than the control.

TABLE 2 RLS medication for the two treatment groups

	Treatment group	Control group
None	9	8
Ropinirole	5	4
Pramipexole	2	3
Gabapentin	1	1
Hydrocodone	0	1

TABLE 3 Decrease in mean IRLS score from baseline; comparison between groups

	Change from baseline (±SD)		
	Control $n=17$	Treatment $n=17$	p-value for t-test of change
Week 1	−2.0 (±3.5)	−4.2 (±3.8)	0.09
Week 2	−3.1 (±4.1)	−9.7 (±7.3)	0.003*
Week 3	−4.4 (±4.7)	−10.1 (±8.2)	0.02*
Week 4	−4.4 (±3.6)	−12.7 (±7.7)	0.001*
Week 1 posttreat	−4.5 (±5.0)	−13.4 (±8.1)	0.001*
Week 4 posttreat	n/t	−8.5 (±6.5)	n/a

*Significant difference between improvement in two groups at an alpha level of 0.05.

Both groups significantly improved over time. The mean decrease in the IRLS score within the treatment group after 4 weeks of treatment was 12.7 (±7.7) compared to a decline of 4.4 (±3.6) within the control group. In the treatment group the range of improvement was as small as 4 points and as large as 30. Two of the 17 subjects in the treatment group reported a complete resolution of RLS symptoms. On average, there was a steady decline in RLS symptoms over the 4 weeks of treatment for the subjects receiving the NIR treatment (Figure 1). All except one subject reported some improvement after the first week of near-infrared light treatment. However, in the control group there was a small initial improvement in symptoms after 1 week of treatment and very small changes after the second and third week of treatment. On the basis of the exploratory analysis, significant differences in symptom improvement between the treatment and control groups might appear as soon as 2 weeks of treatment (Table 3).

In the treatment group at 1 week posttreatment, 7 (41%) subjects reported an increase in symptoms compared to the week before, 5 (29%) reported no change in symptoms, and 5 (29%) reported a continued decrease in symptoms. However, of the 15 subjects who provided data at 4 weeks posttreatment, 10 (67%) reported an increase in symptoms compared to 1 week posttreatment, and 4 (27%) reported improvement. In the control group at 1 week posttreatment, 7 (41%) subjects reported an increase in symptoms from week 4 (conclusion of treatment), 6 (35%) reported no change in symptoms, and 4 (24%) reported a decrease in symptoms.

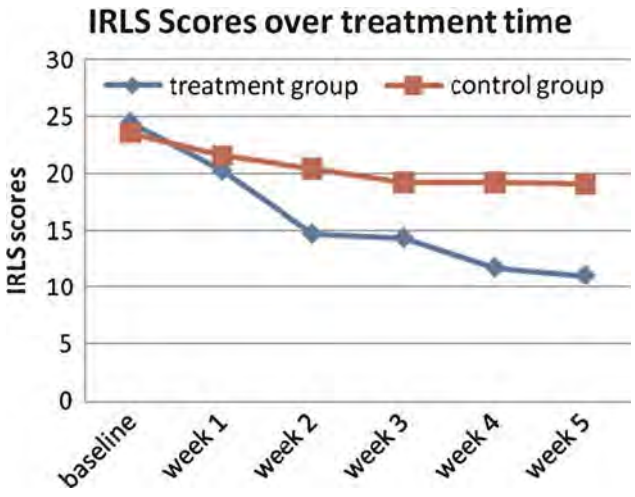

FIGURE 1 Improvement in IRLS scores over 4 weeks of treatment and 1 week posttreatment.

Post hoc analyses

Of the 34 patients who participated in our study, 18 had low ferritin levels; 9 in treatment group (average 19.2 μg/L, 3.4–42.6 μg/L; treatment group average 54 μg/L) and 9 in the control group (average 20.12 μg/L, from 5.8 to 38.7 μg/L; control group average 48 μg/L). The within-group comparisons between subjects with normal and low ferritin level revealed no difference in groups at baseline or after week 4 or 5 for either treatment (p=0.65, 0.13, and 0.43, respectively) or the control group (p=0.12, 0.14, 0.12, respectively).

Within-group comparisons between familial (F) and nonfamilial (NF) RLS were made to assess whether one reacted better to the treatment than the other. There was no difference in F-NF groups at baseline or after week 4 or week 5 for either the treatment (p=0.87, 0.38, and 0.89, respectively) or the control group (p=0.51, 0.21, 0.32, respectively).

DISCUSSION

RLS can be a life-impacting pathology for which only few treatment options exist. This study evaluated the efficacy of infrared treatment to the legs to reduce symptoms associated with RLS. After 12 treatments over 4 weeks the treatment group experienced a significantly greater reduction in RLS symptoms than the control. Two subjects had all of their symptoms associated with RLS abolished, which, in their own words "changed their lives." The symptoms in the treatment group were still significantly decreased from baseline 4 weeks after cessation of treatment, with an average decrease of 8.5 points from baseline (p<0.001).

An average reduction of almost 13 points in the IRLS score implies a significant clinical improvement for the patients suffering from restless legs syndrome. This is evident when it is considered that a 10-point difference on this questionnaire determines the pathology's severity level: "none" (0 points); "mild" (1–10 points); "moderate" (11–20 points); "severe" (21–30 points); or "very severe" (31–40 points). This drop in score is comparable to that of dopamine agonists (Oertel et al, 2007).

Although the average decrease in IRLS score in the control group was significant (4.4 points), this placebo effect, as indicated in the RLS literature (Fulda and Wetter, 2008), was expected. A meta-analysis of the placebo effect in RLS treatment studies using the IRLS showed a pooled weighted response rate of 40.09, indicating that about 40% of the treatment effect was due to a placebo response (Fulda and Wetter, 2008). The authors point out that the placebo

effect for the IRLS was larger than for other RLS scales and that this was possibly due to its multi-dimensional features.

RLS has been associated with low iron levels for 70 years (Ekbom, 1960), whereas "normal" serum ferritin levels are considered to be 12–300 μg/L (with an average of 33.6, 93.4, and 139.9 μg/L for premenopausal women, postmenopausal women, and men, respectively) (Jehn, Clark, and Guallar, 2004). In the RLS literature a low ferritin level is considered to be less than 45–50 μg/L (Thorpy, 2005; Sun et al, 1998). Of the 34 patients who participated in our study, 18 had low ferritin levels, equally distributed among the treatment and control groups. This ratio confirms the findings of others (Aul, Davis, and Rodnitzky, 1998; Ekbom, 1960; O'Keeffe, Gavin, and Lavan, 1994; O'Keeffe, Noel, and Lavan, 1993; Sun et al, 1998), who reported that low ferritin levels are related to RLS development or severity. On average, there was no difference, however, in treatment response for subjects with normal or low serum ferritin levels or with familial and nonfamilial RLS.

The purported mechanism behind the success of near-infrared light treatment for neuropathy is its ability to increase nitric oxide generation (Horwitz, Burke, and Carnegie, 1999). Supposedly, this is achieved two different ways: 1) by activating nitric oxide synthase (NOS-3), an enzyme that catalyzes the degradation of L-arginine to L-citrulline and NO (Buga, Gold, Fukuto, and Ingarro, 1991; Erzurum et al, 2007); or 2) by releasing free NO from hemoglobin. It was suggested that hemoglobin-bound NO might serve as a store of nitric oxide from which free NO can be released by intensive illumination (Vladimirov et al, 2000). Once NO is generated, a cascade of events is initiated, eventually leading to vasodilation (Burke, 2003; Erzurum et al, 2007). The unpleasant symptoms associated with RLS could be a sign of, or a direct effect from, decreased tissue perfusion. This lack of blood flow is usually countered and offset with walking or rubbing of the legs—activities that increase blood flow (Clifford and Hellsten, 2004; Thijssen et al, 2009) and decrease RLS symptoms. One of the diagnosing criteria is an affirmative answer to the question, does movement relieve the RLS discomfort? Hence, nitric oxide's chemical property of vasodilation could conceivably explain a temporary decrease in the symptoms associated with RLS. While light's primary effects on tissue (the direct absorption of photons in the tissue) and secondary anabolic effects (Dyson, 2006) can explain the immediate treatment result, its tertiary effect could account for the relatively long-term benefits incurred by our subjects (Dyson, 2006). The tertiary effect of phototherapy is systemic, which could continue to stimulate NO generation (Dyson, 2006).

Further research is warranted. No published paper has shown whether NO levels actually increase during treatment with near-infrared light. The reason for this probably lies in the difficulty of being able to accurately determine the amount of NO in blood because it is highly reactive with a very short half-life (4 seconds). It very quickly oxidizes to nitrite, which in turn further oxidizes to nitrate (Wennmalm, Benthin, and Petersson, 1992).

Limitations

The treatment and control groups did not have a balanced number of subjects with family history RLS (53% in the treatment group, compared to 71% in the control group); the time of symptoms present was different (17.6 years in the treatment group compared to 12.7 years in the control group); and the gender distribution was dissimilar (71% in the treatment group were female compared to 47% in the control group). The sample size was small but adequate as determined by a priori power analysis. It would be beneficial to expand the study to more subjects, maybe with possible blocking on either gender, familial, and nonfamilial RLS, medication intake, or other variables.

CONCLUSION

This randomized controlled study showed that NIR treatment to the lower legs significantly improved symptoms associated with RLS. The mechanisms for this response have yet to be determined. Nevertheless, NIR treatment could be a new drug-free treatment option, or adjunct treatment, for many RLS sufferers.

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Immediate Effects of Monochromatic Infrared Energy on Microcirculation in Healthy Subjects

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Abstract

Objective: The purpose of this study was to evaluate the influence of monochromatic infrared energy (MIRE) on the microcirculation of the skin surface of the feet in healthy subjects. ***Background data:*** Near-infrared energy was shown to increase microcirculation in an animal study. In humans, only one case study demonstrated that MIRE increases microcirculation in the skin of the lower limbs. ***Methods:*** Thirty healthy volunteers were recruited and randomly allocated into three groups to receive either: (1) active MIRE; (2) sham MIRE (placebo group); or (3) warm packs (control group) on the feet. The MIRE device comprised an array of 60 x 890 nm LEDs attached to flexible pads (3×7.5 cm). Each diode spot size was 0.2 cm^2, and each LED power was 12 mW with a power density of 60 mW/cm^2. The arrays were placed in direct contact with the skin for 30 min delivering a total fluence of 108 J/cm^2 over an area of 22.5 cm^2. Capillary blood cell velocity (CBV) and superficial skin blood flow (flux) were recorded before and after intervention. ***Results:*** Significant differences among the three groups were recorded in both CBV and flux (both $p < 0.05$). Post-hoc comparisons indicated that a significantly greater increase in both CBV and flux occurred in the active MIRE group than in the placebo group and control group (all $p < 0.05$). ***Conclusions:*** A 30-min MIRE produced a significantly greater increase in the CBV and flux of the feet in the active MIRE group than in the placebo and control groups.

Introduction

Monochromatic infrared energy (MIRE) at a wavelength of 890 nm was delivered via diode arrays. It was hypothesized that MIRE may penetrate through the skin with a high absorption rate by hemoglobin,[1–3] and might increase microcirculation in the tissues under and around the diode array.[2] The Food and Drug Administration in the United States has approved the use of MIRE for increasing circulation and reducing pain.[3,4] Various studies have reported that MIRE promotes healing on various types of wounds, including venous and diabetic ulcers.[5–7] In addition, some clinical trials have reported that MIRE can restore sensation in the feet for people with diabetic peripheral neuropathy.[4, 8–12] However, several studies reported negative findings from the use of MIRE on transcutaeous oxygen measurement or sensation restoration for people with diabetic peripheral neuropathy.[13,14]

Red blood cells were thought to be able to store large amounts of nitric oxide, partly in the form of nitrosothiols,[15,16] and hemoglobin has been found to be able to absorb this wavelength of photo energy.[3] Nitric oxide has been documented to be a powerful vasodilator, with only small amounts leading to an increase in cyclic guanosine monophosphate (cGMP) and resulting in the relaxation of contractile proteins found in the smooth muscle walls of vascular tissue.[17] MIRE could promotes the release of small amounts of nitric oxide from the hemoglobin in the red blood cells passing through the blood vessels underneath the diode array, causing vasodilation and an increase in microcirculation.[2] This increase in capillary blood flow would subsequently facilitate the process of oxygenation and the delivery of an endogenous growth factor and white blood cells to the healing tissues, thus promoting a positive healing environment.[2]

Recently, it was demonstrated that near-infrared photo energy, similar to MIRE, could increase blood flow in rats, partly through an effect mediated by endothelial nitric oxide synthase or nitric oxide.[18] In humans, only one case study showed that MIRE increases microcirculation in the skin of the lower limbs.[2] The aim of the present study was to evaluate the immediate influence of MIRE on the microcirculation of the skin surface, using video capillaroscopy to measure blood cell velocity inside the capillaries of nailfold, and laser Doppler flowmetry (LDF) to record the superficial skin blood flow in healthy subjects.

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Materials and Methods

Subjects

Thirty-five healthy subjects, aged 21–65 years, were recruited by convenience sampling. Five subjects (1 female, 4 male) were excluded because their capillary loop over the nailfold of the left big toe could not be identified by the use of video capillaroscopy; therefore, 30 subjects completed the study. Other exclusion criteria were people with diabetic mellitus, peripheral vascular disease, dermatological lesions over their feet, or those with a smoking habit, those taking medications that might influence platelet aggregation or vasodilation, those with a previous injury to the left lower limb that could affect blood circulation, and those with active malignancies or who were pregnant. The study was approved by the Ethics Committee of a local university (reference number: HSEARS20090209004). Written consent was obtained after explaining the purpose and procedures to each subject.

The subjects were then randomly allocated into: (1) the active MIRE group ($n=10$), (2) placebo group ($n=10$), or (3) control group ($n=10$) by drawing lots using the non-replacement method (Fig. 1). Throughout the study, both the subjects and the investigator were blinded to the group allocation.

Procedures

The study was conducted in the same investigation room, in which the temperature was kept at 24 ± 1°C, the relative humidity was kept at ~40–60%, and the environment was quiet. All of the participants were asked to refrain from caffeine for 12 h. They were told to avoid having meals, taking hot baths, using topical agents or creams, or exercising vigorously 2 h prior to the experiment. Demographic data about the age, gender, body weight, and height of the participants were recorded. For acclimatization, the subjects were asked to take a 30-min rest in a supine lying position on a plinth.

Interventions

In the active MIRE group, the subjects received a single 30-min session of MIRE. Four array diode therapy pads of the Anodyne Therapy System (Model 480, Anodyne Therapy Professional System, FL) were placed on the lower left limb of each subject (see Fig. 2). The MIRE device comprised an array of 60 x 890 nm LEDs attached to flexible pads (3 × 7.5 cm). Each diode spot size was 0.2 cm^2, and each LED power was 12 mW with a power density of 60 mW/cm^2. The arrays were placed in direct contact with the skin for 30 min delivering a total fluence of 108 J/cm^2 over an area of 22.5 cm^2. The MIRE system was calibrated before the study, and the output of each diode functioned properly. The four pads were placed on the dorsal aspect of the foot, the plantar aspect of the foot just proximal to the third metatarsal head, and the medial and lateral sides of the calf. The wavelength was 890 nm, and the dosage of the MIRE unit was set at 21.67 mW/cm^2.[10] During the treatment, the participants were asked to rest in a supine lying position with the left foot and ankle supported and stabilized in a neutral position with a footrest holder. For the placebo group, the procedures were the same except that the sham Anodyne Therapy System (no MIRE output was emitted) was used by turning the switch of a switch box in which the output circuit was disconnected. No MIRE was given to the control group. Instead, four warm packs similar in size to the MIRE therapy pads were placed at the same sites on the left foot, and the temperature was maintained at 37°C for 30 min, mimicking MIRE's mildly warm sensation on subjects during its operation. This was done to rule out the possible confounding factor of the mild warming effect itself, rather than the photo energy of MIRE, in changing blood circulation.

Outcome measures

Capillary blood cell velocity (μm/s). A video capillaroscopy (CAM1 Capillary Anemometer CapiScope System, KK Technology, England) was used to measure the capillary blood cell velocity (CBV) in the nailfold parallel to the

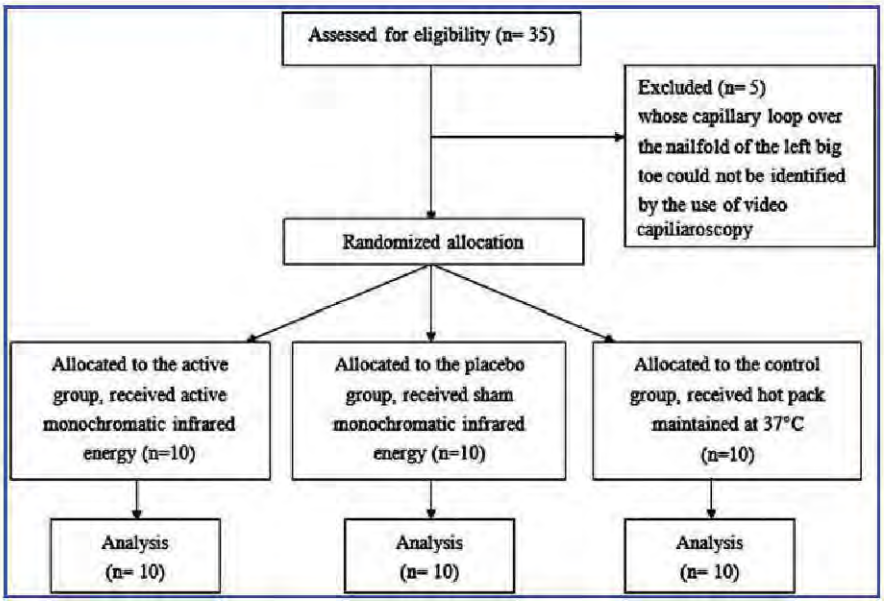

FIG. 1. The consort diagram.

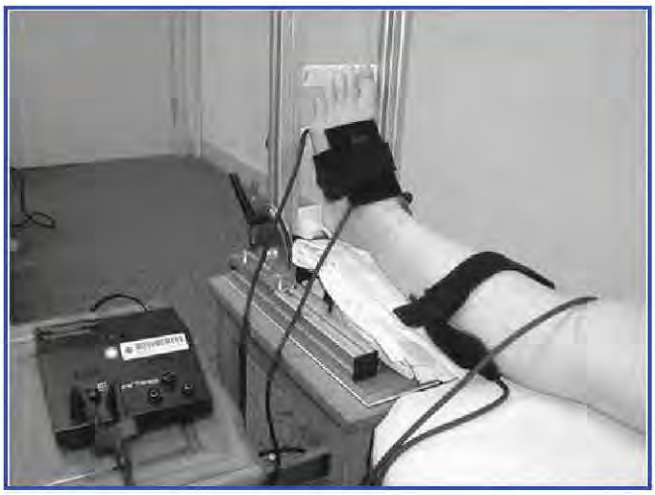

FIG. 2. The placement of the four array diode therapy pads of the monochromatic infrared unit.

surface of the skin when the subject lay in a supine position (Fig. 3). Video capillaroscopy has been validated in previous studies and is commonly used to investigate skin microcirculation by assessing the localized blood cell flow through a direct view of the capillary loops of the nailfold parallel to the surface of the skin of fingers or toes (Fig. 4).[19,20] The left foot was stabilized by the use of a footrest holder. The

FIG. 3. Nailfold capillaries captured by video capillaroscopy for a subject lying in a supine position.

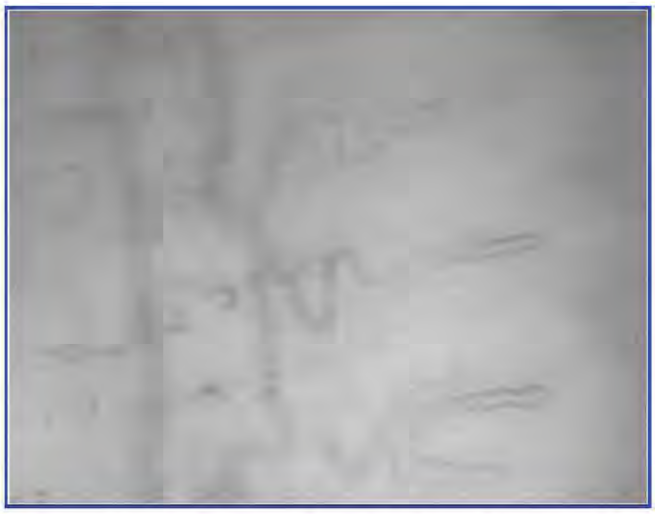

FIG. 4. A typical image of capillary loop shown by video capillaroscopy (original magnification ×200).

location of the skin under investigation (the midpoint of the nailfold of the left great toe) was identified and highlighted with a permanent marker. To minimize laser beam reflections, a drop of paraffin oil was applied to the skin. In order to analyze the capillary blood cell velocity, five capillaries with good optical signals were located. They all showed a good contrast difference between the moving objects and the surrounding tissue.[21] Precise focusing on the nailfold capillaries were performed and their CBVs were recorded for a period of 1 min. The mean CBV of the five identified capillaries of the individual was reported in each before or after the intervention.

Superficial skin blood flow (flux) and skin surface temperature (°C). A LDF (DRT4, Moor Instruments Ltd., England) was used to measure the superficial skin blood flow (flux) and skin surface temperature (°C). LDF is a validated tool for examining microcirculation in superficial tissues.[22] The skin blood flow is presented in flux, which is an arbitrary unit that is directly proportional to the volume of blood flowing in tissues underneath the probe.[23] The two LDF probes were adhered to the dorsal and plantar surface of the third metatarsal head just distal to the therapeutic pads by means of double-sided adhesive tape. The flux and skin surface temperature were recorded for 3 min and the averaged data obtained in the last 2 min were calculated. The two LDF probes were kept in place throughout the whole study period to ensure that the measurement sites remained the same before and after the intervention.

The abovementioned assessment tools were used to examine different aspects of skin microcirculation. Video capillaroscopy can directly assess the local blood cell velocities at the capillary level. Nailfolds are rich in capillaries, where the nutritive blood flow can be assessed. In contrast, LDF examines the compartment flow occurring in various structures including arterioles, venous plexuses, and arteriovenous anastomoses .[24] Furthermore, the assessment site of the video capillaroscopy was relatively distal to the treatment site, whereas the LDF was next to the treatment site, and therefore relatively more proximal.

Statistical analysis

The data were analyzed using the Statistical Package for Social Science (SPSS) version 16. Demographic data (age, weight, and height) and the baseline characteristics of the active MIRE group, placebo group, and control group were compared using one-way ANOVA. The changes in the pre- and post-intervention measurements of the CBV, flux, and skin surface temperature of the three groups were compared by using one-way ANOVA. The α level was set at 0.05. Post-hoc comparisons were performed if significant differences existed among the groups.

Results

Demographic characteristics of the participants

Thirty healthy subjects from 21 to 62 years of age were recruited. Their body weight ranged from 42 to 90 kg, and their height from 140 to 180 cm. There were no significant differences in demographic data or baseline measurements among the three groups (Table 1).

CBV

Figure 5 shows the changes in the mean CBV (CBV of post-intervention – CBV of pre-intervention) of the active MIRE group, placebo group, and control group. The intra-individual variability determined by the coefficient of variation ranged from 15 to 22% before and after treatment in the three groups. We found positive changes in CBV in both the active MIRE group and the control group, indicating an increase in microcirculation. In contrast, there was a negative change in CBV in the placebo group, indicating a decrease in microcirculation. The group difference reached significance ($F=11.98$, $df=2,27$, $p<0.001$). Post-hoc Tukey Honestly Significant Difference (HSD) test showed that the differences

Table 1. Demographic Characteristics of Participants and Baseline Measurement

Characteristics	*Active MIRE*	*Placebo (sham MIRE)*	*Control (warm pack)*	p *Value*
$n=30$	10	10	10	
Men/women	6/4	5/5	6/4	
Age (years)	33.7±13.4	32.3±14.4	35.1±12.6	0.90
Weight (kg)	63.7±12.9	57.6±9.5	63.5±15.9	0.50
Height (cm)	170±1.0	160±1.0	160±1.0	0.78
CBV (μm/s)	65.7±26.0	75.6±43.6	74.0±20.6	0.76
Flux over plantar surface (arbitrary unit)	59.2±60.2	65.5±60.8	58.3±71.5	0.96
Flux over dorsal surface (arbitrary unit)	14.3±5.2	16.5±8.4	12.4±4.8	0.37
Skin temperature over plantar surface (°C)	28.7±1.9	28.3±2.2	28.5±2.5	0.92
Skin temperature over dorsal surface (°C)	29.8±1.5	29.3±2.0	29.4±1.6	0.82

Data are mean±SD; no significant difference was found in any of the demographic characteristics and baseline measurement.

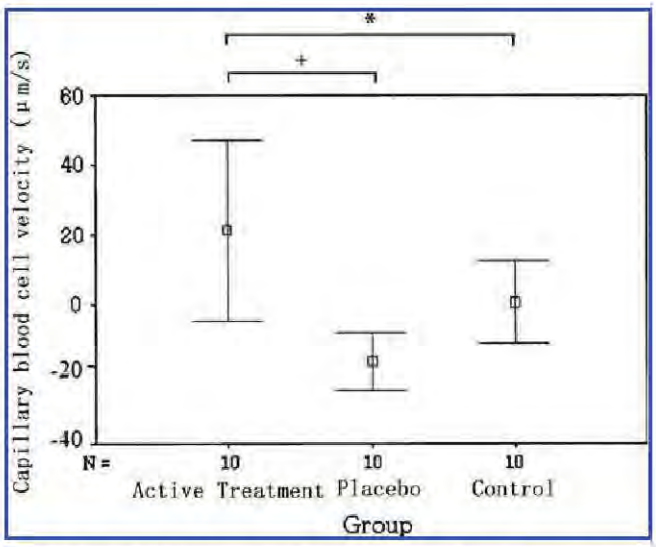

FIG. 5. The changes in the mean capillary blood cell velocity (CBV) of the three groups. The error bars correspond to the standard deviation $^{*}p<0.05$; $^{+}p<0.001$.

mainly came from the comparisons made between the active MIRE group and control group ($p=0.032$), and the active MIRE group and placebo group ($p<0.001$). No significant difference was found between the control group and the placebo group ($p=0.089$).

Superficial skin blood flow (flux) and skin surface temperature (°C)

Flux and skin surface temperature were measured on both the plantar and dorsal aspects of the left foot before and after the intervention. Figure 6 shows the changes in the mean of the flux (flux obtained post-intervention – flux obtained pre-intervention) of the active MIRE group, placebo group, and control group. We found a positive change in the flux of the active MIRE group, indicating an increase in microcirculation. In contrast, there was a negative change in the flux

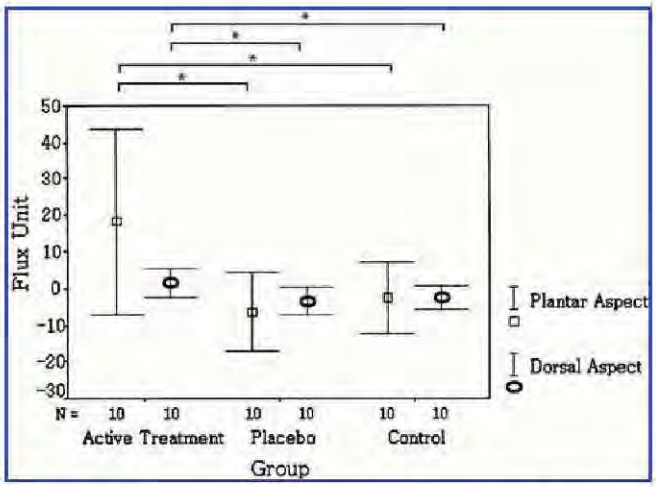

FIG. 6. The changes in the mean flux unit of the three groups. The error bars correspond to the standard deviation $^{*}p<0.05$.

of both the control group and the placebo group over both the plantar and dorsal aspects, indicating a decrease in microcirculation. One-way ANOVA demonstrated a significant difference among the three groups over both the plantar and dorsal aspects (plantar aspect: $F=6.08$, $df=2,27$, $p=0.007$; dorsal aspect: $F=5.46$, $df=2,27$, $p=0.010$). Post-hoc Tukey HSD test showed that the differences mainly came from the comparisons between the active MIRE group and control group ($p=0.028/0.009$), and the active MIRE group and placebo group ($p=0.045/0.012$) for the plantar and dorsal aspects, respectively. No significant difference was found between the control group and placebo group for either the plantar or the dorsal measurements ($p=0.872/0.832$).

For skin surface temperature over the plantar aspect of the foot, no noticeable changes in mean temperature were recorded in the active MIRE group and control group (0.02°C/0.06°C), but a small decrease was recorded in the placebo group (-0.33°C). For the dorsal aspect of the foot, a small decrease was observed in all three groups (active MIRE group: −0.14°C, placebo group: −0.32°C, and control group: −0.05°C). However, no significant difference in skin temperature was found among the three groups on either aspect of the foot (all $p>0.05$).

Discussion

Our findings demonstrated that a 30-min application of MIRE can significantly increase the microcirculation of the skin of the foot at both the capillary and compartment levels, as compared to a placebo group and control group. This was the first randomized, controlled study to investigate the effects of MIRE on microcirculation and show positive findings. Previously, a case study showed that a 30-min treatment of MIRE produced a 400% increase in local blood flow of the tissues as compared to the baseline, using scanning laser Doppler as the assessment tool.[2] In our present study, the 30-min MIRE treatment only produced an increase of ~30% in microcirculation as measured by video capillaroscopy and a 20% increase as measured by LDF. Unfortunately, the dosage of MIRE used in Burke's study[2] was not clearly mentioned, and therefore it was difficult to compare their results with our findings. The increase in microcirculation in the foot can improve blood supply to nutritive capillary blood flow, which may be useful for promoting wound healing in people with diabetic ulcer.

Recently, a randomized and controlled study examined the effects of a 12-session treatment of MIRE on peripheral circulation and sensation in people with diabetic peripheral neuropathy. Peripheral circulation was indirectly evaluated by measuring the perfusion of oxygen in local tissue.[25] The authors of that study reported that MIRE might produce a greater increasing trend in the perfusion of oxygen in local tissue as compared with the sham group, but the between-group difference was just short of significance ($p=0.07$). They explained that the lack of significance could be partly caused by the small sample size and unequal baseline measurement of the oxygen perfusion values between groups. The present study was performed on healthy subjects who were free from any disease that could influence their circulation; no difference was found in any baseline measurement among the groups. This allowed for comparisons to be made more easily among the groups after the intervention. However, patients with disease may respond differently from healthy subjects.

The present study recruited the warm pack group as a control group. The warm pack that we used was a disposable type of warm pack, in which the heat energy was released by chemical reaction and the temperature was supposed to be able to keep warm for 4–6 h. We only observed mild elevation in skin temperature at the plantar of foot after intervention in both the active MIRE group (0.02°C) and control group (0.06°C). Note that the warm packs were delivered at 37°C, to mimic the warm sensation produced by the MIRE. The room temperature of the study room was controlled at ~24°C. The heat energy provided by the four warm packs or MIRE treatment pad were adequate to compensate for the heat loss caused by the cool temperature in the room or the 30-min resting for acclimatization. This may explain why a mild decrease in microcirculation but no significant changes in mean temperature were recorded in the feet of the control group who received the warm pack treatment.

Interestingly, even though the skin temperature for the MIRE group was similar to that of the control group, the microcirculation in the active MIRE group was significantly greater than in the control group. This indicates that the increase in microcirculation by MIRE cannot be explained by the warming effect of MIRE alone. Instead, it is caused by the photostimulation produced by MIRE, which may the result of an increase in the release of nitric oxide to the blood vessels.[2] As suggested by previous studies, nitric oxide may be released by endothelial cells or red blood cells, or both.[26,27] This release in nitric oxide may improve microcirculation via an alteration of cGMP-mediated vasodilation at the site of the treatment.[28] Nitric oxide was not measured in any subjects during MIRE treatment in our study. Future study examining the change of nitric oxide content will be needed to confirm this postulation.

Our findings demonstrated that active MIRE produced a greater increase in flux over the plantar surface after the intervention (change in mean flux: 18.1 unit), as compared to the dorsal surface of the feet (change in mean flux: 1.5 unit). The change in flux observed at the dorsal and plantar aspects of the feet were to a different extent, probably because of the structural difference in the skin. The apical (glabrous) skin is present at the plantar surface of the foot where numerous arteriovenous anastomoses are present, which are controlled by sympathetic vasodilator nerves for thermoregulation.[29] In contrast, predominantly non-apical (hairy) skin is present over the dorsal aspect of the foot. Within this type of skin, very few arteriovenous anatomoses are found and they are innervated by both sympathetic vasodilatory and vasoconstrictor nerves.[29] Our findings demonstrated that MIRE appears to produce greater change in flux at the plantar surface of the foot, which seems to be mainly the result of the influence on the arteriovenous anatomoses.

Small sample size is a limitation of the present study. It is well known that there are individual differences in the measurement of flux by LDF . The variation of the baseline flux can be attributed to individual differences. Therefore, the present study calculated the changes of flux before and after intervention, and the differences among groups were compared. Hence, each subject served as his or her own control, and this can minimize the impact of individual difference on the experimental findings.

The present study only examined the effects of a single session of MIRE treatment on microcirculation. A future study can evaluate the effects of a course of MIRE on microcirculation with a longer follow-up period.

Conclusions

Very limited studies have examined the effects of MIRE on microcirculation. The present study evaluated the influence of MIRE on the microcirculation of the skin surface of the feet in healthy subjects. We found that 30 min of MIRE produced a significantly greater increase in both the CBV and flux of the feet of healthy subjects than in the placebo group or control group (all $p < 0.05$).

Following 30 min of active treatment with MIRE, a significantly greater increase in both the CBV and flux of the feet was observed in healthy subjects, as compared with a sham MIRE group and a control group.

Author Disclosure Statement

No competing financial interests exist.

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Research Article

Local and Systemic Cardiovascular Effects from Monochromatic Infrared Therapy in Patients with Knee Osteoarthritis: A Double-Blind, Randomized, Placebo-Controlled Study

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Infrared (IR) therapy is used for pain relief in patients with knee osteoarthritis (OA). However, IR's effects on the cardiovascular system remain uncertain. Therefore, we investigated the local and systemic cardiovascular effects of monochromatic IR therapy on patients with knee OA in a double-blind, randomized, placebo-controlled study. Seventy-one subjects with knee OA received one session of 40 min of active or placebo monochromatic IR treatment (with power output of 6.24 W, wavelength of 890 nm, power density of 34.7 mW/cm^2 for 40 min, total energy of 41.6 J/cm^2 per knee per session) over the knee joints. Heart rate, blood pressure, and knee arterial blood flow velocity were periodically assessed at the baseline, during, and after treatment. Data were analyzed by repeated-measure analysis of covariance. Compared to baseline, there were no statistically significant group x time interaction effects between the 2 groups for heart rate ($P = 0.160$), blood pressure (systolic blood pressure: $P = 0.861$; diastolic blood pressure: $P = 0.757$), or mean arterial blood flow velocity ($P = 0.769$) in follow-up assessments. The present study revealed that although there was no increase of knee arterial blood flow velocity, monochromatic IR therapy produced no detrimental systemic cardiovascular effects.

1. Introduction

Osteoarthritis (OA) generally involves articular cartilage, anabolic and catabolic mechanisms, and bony structures in the synovial joints [1]. Weaker quadriceps muscle strength, lower knee proprioception, and poor balance with increased postural swaying were noted in subjects with knee OA than in age- and gender-matched controls [2]. Pain and decreased postural stability may be accompanied by difficulties in performing basic and instrumental daily activities, increased fall risks among community-dwelling elderly [3, 4], and a decreased quality of life [5].

Physical modalities are commonly used to treat older patients with knee OA to ameliorate pain and improve functional performance in the rehabilitation medical field. Physical modalities, such as hot packs, pulse ultrasound, transcutaneous electrical nerve stimulation, and phototherapy, are commonly applied to patients with musculoskeletal pain to increase local circulation [6]. However, there are few high-quality clinical studies with randomized placebo-controlled designs on physical modalities' therapeutic effects in the rehabilitation medicine field [7].

Light encompasses a portion of the electromagnetic spectrum. Infrared (IR) radiation wavelengths range from 750 nm to 1 mm. In 2002, the US Food and Drug Administration approved IR therapy for pain relief associated with neck and head pain, arthritis, and carpal tunnel syndrome [8]. IR therapy is commonly used for patients with wounds,

lower-limb peripheral neuropathies, and musculoskeletal disorders such as knee OA [7, 9–19]. Photoenergy exerts bioenergetic, biostimulating, biochemical, and bioelectrical effects on cells [20, 21]. The biological effect of phototherapy is related to photochemical cellular reactions rather than thermal reactions [22]. Phototherapy has been found to improve microcirculation by increasing arterioles diameter and blood flow velocity [23–25]. Improving microcirculation at the local and systemic levels is one of the most important phototherapy effects [26, 27]. It is speculated that vessel dilatation, increase of blood flow rate, and improved blood rheologic properties are mediated by NO, prostacyclin, and endothelial-derived hyperpolarizing factors, all of which are produced by endothelial cells [26, 28]. NO causes rapid transduction and increases local blood flow followed by prostacyclin and endothelial-derived hyperpolarizing factors in changing microcirculation at the systemic level [26, 29]. In addition to mediation by enhancing NO synthesis and increasing microcirculation, phototherapy also relives pain by other pathways and mechanisms, such as by modulating inhibitory cyclooxygenase and prostaglandin E2, modulating nerve transmission, increasing endorphin and serotonin release, and stimulating metabolism [8, 21, 30].

A series of IR treatments had been confirmed to have significant efficacy in improving pain, function, and quality of life in patients with knee OA [17, 31, 32]. Possible mechanisms include peripheral nerve stimulation, microcirculation enhancement, analgesic effects, inflammation resolution, chondrocyte proliferation enhancement, and increased matrix synthesis [17, 33]. Due to significant efficacy of OA knee treatment with IR therapy as a series of sessions, it is necessary to provide evidence that IR therapy does not produce any detrimental systemic cardiovascular effect. However, to our knowledge, no comprehensive study has focused on IR therapy's cardiovascular effects in patients with knee OA [32, 34, 35].

If IR therapy in patients with knee OA can improve the knee arterial blood flow velocity without producing detrimental systemic cardiovascular effects, then the increased blood flow in and/or around the knee joint may infer benefits to the knee joint such as pain reduction in patients with knee OA by long term, repeated IR treatments. Therefore, we hypothesized that IR therapy presumably would influence knee joint tissue perfusion by increasing the local arterial blood velocity at the knee without producing detrimental systemic cardiovascular effects. In our research, we conducted a double-blind, randomized, and placebo-controlled study to examine local and systemic cardiovascular effects from monochromatic IR therapy in patients with knee OA.

2. Materials and Methods

This study was conducted at Shin Kong Wu Ho-Su Memorial Hospital, a teaching hospital with 921 beds located in northern Taiwan. In total, 73 subjects confirmed to have knee OA were identified and recruited from the clinic of the Department of Physical Medicine and Rehabilitation at the hospital. All patients fulfilled the combined knee OA clinical and radiographic criteria established by the American College of Rheumatology [36]. Anteroposterior radiographic views of both knees were taken while bearing weight. A qualified senior physiatrist was in charge of reading the X-rays to classify subjects' Kellgren-Lawrence scores. The hospital's Institutional Review Board for the Protection of Human Subjects approved this study. Written informed consent was obtained from each subject. Subjects with a history of stroke, peripheral vascular disease, peripheral neuropathy, a previous knee operation with an implant, a malignancy, or who were pregnant or planning to become pregnant were excluded.

General information, including age, gender, educational level, marital status, work status, smoking and drinking habits, and comorbidities, was recorded. The body mass index (BMI) was calculated. The self-reported OA knee-specific health status was assessed with the Chinese version of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) [37]. Using a visual analog scale, total WOMAC scores of pain, stiffness, and physical function, respectively vary from 0 to 500, 0 to 200, and 0 to 1700. Higher scores represent worse symptoms with greater functional limitation. The reliability and validity of the three visual analog scale versions are excellent [37–40].

After completing basic data recording, patients were allocated to a treatment group (active treatment) or a placebo group (inactive treatment) following the block randomization principle (with a block size of four). The allocation was initially concealed. An envelope was opened for each consecutive subject to reveal his or her group assignment at the time when he or she was recruited to the study. All patients, regardless of group assignment, underwent 40 min of monochromatic IR therapy with either power on (treatment group) or power off (placebo group) (Figure 1).

Each subject laid down on a standard bed with socks, shoes, and pants removed and rested for 15 min before the intervention in a quiet room with air conditioning. An Anodyne Therapy Professional System (Anodyne Therapy Professional System 480) was used in this study. The device has a main power unit with 8 flexible therapy pads. Each pad contains 60 superluminous gallium-aluminum arsenide diodes that emit an 890 nm light energy wavelength. Eight therapeutic pads were used in this study for both knees, and subjects in the treatment group received a total energy of 41.6 J/cm^2 per knee per session (with a radiant power output of 6.24 W, at a wavelength of 890 nm, and a power density of 34.7 mW/cm^2 for 40 min).

Four therapy pads were placed over the following sites in each knee: the anterior knee joint, the posterior knee joint, and the medial and lateral knee joints (Figure 2). The pads were held in place with neoprene straps supplied by the manufacturer. All subjects were told that they may or may not feel anything from the treatment. Subjects received 1 session of monochromatic IR therapy for 40 min with either the power on or off. The manufacturer checked the monochromatic IR device before the intervention began on the first participant.

The heart rate and blood pressure were measured over the brachial artery with an automated sphygmomanometer (Tango$^+$ Stress BP, Sun Tech Medical Instruments) by

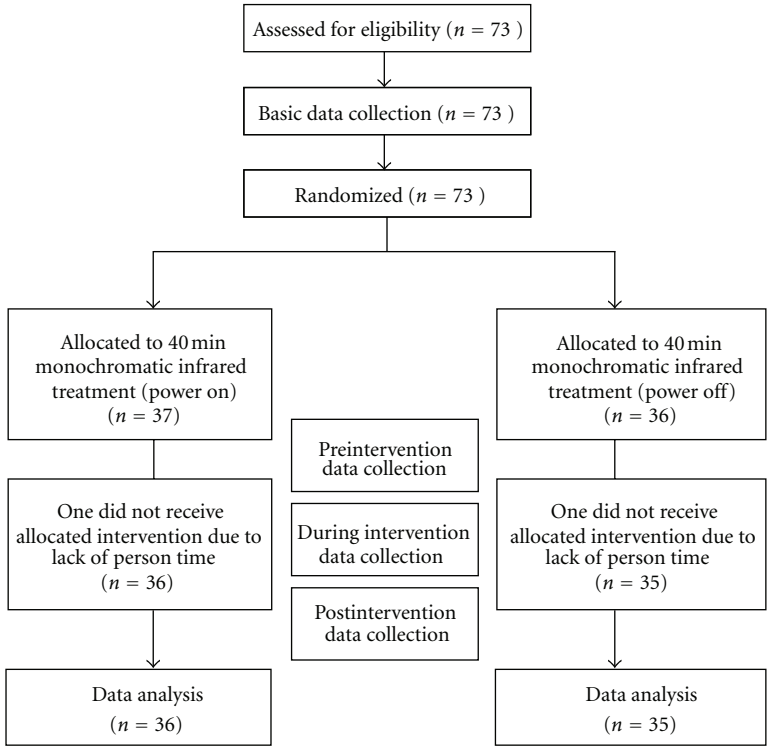

Figure 1: Consort flow diagram.

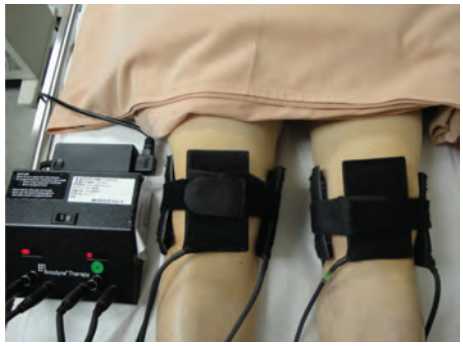

Figure 2: Monochromatic infrared therapy application.

a well-trained technician. The blood pressure measurement had good reliability and validity [41–43]. The instrument was calibrated, and the same cuff was used for all subjects. The heart rate was monitored before treatment, immediately after completing 40 min of treatment, and 5, 10, and 15 min after completing treatment. Systolic and diastolic blood pressures were automatically recorded before monochromatic IR treatment, every 10 min during the 40 min of treatment, and 5 and 15 min after completing treatment. No conversation was allowed between the participants and the technician during the whole course of heart rate and blood pressure measurements.

Color Doppler ultrasonography (LOGIQ P5, GE Ultrasound Korea, General Electric) was performed on patients in a prone position by a qualified senior physiatrist who was not informed of each patient's group allocation. The peak popliteal arterial systolic blood flow velocity (meters/second) was measured in each subject by high-resolution B-mode ultrasound images using standardized parameters with a 7.5 MHz linear array transducer. The peak popliteal arterial blood flow velocity was measured before IR radiation treatment; immediately after completion of 40 min of treatment; and 5, 10, and 15 minutes after treatment. It has high reliability [44, 45].

Except for the physical therapist performing the monochromatic IR treatments, neither the subjects receiving the treatment nor the investigators (including the technician who measured patients' heart rates and blood pressures, and the physiatrist who conducted the Doppler study) were aware of the monochromatic IR therapy's operating status during the study's treatment and data collection periods.

The results are expressed as the mean ± the standard deviation. A chi-squared test or t-test was used to analyze demographic data such as age, gender, educational level, marital status, occupation, comorbidities, smoking and drinking habits, BMI, Kellgren-Lawrence scores, and knee OA-specific measures of pain, stiffness, and physical function of the treatment and placebo groups. Repeated-measure analysis of covariance (ANCOVA) was used to assess the heart rate, systolic and diastolic blood pressures, and mean arterial knee joint blood flow in patients with knee OA between the follow-up assessments in each group, using the pretreatment baseline as the covariate. The group effect, time effect, and group x time interaction effect for the 2 groups at the follow-up assessments were analyzed. We report the

Table 1: Patient's basic demographics.

Variables	Groups		P value
	Treatment $n = 36$	Placebo $n = 35$	
Gender			
Female	33 (92%)	28 (80%)	0.189
Male	3 (8%)	7 (20%)	
Age (yr)	61.1 ± 9.3	61.3 ± 12.0	0.931
Body mass index (kg/m^2)	26.4 ± 5.0	26.0 ± 4.5	0.765
Married			
Yes	28 (78%)	26 (74%)	0.730
Educational level			
Below 9th grade	21 (58%)	19 (53%)	0.650
Above 9th grade	15 (42%)	16 (47%)	
Work status			
Yes	6 (17%)	4 (12%)	0.735
Comorbidities			
Yes	18 (50%)	21 (62%)	0.322
Smoking			
Yes	0 (0%)	0 (0%)	1.000
Alcohol consumption			
Yes	3 (8%)	3 (9%)	1.000
Kellgren-Lawrence scores	2.7 ± 0.7	2.7 ± 0.7	0.962
WOMAC*			
Pain	130.0 ± 87.9	116.9 ± 84.4	0.493
Stiffness	40.4 ± 47.2	40.6 ± 40.6	0.986
Physical function	413.3 ± 318.1	413.5 ± 326.8	0.999

Note: the scores are presented as the number of cases (percentage) or the mean (standard deviation) for each variable.
*WOMAC: Western Ontario and McMaster University Osteoarthritis Index.

results of the ANCOVA by providing the F statistic, degrees of freedom, and the P value for all 71 participants. The level of statistical significance was set at $P < 0.05$.

3. Results

Seventy-three subjects were enrolled in this study. Two subjects refused to participate after completing basic data collection due to personal time constraints. There was no statistically significant difference in the 2 groups in age, gender, educational level, marital status, occupation, comorbidities, smoking and drinking habits, BMI, or severity of knee OA according to the Kellgren-Lawrence scores and WOMAC assessments. Detailed demographic data for both groups are shown in Table 1.

Compared to pretreatment, there was no statistical significance demonstrated in the heart rate between the 2 groups (group effect: $P = 0.918$; time effect: $P = 0.340$; group x time interaction effect: $P = 0.160$) during the 4 follow-up assessments (after 40 min of treatment; and 5, 10, and 15 min after treatment) (Table 2, Figure 3).

As shown in Table 2 and Figure 4, there was no statistically significant difference in systolic blood pressure (group effect: $P = 0.281$; time effect: $P = 0.180$; group x time interaction effect: $P = 0.861$) or diastolic blood pressure (group effect: $P = 0.262$; time effect: $P = 0.663$; or group x time interaction effect: $P = 0.757$) between the 2 groups during the 6 follow-up assessments (after 10, 20, 30, and 40 min of the treatment; and 5 and 10 min after the treatment was completed).

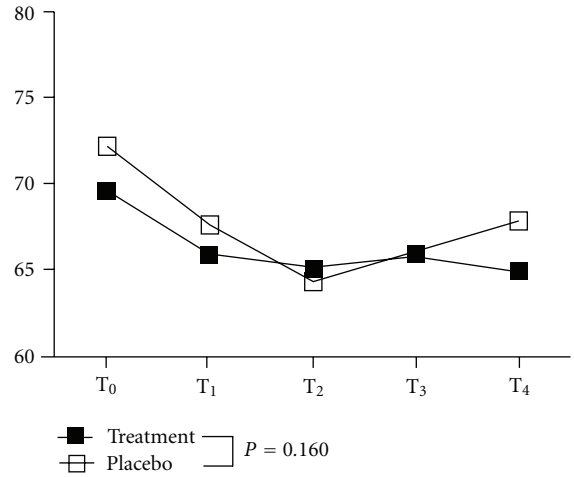

Figure 3: Changes in the heart rate with monochromatic infrared treatment. Solid square: treatment group; hollow square: placebo group; T_0: before treatment; T_1: after 40 min of treatment; T_2: 5 min after treatment; T_3: 10 min after treatment; T_4: 15 min after treatment. Between groups by repeated-measure ANCOVA: group effect: $P = 0.918$ ($F_{1,68} = 0.01$); time effect: $P = 0.340$ ($F_{3,204} = 1.12$); group x time interaction effect: $P = 0.160$ ($F_{3,204} = 1.74$).

As for the popliteal arterial blood flow velocity, compared to pretreatment, there was no statistically significant difference in the blood flow (group effect: $P = 0.666$, time effect: $P = 0.323$, group x time interaction effect: $P = 0.769$) at the 4 separate follow-up assessments between the 2 groups (after 40 min of treatment; and 5, 10, and 15 min after treatment) (Table 2, Figure 5).

No local or systemic side effects were reported during or after the intervention.

4. Discussion

A series of IR treatments are demonstrated to have significant efficacy in improving pain in patients with knee OA. However, the cardiovascular effects by these treatments remain uncertain. To our knowledge, this is the first study to demonstrate the local and systemic cardiovascular effects of monochromatic IR therapy in patients with knee OA. Our results revealed that although there was no knee arterial blood flow velocity increase, monochromatic IR therapy produced no detrimental systemic cardiovascular effects.

A significant microcirculation increase began after 20 min of IR therapy and reached a maximal level 15 min after treatment termination [46]. Therefore, we conducted 40 min of monochromatic IR therapy and followed up for 15 min after treatment termination to examine the local and systemic cardiovascular effects in patients with knee OA in the present study. There has been a tendency to shift from

Table 2: Changes in heart rate, blood pressure, and blood flow velocity.

Time point	Treatment group	Placebo group	Mean between group difference	Repeated-measure ANOVA P value (F value)		
	Mean (SD)	Mean (SD)	(95% confidence interval)	Group	Time	Time × group
Heart rate (beats/min)						
Initial score	69.6 (10.2)	72.2 (11.5)	−2.3 (−7.4, 2.8)	0.918	0.340	0.160
After 40 min of treatment	65.8 (8.0)	67.6 (11.2)	−1.8 (−6.4, 2.8)	($F_{1,68} = 0.01$)	($F_{3,204} = 1.12$)	($F_{3,204} = 1.74$)
5 min after treatment	65.1 (8.5)	64.3 (10.4)	−0.2 (−4.8, 4.5)			
10 min after treatment	65.8 (9.2)	65.8 (10.7)	−0.9 (−5.9, 4.1)			
15 min after treatment	64.9 (10.1)	67.8 (11.7)	−3.6 (−8.7, 1.6)			
Systolic blood pressure (mmHg)						
Initial score	120.3 (16.5)	121.1 (17.6)	−0.8 (−8.9, 7.3)	0.281	0.180	0.861
After 10 min of treatment	111.8 (17.0)	114.0 (20.7)	−2.2 (−11.1, 6.8)	($F_{1,68} = 1.18$)	($F_{5,335} = 1.53$)	($F_{5,335} = 0.38$)
After 20 min of treatment	109.3 (17.3)	114.6 (24.8)	−5.3 (−15.4, 4.8)			
After 30 min of treatment	111.6 (17.5)	117.3 (21.0)	−5.7 (−14.8, 3.5)			
After 40 min of treatment	112.8 (20.4)	116.4 (14.5)	−3.6 (−12.0, 4.8)			
5 min after treatment	116.1 (16.8)	117.4 (19.6)	−1.3 (−10.0, 7.3)			
15 min after treatment	114.1 (15.0)	119.9 (17.3)	−5.9 (−13.6, 1.8)			
Diastolic blood pressure (mmHg)						
Initial score	73.8 (12.0)	70.8 (11.3)	3.0 (−2.5, 8.5)	0.262	0.663	0.757
After 10 min of treatment	73.1 (12.0)	70.5 (12.0)	2.6 (−3.1, 8.3)	($F_{1,68} = 1.28$)	($F_{5,335} = 0.65$)	($F_{5,335} = 0.53$)
After 20 min of treatment	69.7 (12.7)	70.1 (12.7)	−0.4 (−6.5, 5.6)			
After 30 min of treatment	70.6 (10.8)	72.9 (14.5)	−2.3 (−8.4, 3.7)			
After 40 min of treatment	72.3 (14.1)	72.8 (11.8)	−0.5 (−6.6, 5.7)			
5 min after treatment	73.7 (11.1)	74.6 (10.7)	−0.9 (−6.1, 4.3)			
15 min after treatment	73.8 (12.0)	74.9 (12.1)	−1.1 (−6.8, 4.7)			
Blood flow velocity (meters/sec)						
Initial score	36.3 (11.0)	40.5 (10.9)	−3.7 (−8.9, 1.5)	0.666	0.323	0.769
After 40 min of treatment	39.6 (10.8)	41.1 (11.3)	−1.4 (−6.6, 3.8)	($F_{1,68} = 0.19$)	($F_{3,204} = 1.17$)	($F_{3,204} = 0.38$)
5 min after treatment	40.6 (11.6)	41.6 (11.5)	−1.0 (−6.4, 4.3)			
10 min after treatment	40.8 (11.6)	40.3 (10.5)	−0.2 (−5.5, 5.2)			
15 min after treatment	39.7 (10.6)	40.9 (10.5)	−1.2 (−6.2, 3.8)			

Note: scores are presented as the mean (standard deviation) for each variable.

treatment with laser-based devices to treatment by light-emitting diodes in recent years due to the lower cost, lack of coherence, and larger spot size in light-emitting diode devices [8, 47, 48]. Therefore, we used the light-emitting diodes in this study. Color Doppler sonography was used for local blood flow velocity evaluation, and it is widely used in clinical medicine because it is a rapid, simple, accurate, and noninvasive method of objectively monitoring blood flow [49, 50]. However, this study did not demonstrate an increase in the local arterial blood flow velocity after 40 min of monochromatic IR therapy over the knee joints in patients with knee OA.

Measuring blood pressure with a conventional manual sphygmomanometer used by a physician in routine clinical practice often reported inconsistent and imprecise blood pressure readings due to patient-physician interaction, failure to minimize patient anxiety, or poor measurement techniques [51]. The "white coat" bias has been demonstrated to be 15% to 20% in patients with hypertension [52]. Therefore, blood pressure measurement taken outside the clinic using ambulatory blood pressure monitoring is the gold standard measure [53]. However, due to cost and convenience considerations, automatic devices are commonly used in clinics for blood pressure measurements.

Measuring blood pressure using an automatic device in a clinic and leaving the patient alone in a quiet room for at least 14 minutes rest before measurement were found to minimize the white coat effect and yielded values that were comparable to the ambulatory blood pressure measurements [54–56]. The most innovative features to measure blood pressure by automatic devices were that the cuff must be wrapped snugly around the arm, and the patient must keep proper posture during measurement [57]. Therefore, in this study, to avoid the resting effect on heart rate and blood pressure (as the subjects were lying down for up to 60 min for treatment and followup) and the white coat effect, all

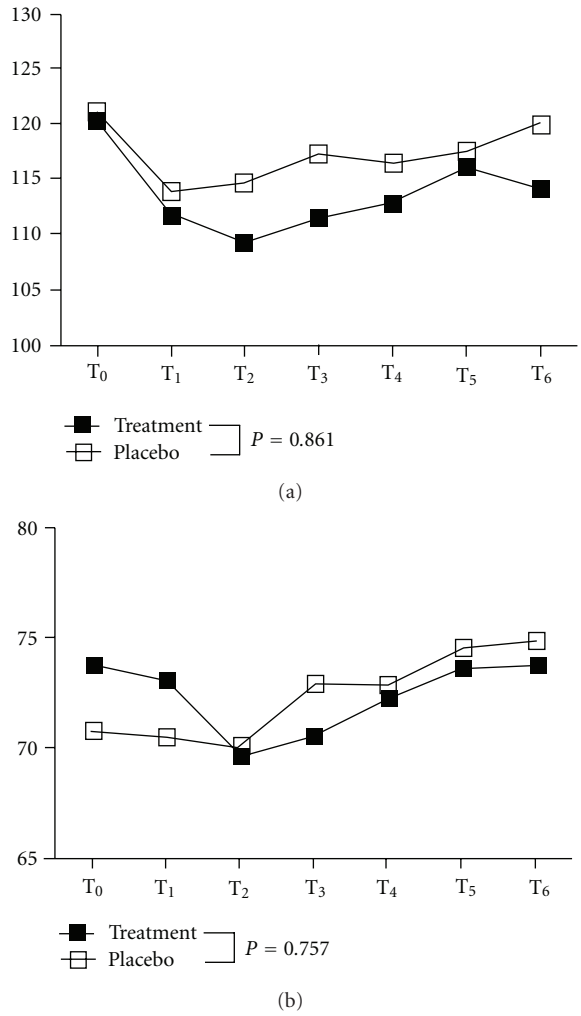

Figure 4: Changes in blood pressure with monochromatic infrared treatment. Solid square: treatment group; hollow square: placebo group; T_0: before treatment; T_1: after 10 min of treatment; T_2: after 20 min of treatment; T_3: after 30 min of treatment; T_4: after 40 min of treatment; T_5: 5 min after treatment; T_6: 15 min after treatment. (a) systolic blood pressure; (b) diastolic blood pressure. Between groups by repeated-measure ANCOVA: systolic blood pressure: group effect: $P = 0.281$ ($F_{1,68} = 1.18$); time effect: $P = 0.180$ ($F_{5,335} = 1.53$); group x time interaction effect: $P = 0.861$ ($F_{5,335} = 0.38$); diastolic blood pressure: group effect: $P = 0.262$ ($F_{1,68} = 0.19$); time effect: $P = 0.663$ ($F_{5,335} = 0.65$); group x time interaction effect: $P = 0.757$ ($F_{5,335} = 0.53$).

participants were asked to lie on the bed in a quiet room for 15 min before beginning the blood pressure measurement and intervention. The blood pressure measuring point was 8 cm above the right elbow joint [57], and all measurements were taken on the right arm. A technician rather than a physician completed the blood pressure measurement. In terms of heart rate and blood pressure, there was no significant difference between the treatment group and placebo group during the 40 min of treatment or 10 to 15 min after treatment termination.

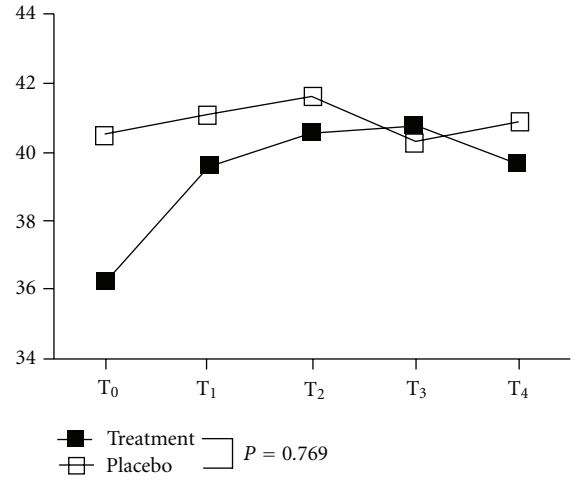

Figure 5: Changes in the blood flow velocity with monochromatic radiation treatment. Solid square: treatment group; hollow square: placebo group; T_0: before treatment; T_1: after 40 min of treatment; T_2: 5 min after treatment; T_3: 10 min after treatment; T_4: 15 min after treatment. Between groups by repeated-measure ANCOVA: group effect: $P = 0.666$ ($F_{1,68} = 0.19$); time effect: $P = 0.323$ ($F_{3,204} = 1.17$); group x time interaction effect: $P = 0.769$ ($F_{3,204} = 0.38$).

Compared to a previously conducted, community-based cohort study in Taiwan [58], although the mean age of participants was relatively older, the systolic blood pressure and the diastolic blood pressure mean value ranges were relatively lower in the present study (the respective values for the previously-conducted study in contrast to the present study are as follows: mean age (years): 56.3 in contrast to 61.2; mean heart rate (beats/min): 64.8 in contrast to 67.1; mean systolic blood pressure (mmHg): 120.2 in contrast to 115.4; mean diastolic blood pressure (mmHg): 74.1 in contrast to 72.4). In contrast to participants' blood pressures being measured by a conventionl, manual sphygmomanometer in a clinic by a physician without mentioning full rest as in the previous study, the participants' blood pressure monitors were applied by a technician, blood pressure was measured automatically in a quiet room after resting for 15 minutes, and conversation between the technician and participants during heart rate and blood pressure measurements was prohibited in the current study. All of these procedures would effectively minimize the white coat effect and measure blood pressure more accurately. This could partially explain why the ranges of systolic and diastolic blood pressure are lower than the average ranges for 56 years old.

Although all participants were told that they may or may not feel anything from monochromatic IR therapy, active monochromatic IR therapy actually emits mild, tangible heat. Therefore, subjects would expect a difference in perception from monochromatic IR therapy between the 2 groups, which could have given subjects in the treatment group a greater perception that they were being treated in contrast to those in the control group. The percentage of patients who perceived heat in the control group in contrast to the experimental group was 33% versus 58% ($P = 0.101$).

Stratified analysis according to whether the participants perceived heat feeling or not was further performed to control for this factor. For the participants who perceived a heat feeling, we found statistically significant group x time interactions for heart rate, with higher trends in the control group ($P = 0.033$), and no statistically significant group effect ($P = 0.762$) or time effect ($P = 0.708$). There was no statistically significant group x time interaction effect for systolic blood pressure ($P = 0.543$), diastolic blood pressure ($P = 0.940$), or knee arterial blood flow velocity ($P = 0.323$). For participants who did not perceive a heat feeling, there was no significant group x time interaction for heart rate ($P = 0.523$), systolic blood pressure ($P = 0.779$), diastolic blood pressure ($P = 0.574$), or knee arterial blood flow velocity ($P = 0.444$). Although the perceived heat feeling by active monochromatic IR therapy could compromise the experiment's blindness on the patients' side, it does not affect the results after we had controlled for that factor.

Because the effects of monochromatic IR therapy are time-dependent [59], the level of photoenergy delivered would have affected the study's results. Compared to previous studies that applied total energies of 52.0–58.5 J/cm^2 [11, 18, 19], the present study used 34.7 mW/cm^2 for 40 min for a higher total energy of 83.2 J/cm^2. At this higher energy, monochromatic IR therapy still had no detrimental systemic cardiovascular effects on patients with knee OA as measured by the heart rate and blood pressure.

OA is often associated with obesity and several cardiovascular conditions, including coronary artery disease, hypertension, and diabetes mellitus [60]. Because obesity, hypertension, and cardiovascular diseases are present in metabolic syndrome, it is hypothesized that OA may represent another aspect of metabolic syndrome [61, 62]. Potential mechanisms for joint OA include the following: (1) reduced blood flow from small vessels and interstitial fluid flow in the subchondral bone and (2) subchondral ischemia with compromised gas and nutrient exchange in the articular cartilage [63]. A higher rate of blood flow is associated with an increased bone remodeling rate [63]. On the contrary, compromised blood flow in the subchondral bone could have deleterious effects on the bone and have implications for the cartilage's integrity [63]. There was a positive association between increased popliteal artery vessel wall thickness and generalized OA [62]. These evidences showed that vascular pathology plays a role in joint OA initiation and/or progression [63]. There may be common pathogenic mechanisms that affect the vascular system and joints [61]. Furthermore, most patients with knee OA who require medication for pain relief are likely to be older and at high risk for both adverse cardiovascular and gastrointestinal effects [60]. Therefore, from the point of no detrimental systemic cardiovascular effects, monochromatic IR therapy can be safely applied to elderly people with knee OA and cardiovascular diseases.

Although the present study did not support our previous hypothesis and found no evidence that monochromatic IR therapy increased knee arterial blood flow velocity in patients with knee OA, we acknowledge that there are many factors that could have affected the study results: the photosource, wavelength, power, energy density, duration of treatment, method of application (noncontact mode in contrast to contact mode), site of stimulation, size of the exposure area, and so forth. Therefore, these results cannot be considered conclusive. Our research presents a reasonable initial foray into the local and systemic cardiovascular effects of clinical monochromatic IR therapy application in patients with knee OA.

There are some limitations to the present study. First, no direct NO, prostacyclin or endothelial-derived hyperpolarizing factor productions were measured. Second, whether the increased popliteal blood flow velocity was related to the increased knee joint blood flow and/or arteriole dilatation remains uncertain.

5. Conclusions

In this study, we applied monochromatic IR therapy in a double-blind, randomized, and placebo-controlled trial to subjects with knee joint OA. Our results revealed that although there was no increase in knee arterial blood flow velocity, monochromatic IR therapy produced no detrimental systemic cardiovascular effects. Therefore, it can be applied to patients with knee OA and cardiovascular diseases safely. Further studies on the effects of monochromatic IR therapy are warranted in the future using different settings for the power, wavelength, energy density, stimulation duration, and stimulation location.

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Research Article

Monochromatic Infrared Photo Energy in Diabetic Peripheral Neuropathy

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Diabetes is a very common cause of peripheral neuropathy, and there is no optimal intervention universally accepted by clinicians. Monochromatic infrared photo energy is a relatively new modality used in the United States for reducing pain and increasing circulation. This study investigated the effects of monochromatic infrared photo energy on reducing pain, improving sensation, and increasing balance in patients with diabetic peripheral neuropathy. Thirty-five patients with diabetic peripheral neuropathy completed the program and were randomly assigned into two groups. Group 1 (experimental, $n = 18$) received monochromatic infrared photo energy, therapeutic exercises, and balance training. Group 2 (control, $n = 17$) received therapeutic exercises and balance training. Both groups received three treatment sessions per week for 4 weeks. Outcome included pain intensity measured on a visual analogue scale, sensation measured with the Semmes-Weinstein monofilament 5.07, and balance measured with the Berg score, before and after the 12 therapy sessions (1 month after the start of the intervention). Analysis of covariance tests revealed statistically significant improvements, specifically, $P = .01$, .014, and .0001, for pain, sensation, and balance, respectively, in the experimental group. Within the limitations of this study, monochromatic infrared photo energy may play a role in treating diabetic peripheral neuropathy by reducing pain, improving sensation, and increasing balance.

1. Introduction

Diabetic peripheral neuropathy (DPN) is a common progressive complication of diabetes mellitus [1], and it may result, in part, from microvascular dysfunction. DPN represents a huge economic burden to the health care system and is prevalent worldwide [2]. Peripheral neuropathy is also linked to substantial reductions in the quality of life, and the condition is associated with diabetes mellitus and other metabolic diseases, chemotherapy, alcohol abuse, infection, environmental toxins or drugs, scar tissue formation following surgery or radiation, as well as idiopathic causes [3, 4]. Approximately 15% of the population over 40 years of age experiences peripheral neuropathy, and, in those with diabetes, the prevalence is approximately 29% [5]. Of these patients, about 50% are insensitive to the 5.07 Semmes-Weinstein monofilament (SWM) at two or more of six measured plantar sites [5]. Despite the prevalence of DPN, many patients are asymptomatic and therefore do not seek care for it [5].

Patients with early DPN usually experience pain that worsens at night: perceived numbness, and a tingling sensation in the feet and hands. Patients may show reduced ability to detect temperature changes and/or pressure in the feet in advanced stages, and these symptoms are associated with postural instability, loss of leg and foot strength, and reduced proprioceptive thresholds in foot inversion, eversion, plantar flexion, and dorsiflexion [6]. Therefore, patients with DPN often develop gait and balance dysfunction that leads to an increased risk of falling, foot ulcers, and amputations. Consequently, patients are often encouraged to use compensatory strategies such as walking aids (cane or walker), and learn about palliative and protective foot care in an effort to identify potential environmental hazards that could lead to pedal cutaneous compromise or injury.

Although there is no definitive intervention for the treatment of DPN, the mainstay generally hinges on rigorous glycemic control and reduction of pain and paresthesia by either topical or systemic means [6]. Therefore, there is a need for a complementary approach to help improve circulation and reduce pain to be used along with medications.

Various types of electrotherapy, such as transcutaneous electrical nerve stimulation (TENS), pulsed electromagnetic fields (PEMF), static magnetic field therapy, external muscle stimulation, and frequency-modulated electromagnetic neural stimulation, have been reported to decrease pain and increase circulation. However, results of the studies describing the effects of these modalities on peripheral neuropathy remain controversial, and randomized-controlled studies with larger sample sizes and long followup periods are needed in order to better elucidate the efficacy of these modalities. And, although electrotherapy modalities may help decrease pain [7], they do not restore blood flow, which may limit their ability to improve sensation. Therefore, there is a need for a modality that works to restore blood flow.

Monochromatic infrared photo energy (MIPE) represents another approach to the management of DPN. MIPE was cleared by the United States Food and Drug Administration in 1994 for increasing circulation and reducing pain. MIPE at a wavelength of 890 nm is produced by an array of 60 gallium aluminum arsenide light-emitting diodes located on flexible pads and the near infrared photo energy is delivered in a noninvasive, drug-free manner. The diode array must be placed in direct contact with the target skin, as MIPE energizes cells in the epidermis and the most superficial portion of the dermis, thereby warming the skin. The 890 nm photo energy penetrates the skin enough to be absorbed by hemoglobin in the rete capillary loops in the papillary dermis, rather than just water in the more superficial layers [8]. At 890 nm, MIPE was shown to increase the concentration of plasma nitric oxide in nondiabetic volunteers and increasing the microcirculation [9, 10], and it has, in fact, been shown to reduce the incidence of new foot wounds in elderly patients with diabetes mellitus [11].

A few studies have investigated the efficacy of MIPE at reducing pain, improving foot sensation, and increasing balance in patients with peripheral neuropathy. However, we believe that the results of these previous studies were adversely influenced by methodological limitations that threatened the authors' conclusions, including the lack of a control group [12, 13]. Three retrospective observational studies [14–16] showed MIPE to be effective based on chart review. Interestingly, a randomized controlled trial of photo energy used at home failed to show the modality to be therapeutically effective [17]. In that particular study, moreover, patients were trained to use a MIPE machine at home and were evaluated before and after 90 days of treatment. However, patient activities were not controlled and the treatment was not supervised. Based on understanding of the limitations of the previously published investigations, as well as the purported effects of photo energy on DPN, the author undertook the investigation described in this report in an effort to test the research hypothesis that MIPE could be used to reduce pain, improve sensation, and increase balance in patients with DPN.

2. Participants and Methods

2.1. Research Design. A randomized controlled study was undertaken with participants randomly assigned to one of two intervention groups: group 1 received MIPE, therapeutic exercises, and balance training, whereas the participants in group 2 received therapeutic exercises and balance training without MIPE. The duration of intervention was 4 weeks per participant, and each participant was scheduled to undergo 3 therapy sessions per week. Measurements were taken at baseline and after end of treatment (4 weeks).

2.2. Participants. Participants were recruited from an outpatient rehabilitation setting and were treated between December 2010 and April 2011. To be included in the study, participants had to have diabetes mellitus, either type 1 or type 2. The maximum allowable HbA1c level required for inclusions was ≤7%. Furthermore, to be included, participants' drug regimen, as well as interventions to promote blood flow in the lower extremities, had to remain stable for one month prior to commencement of the investigation, and throughout the course of the investigation once the study commenced. A 1-month washout period was also required for any participant taking any drug aimed at promoting lower extremity arterial perfusion. Still further, to be included, participants had to have DPN as evidenced by insensitivity to the 5.07 SWM on at least 2 of 5 (great toe, fourth toe, and 3 of the 5 metatarsal heads) plantar surfaces of both feet.

The Berg balance score (BBS) [18] was used to measure balance, and patients with scores ranging from 21 to 40 (medium fall risk) were considered eligible to participate in the study. Patients were excluded from the study if they had a history of knee or back surgery, or malignancy. All potential subjects signed a consent form permitting the use of their data for research purposes, and confidentiality was assured by the use of an anonymous coding system. The consent form also included a clear explanation of the benefits and expected possible risks of the study, and the rights of human subjects were protected at all times.

Participants who met the inclusion criteria were randomly assigned to one of the two treatment groups. The randomization process involved blank folders numbered from 1 to 100 and containing hidden codes for group assignment, and a random-number generator had determined the codes. When a participant was eligible and gave consent to participate, the investigator drew the next folder from the file, which determined treatment allocation. Each participant was then tested using a visual analogue pain rating scale, the 5.07 SWM, and the BBS.

An independent investigator, blinded to group allocation, conducted the testing procedures. This investigator assessed participants in both groups at both the initial and final sessions. After initial testing, participants began the intervention on the same day. A licensed physical therapist performed all interventions with the participants from both groups. All participants underwent 3 sessions per week for 4 weeks.

A coworker helped procure data used in this investigation by taking measurements following the study protocol, although that individual did not devise the study or participate in the analysis or interpretation of the data.

2.3. Intervention. MIPE intervention was administered using the Anodyne Therapy System, model 480 (Anodyne Therapy, LLC, Tampa, FL). The device consisted of a base power unit and 8 therapy pads, each containing 60 gallium aluminum arsenide diodes. The area of light-emitting diodes per therapy pad was 22.5 cm^2, yielding a total intervention area of 180 cm^2. The diodes delivered MIPE pulsed at 292 Hz at a wavelength of 890 nm and provided an energy density of 62.4 Joules/cm^2 [8]. The participants in group 1 received MIPE for 30 to 40 minutes per treatment session, and 4 therapy pads were placed on each lower extremity. The therapist placed one pad at the medial and lateral aspect of each leg immediately above the ankle, and one on the plantar and one on the dorsal surface of each foot. Each subject sat comfortably in a quiet room at 21°C, and the skin of the intervention area was covered with plastic wrap as a barrier between the skin and the diodes to ensure compliance with infection control procedures. The energy setting on the device was preset at 10 bars for every patient, in accordance with the manufacturer's recommendations. The diodes and plastic wrap were removed at the end of the treatment session. Intervention with MIPE was followed by a physical therapy exercise program that focused on strengthening and balance training (described below).

Participants in group 2 underwent only the physical therapy that was the same regimen undertaken by the participants in group 1. The physical therapy program included static and dynamic balance retraining, as well as active lower extremity strengthening (hip extensors, hip abductors, hip adductors, quadriceps, ankle dorsiflexors) and stretching of the hip, knee, and ankle flexor musculature. Participants in both groups were educated as to the rationale for the therapy, and they received verbal and written instructions related to the proper method of exercise, and they demonstrated to the treating therapist their ability to properly perform the prescribed exercises. All participants were instructed to exercise at home on the days that they did not go to the clinic for supervised intervention, and the home program was monitored by asking the participants to record exercise using weekly self-reported exercise logs.

2.4. Outcome Measurements. The 10 cm visual analogue pain rating scale was used to measure neuropathic pain because it is reliable and provides a valid assessment of pain intensity [19]. Light touch sensation was assessed with use of the 5.07 SWM [20], which is generally accepted as an effective, inexpensive, portable, painless, easy to administer, and reliable screening method for assessing touch-pressure sensation in a valid fashion. In fact, the SWM was shown to be more sensitive than the vibration perception threshold in measuring peripheral sensation [21, 22]. The tester asked blindfolded participants to indicate by stating the word—now when and where on their foot they sensed the pressure of the monofilament. Ten specific anatomic sites were tested with the monofilament, including (1) the dorsal midfoot, (2–4) the plantar aspect of the pulp of the first, third, and fifth toes, (5–7) the plantar aspect of the first, third, and fifth metatarsal heads, and (8–10) the medial and lateral aspects of the midfoot (midtarsal joint) and the calcaneus. The tester pressed the monofilament at each site until the filament was grossly observed to bend [20]. The assessor added the number of sites recognized by the participant, with a maximum of 10 and a minimum of zero. Since previous research [23] has shown that monofilaments have variable accuracy and durability with significant reduction of the loading force required to bend the filament after repetitive loading, we replaced the monofilaments after assessing every 10 participants.

Balance was assessed using the BBS, which has been shown to be reliable (intraclass interrater reliability correlation coefficient =.99) [18]. The BBS tests static and dynamic balance activities and grades 14 items on a scale that ranges from 0 to 4. A score between 21 and 40 indicates medium balance impairment and fall risk. While a score below 20 indicates high balance impairement and fall risk. A score between 41 and 56 indicates low balance impairement and fall risk. The BBS testing involves the use of chairs with and without arms, a stopwatch, a ruler, and a 6-inch step, and the test must be completed within a 15-minute time limit [18]. It has been suggested that the BBS is the single best predictor of the risk of falling [24]. These outcome measurements were obtained a baseline, prior to intervention, and again at 4 weeks following the intervention.

2.5. Data Management and Analysis. Data analysis was performed using SPSS for Windows, version 18.0. Data were analyzed using the analysis of covariance (ANCOVA), with the pretest (baseline) scores for the outcomes or interest as the covariates. The ANCOVA was used to take into account the baseline measurements for each patient. When baseline information is available, this provides a more precise estimate of the treatment effect than either raw outcomes or change scores [25]. Analyses of covariance were performed to determine whether there is a difference between the two groups on the posttest scores of pain as measured by the visual analogue scale, light touch as measured by the 5.07 SWM, and balance as measured by the BBS. Demographic characteristics of the participants were described in a statistical fashion, and the Bonferroni adjustment and the statistical significance was defined at the 1.6% ($P \leq .016$) level.

3. Results

A total of 41 patients met the inclusion criteria, including 18 (43.9%) males and 23 (56.1%) females. Of these, 10 (24.39%) had type 1 diabetes mellitus, and 31 (75.61%) had type 2. Random allocation placed 21 (51.22%) into group 1 (to receive MIPE + training) and 20 (48.78%) into group 2 (training only). In group 1 ($n = 21$), there were 10 (47.62%) males and 11 (52.38%) females, and in group 2 ($n = 20$), there were 8 (40%) males and 12 (60%) females. Three (14.29%) participants withdrew from the MIPE group, 1 (4.76%) due to the inability to arrange transportation (in

Table 1: Physical characteristics of the participants (number = 35 participants)*.

Variable	Group 1—training + MIPE^ ($n = 18$)	Group 2—training only ($n = 17$)	P value†
Age (years)	62.03 ± 11.01	59.4 ± 8.51	>.05
Height (cm)	161.34 ± 6.21	158.23 ± 5.82	
Body weight (kg)	68.32 ± 10.19	73.1 ± 9.61	
Body mass index (kg/m^2)	24.25 ± 7.21	21.8 ± 4.14	

* Values are mean ± standard deviation.
^MIPE: monochromatic infrared photo energy.
†Independent sample t-test revealed no statistically significant differences between the treatment groups, as would be expected with random allocation of the intervention.

essence, another scheduling problem), and 1 (4.76%) due to scheduling difficulties, 1 (4.76%) due to the development of congestive heart failure (CHF). In the training only group, 3 (15%) participants withdrew, 2 (10%) due to scheduling difficulties (1 was too busy with work, and another had to take care of a sick relative), and 1 (5%) for reasons that we could not ascertain.

The loss of participants to follow up was associated with difficulties primarily related to scheduling the intervention sessions in both groups (2 (9.52%) of 21 in the MIPE group, and 2 (10%) of 20 in the training only group), and for scheduling conflicts in 2 other participants (the 1 (4.76%) who developed CHF in the MIPE group and the 1 (5%) lost for unknown reasons in the training only group). For these reasons, a total of 35 participants, 18 (51.43%) in the MIPE group and 17 (48.57%) in the training only group, were included in the final analysis.

Baseline demographic characteristics describing the participants who completed the investigation are depicted in Table 1. As expected with random allocation of the intervention, there were no statistically significant differences between the treatment groups in regard to age, height, body weight, and body mass index ($P > .05$). Data were normally distributed. Mean values and standard deviations of pain intensity, sensation score, and balance score at baseline and at 4 weeks are presented in Table 2. Table 2 depicts the results of dependent samples t-tests comparing baseline to 4 week outcomes for pain, monofilament sensation, and Berg balance scores, within the intervention groups. These results showed significant differences in all dependent variables before and after intervention in both groups ($P \leq .05$). No adverse events were observed or reported by any participant in either intervention group.

Table 3 depicts the results of the ANCOVA, which showed statistically significant differences between the intervention groups relative to pain ($F_{1,32} = 8.16$, $P = .01$), sensation ($F_{1,32} = 4.2$, $P = .014$), and balance ($F_{1,32} = 12.06$, $P = .0001$). The MIPE group displayed lower mean posttest pain scores, fewer sites of pedal insensitivity as measured with the 5.07 SWM, and higher mean Berg balance scores.

4. Discussion

All of the participants in this investigation showed reduction in pain, increased foot sensation, and increased balance scores, in both intervention groups, although the improvements were statistically significantly greater in the group of participants that received MIPE (Tables 2 and 3). In regard to pedal sensation, there was a decrease in number of sites insensitive to the 5.07 SWM in both intervention groups. In the MIPE+ training group, the mean number of insensate sites was 1.4 ± 2.1 after 4 weeks, compared to 7.2 ± 1.8 at baseline, and this difference was statistically significant ($P = .025$). In the training only group, the mean number of insensate sites was 7.2 ± 1.3 after 4 weeks, compared to 8.3 ± 0.9 at baseline, and this difference was not statistically significant ($P = .06$).

The basic idea of this study was to treat the two groups exactly the same in every detail except one (MIPE). The author examined the two groups to see if the MIPE made a difference between them. The difference between groups was attributed to the MIPE.

Although the exact mechanism by which MIPE improves sensation in the diabetic neuropathic foot is not precisely known, it has been proposed that it leads to increased release of nitric oxide and improved microcirculation for the following reasons

(1) Nobel Laureate Robert Furchgott reported that photo energy modulates circulation, and it has been shown that exposure to 890 nm near infrared photo energy promotes increased blood flow for several hours in rats by mediating endothelial nitric oxide synthase [26].

(2) Photo energy absorbed by hemoglobin increases the amount of nitric oxide in red blood cells, in the form of nitrosothiols, and therefore MIPE is likely to increase vasodilatation secondary to release of nitric oxide [27].

(3) Diabetic glycosylated hemoglobin binds nitric oxide and inhibits its release from hemoglobin at microcirculatory sites, and MIPE is likely to enable release of nitric oxide from glycosylated hemoglobin [28].

Since patients with DPN often have concomitant decreased capillary blood flow to tissues of the feet and impaired circulation to the peripheral nerves, it is plausible that improved oxygenation and nutrition related to nitric oxide metabolism related to MIPE could promote nerve growth and reestablish nerve membrane potentials that had been reduced by the hypoxic conditions associated with diabetes [29]. Moreover, physical therapy methods and exercise are often used to decrease pain and increase balance in patients with DPN. In a rat model, it was shown that exercise

Table 2: Outcomes at baseline and 4 weeks, by intervention group (number = 35 participants)*.

Outcome		Group 1—training + MIPE^ ($n = 18$)	Group 2—training only ($n = 17$)
10-cm analogue pain scale	Baseline	6.2 ± 2.1	7.3 ± 1.1
	4 weeks	3.9 ± 1.8	5.1 ± 2.3
P value†		≤.05	
Monofilament sensation¶	Baseline	7.2 ± 1.8	8.3 ± 0.9
	4 weeks	1.4 ± 2.1	7.2 ± 1.3
P value†		.025	.06
Berg balance score§	Baseline	31 ± 9.27	28.58 ± 10.16
	4 weeks	47.61 ± 10.16	32.52 ± 9.54
P value†		≤.05	

*Values are mean ± standard deviation.
^MIPE: monochromatic infrared photo energy.
†Dependent sample *t*-test revealed statistically significant differences within the treatment groups except within the second group difference for the sensation measurement.
¶Possible score ranging from 0 to 10, indicative of the number of separate pedal anatomic sites where 5.07-monofilament touch-pressure was not appreciated by the participant (lower score indicative of more sensation).
§A score of 21–40 indicates balance impairment and a heightened medium risk of falling.

Table 3: Results of analysis of covariance between the groups at 4 weeks after intervention (number = 35 patients)*.

Outcome	Group 1—training + MIPE^ ($n = 18$)	Group 2—training only ($n = 17$)	*F* statistic†	*P* value†
10-cm analogue pain scale	3.9 ± 1.8	5.1 ± 2.3	8.16	.01
Monofilament sensation¶	1.4 ± 2.1	7.2 ± 1.3	4.2	.014
Berg balance score§	47.61 ± 7.39	32.52 ± 9.54	12.06	.0001

*Values are mean ± standard deviation.
^MIPE: monochromatic infrared photo energy.
†Analysis of covariance.
¶Possible score ranging from 0 to 10, indicative of the number of separate pedal anatomic sites where 5.07-monofilament touch-pressure was not appreciated by the participant (lower score indicative of more sensation).
§A score of 21–40 indicates balance impairment and a medium risk of falling.

could reduce pain by increasing the production of endogenous analgesics [30].

There has been some research into the efficacy of exercise as it pertains to increasing balance in patients with DPN [31]. For example, a meta-analysis concluded that exercise reduced the risk of falling and improved balance in the elderly [32]. However, that particular study did not include those with DPN. In another meta-analysis, investigators found that physical therapy interventions led to minimal improvements in balance or reduction in fall risk in the elderly and those with distal neuropathy, and the authors of that report concluded that patients continued to experience deficits in balance and sensation after the intervention [33].

Moreover, Kruse et al. [34] conducted a 12-month randomized controlled study to investigate the effects of exercise and walking intervention on balance, lower-extremity strength, and fall incidence in 79 patients with DPN. The training included leg strengthening and balance exercises, and the authors of that study did not find statistically significant differences in the incidence of falling between the groups during followup, although they did show a small increase in the amount of time that patients in the intervention group could stand on one leg with their eyes closed at the 1-year follow up, which led the investigators to conclude that exercise may increase activity without increasing balance or decreasing the incidence of falling. Interestingly, few authors have found favorable results advocating the use of exercise to increase balance and reduce the risk of falls in people with DPN. Song et al. [35] found that a balance exercise and trunk proprioception program improved balance and trunk proprioception in patients with DPN. They reported statistically significant ($P < .05$) decreases in postural sway and trunk repositioning errors, and statistically significant increases ($P < .05$) in dynamic balance using the Berg balance scale, functional reach test, timed up and go test, and 10 m walking time after balance exercise. Based on the existing literature, we feel that controversy exists in regard to the efficacy of exercise as it relates to improving balance in patients with DPN.

There are a number of published articles [12–17] that focus on the use of MIPE to increase balance, reduce pain, and restore sensation in patients with DPN, although the general conclusion of these reports is that MIPE is a recommended intervention in patients with DPN. Unfortunately, the conclusions of the existing literature are threatened by numerous methodological shortcomings. Leonard et al. [12] investigated the effects of MIPE in regard to sensation, pain, and balance in 18 diabetic patients with DPN, and measured outcomes in terms of the 5.07 monofilament and the modified Michigan neuropathy screening instrument

obtained before the first and seventh visits, and after the twelfth visit. Although these investigators showed improved outcomes with MIPE, their conclusions were threatened by the lack of a control group. Another investigation [13] considered the effect of MIPE along with other physical therapy interventions in 38 patients with peripheral neuropathy due to diabetes, alcohol abuse, and peripheral vascular disease. He assessed foot sensation and balance using the 5.07 monofilament and the Tinetti assessment tool, and observed improved sensation, increased balance, and reduced fall risk at the end of 12 sessions and at the 3-month followup. The major limitation of their study was, once again, the lack of a control group, and they did not take into consideration the potential influence that psychoactive drugs may have had on the risk of falling, other medications, or comorbidities (stroke, other neuropathies) which may have had on your participants.

A third report [14] aimed to evaluate the responses of 252 patients with DPN to a health status questionnaire by phone interview following the end of MIPE intervention in patients >64 years of age, the participants having been identified from insurance billing records of two providers who used monochromatic energy devices for use at home. After 1 year of followup, they found a reduced incidence of falls (78%) and fear of falling (79%) at 1 month, and increased daily living activities (72%), although the findings of this investigation were limited by recall and ascertainment biases-related patient memory.

A fourth report [15] described decreased pain, improved sensation, and increased balance in 2239 diabetic patients who received MIPE, balance and strengthening exercises in a group of outpatient physical therapy centers, although their findings were limited by the retrospective nature of the investigation, as well as biases related to possible (and likely) insurance coding errors. In a fifth previously published report [16], researchers performed a retrospective study to assess the effect of MIPE and therapeutic exercises in regard to pain reduction, 5.07 monofilament sensation, and Tinetti balance scores in 272 patients (mean age 69 $\pm$ 12.3 years) with peripheral neuropathy due to a variety of etiologies, treated at 8 different outpatient physical therapy centers. They also reported statistically significant beneficial effects related to the intervention, including a 38% decrease in pain, 77% improvement in sensation, and 73% decrease in balance deficits, although the validity of the results is also threatened by the same limitations that jeopardized the findings of the previously mentioned investigations.

Finally, a sixth published report [17] described a randomized, sham-controlled clinical trial, wherein MIPE was shown to have no effect in reducing pain, improving foot sensation, or increasing quality of life in 60 patients with DPN. In that investigation, the participants received MIPE at home for 40 minutes daily over 90 consecutive days, via 4 pads (dorsal and plantar foot, medial and lateral aspects of the calf). The participants were trained to use the photo energy machine at home, and to log their use, and they were checked after 2 weeks of therapy to verify that the intervention was being used correctly.

Potential limitations of this particular report include the usual problems associated with patients logging their activities, and other biases related to unmeasured confounders. Loss to follow up was mostly due to scheduling difficulties or taking the time to participate in the study in each group. Therefore, it cannot be argued that participants withdrew due to the interventions. There are a number of potential biases that could threaten the validity or conclusions, and for these reasons we realize that future investigation remains necessary in order to better understand the clinical value of MIPE in the management of DPN.

Perhaps the biggest limitation of this study relates to the fact that the author did not employ sham MIPE, and the improvements in the dependent variables could have been due to the placebo effect. Both groups received therapeutic exercises and balance training which may have influenced the improvement. Moreover, the author did not undertake an explanatory analysis, nor did we take into consideration every independent variable that experienced clinicians may think of as important in regard to the treatment of DPN. For instance, the participants were not asked to change any aspect of diet, exercise, drugs, and the author did not analyze the potential influence of psychoactive drugs and other intrinsic risks for falling. Moreover, the neuropathic pain questionnaire could have been used instead of the visual analogue score to measure neuropathic pain [36].

Still further, additional research is needed to more precisely identify the role that nitric oxide plays in these outcomes, and whether or not the improvement in sensation, pain, and balance that were observed in this 1-month follows-up study is sustained longterm. Treatment only lasted for 4 weeks which is too short and it is questionable whether improvement would be lasting. It is also recommend comparing MIPE to other photo energy modalities such as laser to establish its superiority over these modalities. Based on the results of this randomized, controlled clinical trial, MIPE may be effective in decreasing pain, restoring sensation, and increasing balance in patients with DPN.

Conflict of Interests

The author declares that there is no conflict of interests.

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Anodyne therapy versus exercise therapy in improving the healing rates of venous leg ulcer

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ABSTRACT

Objective: The purpose of this study was to determine the best physical therapy program to increase wound healing rates in patients suffering from venous leg ulcer.
Methods: Forty patients who had venous leg ulcer for more than 4 weeks and not respondent well to medical treatment. Patients were classified into 4 equal groups 10 of each, Group (1): received 40 minute of monochromatic infrared energy (MIRE), Group (2): received 40 minutes of exercise program consisted of stretching and resisted exercise (RE), Group (3): received 20 minutes of exercise in addition to 20 minutes of resisted exercise (MIRE/RE), and group (4): control group which received conventional therapy of the ulcer. All groups received treatment 5days per week for 12days. Measurements of ulcer surface area and PUSH scale were conducted before treatment, post 6 days of treatment, and after 12 days of treatment.
Results: The one way analysis of variance was used to compare ulcer surface area and PUSH score which revealed that both treatment groups (MIRE and RE) had significant ($P< 0.05$) decrease in ulcer surface area and PUSH scale after 6 and 12days post application of treatment. On the other hand, the combination of MIRE and RE showed a highly significant decrease in ulcer surface area and PUSH score when compared with control or with individual treatment.
Conclusion: The results of this study suggest that combination of MIRE to RE is more effective than individual treatment to enhance the healing rate of venous ulcer of the leg.

Keywords: Venous ulcer, Monochromatic Infrared energy, Exercise

INTRODUCTION

Leg ulcers are a major health concern in the older population[1], affecting 1-3 % of the population aged over 60 years.[2,3] leg ulcers can take years to heal and profoundly impact the mental and social well being of the individual.[3] approximately 1 % of the total health care costs in the western world are likely to be used for management of chronic leg ulcers.[4]

A venous leg ulcer is the result of sustained venous hypertension associated with chronic venous insufficiency[5] which is believed to be caused by varying combinations of venous reflux, venous obstruction, and a poor functioning calf muscle pump.[6] Failure of the calf muscle pump to effectively promote venous return leads to abnormality high venous ankle pressures and produces evidence of chronic venous disease; leg ulcers are the end result of this process.[7]

Studies have found that the presence of venous insufficiency and subsequent venous hypertension may lead to calf muscle changes such as muscle fiber atrophy,[8] abnormal gait,[9] and reduced strength and functioning of the calf muscle.[10,11] There is evidence to suggest that exercise does improve calf muscle function in this patient population.[11,12] However, until very recently only one other study[12] has considered if improving the calf muscle pump function results in improved healing rates.

The Anodyne Professional Therapy System is a MIRE device that received marketing clearance from the U.S. Food and Drug Administration (FDA) in 1994 through the 510(k) process. The labeled indication is for "increasing circulation and decreasing pain." MIRE devices have been investigated as a treatment of multiple conditions including cutaneous ulcers, diabetic neuropathy, musculoskeletal and soft tissue injuries, including temporomandibular disorders, tendonitis, capsulitis, and myofascial pain. It delivers monochromatic near infrared energy through therapy arrays, each containing 60 superluminous diodes (890 nanometers, near infrared wave- length). These diode arrays are attached to a control unit that pulses MIRE at 292 times/second.[13]

The therapy arrays are placed in direct contact with the skin to temporarily increase local microcirculation. The ability of photo energy to increase microcirculation, possibly through the release of nitric oxide, has been documented in clinical literature.[14]

All light, visible or invisible, consists of photons. The size or mass of the photons is dependent on the specific wavelength of the light. Target tissues must first absorb light in order to have a biological effect. Additionally, absorption is best achieved when the light is 1) directed perpendicular to the skin, and 2) placed in direct contact with the skin. Moreover, photo energy emitted from a source that produces of a homogenous wavelength is often more effective therapeutically than light composed of several wavelengths.[15]

The purpose of the current study is to investigate the best treatment program in the enhancement of healing of chronic venous ulcer either MIRE or resistance exercise alone or in combination.

METHODS

Research design

A randomized controlled study was undertaken with participants randomly assigned to one of three intervention groups and control group.

The study was conducted at a dedicated clinic within Naser Hospital, Cairo, Egypt for 12 months commencing from June 2011. Patients were referred into the study by their general practitioners (GPs), practice/community nurses or consultants. To confirm eligibility, patients referred to the study underwent a specialist assessment in the vascular unit at the Naser Hospital, Cairo, Egypt. This assessment included a drawing photograph of ulcer, bacterial swab and pain assessment of the ulcer; ankle brachial pressure index (ABPI); blood pressure and mean arterial pressures.

Inclusion criteria specified that the ulcer was venous in origin with diagnosis by clinical examination and ankle brachial plexus index, ABPI $\geq$ 0.80; the current ulcer should not have been previously treated with high compression bandaging; ulcer size was between 1 cm^2 and 20 cm^2 and located between the knee and ankle. The patient's venous ulcer should have demonstrated unsatisfactory healing for at least the previous 4 weeks.

Patients were excluded if they were diabetic or had a co-existing mobility problem, e.g. major joint arthritis, had a body mass index (BMI) of $\geq$35 or ulcer size were greater than 20 cm^2. Ulcer patients who completed the study were age and gender matched.

Group Assignment

Forty patients was recruited into this study and was randomly assigned into four group: Group (1): consisted of 10 patients with venous leg ulcer and received MIRE treatment in addition to conventional venous leg ulcer treatment for 12 days, Group (2) consisted of 10 patients with venous leg ulcer and received resisted exercise (RE) in addition to conventional venous leg ulcer treatment for 12 days, Group (3) consisted of 10 Patients and received both MIRE and RE in addition to conventional venous leg ulcer treatment for 12 days, and lastly Group (4) which served as control group and received conventional venous leg ulcer treatment.

Instrumentations

For evaluation

Digitizer tablet with a stylus pen and cordless mouse (Genius Mouse Pen 8 x 6).

Figure 1: Digitizer stylus pen and cordless mouse (Genius Mouse Pen 8x6).

For treatment

Anodyne Therapy Model 120 for Professionals. Figure 2: Anodyne therapy system is a non invasive, drug – free device that delivers monochromatic infrared energy (MIRE) through infrared light emitting diodes, with a wave length of 890 nm, that are mounted in flexible therapy pads. When the therapy pads were placed in direct contact with the skin, the invasive infrared light, is absorbed by cells in the body and blood vessels begin to dilate, resulting in increased circulation in that area.

Figure 2: Anodyne therapy Model 120.

Procedures

For Evaluation

Measurement of wound surface area by using transparent films (Visitrak Digital Tracing Method) (Smith & Nephew Medical Limited, Hull, England) which enables the measurement of wound surface area and has been validated as a reliable measure of ulcer size with high intra-inter reliability:[16] The patient was positioned in a comfortable position with exposure of the foot. Double sterilized transparent plastic films (Tagaderm) was placed directly flat and attached to the skin around the wound area with avoiding any movement and distortion of the foot. Ulcer margins were traced by the same investigator to establish reliability of measurements. The tracing was taken before, and after two weeks of follow up. Then the traced ulcer margins was converted to a digitizer vector image by using a digitizer tablet and a stylus pen where the traced transparent film was placed flat on the digitizer tablet the stylus delineated the margins of traced wound. The digitized ulcer surface area was calculated by specialized software program (Autovue Professional, Cimmetry Systems, Inc).

Pressure Ulcer Scale (PUSH)

Progress in ulcer healing was also measured using the Pressure Ulcer Scale for Healing (PUSH). The PUSH scale was developed in 1997 and revised by Stotts et al.,[17] and includes three dimensions of ulcer healing, providing a more sensitive measure of healing than examining changes in ulcer area alone. The three subscales cover the area of the ulcer, the amount of exudates (i.e. light, medium and heavy) and the type of tissue (i.e. epithelial, granulating, slough or necrotic), giving a total score ranging from 17. Validation and reliability information has been reported in Stotts et al.[17] and Pompeo.[18]

Treatment Program

A. MIRE program: Each patient of group (1) received five sessions per week for a period of successive 2 weeks. The duration of each session was applied for 40 minutes. The treatment program was applied according to the following procedure: The patient was placed in a comfortable position such as long sitting on the bed. The places on which the electrodes were applied should be cleaned. The electrode pads were wrapped with a clear plastic wrapping to prevent contamination. The pads were placed with direct contact with the ulcer and the cables were connected to the base unit. The device was switched on after completing the treatment session of forty minutes the device was switched off and the pads were removed.

B. RE program: Each patient of group (2) received five sessions per week for a period of successive 2 weeks. The duration of each session was applied for 40 minutes. The treatment program was applied according to the following procedure: The patient was placed in a comfortable position such as long sitting on the bed. Each session of exercise started and ended by passive stretching exercise of the calf muscle to the level of tension but not the level of pain. The total duration of stretching exercise is 20 minutes (10 minutes before resisted exercise, and 10 minutes after resisted exercise). The core exercise is isometric exercise for planter and dorsi- flexor of the ankle which last for 20 minutes.

C. MIRE-RE program: Each patient of group (3) received five sessions per week for a period of successive 2 weeks. The duration of each session was applied for 40 minutes. The treatment program was applied according to the following procedure: MIRE treatment was applied for 20 minutes followed by RE for another 20 minutes as described earlier.

D. Conventional Therapy: Conservative treatment consisted of cleaning the wound with normal saline and applying a paste bandage covered by an elastic diachylon bandage with a pressure of roughly 15-25 mmHg.

Data analysis

This study was a controlled post test experimental design with a control and a three treatment groups. Groups were compared for differences at different time interval,

ANOVA multiple comparisons followed by Tucky Kramer post hoc test was used for comparing differences between 3 treatment groups and control group. The level of significance was set at 0.05 for all statistical tests.

RESULTS

Patients were divided into four groups as described earlier in the material and methods section, there was no significant difference between them regarding age, and the duration of ulcer prior to treatments intervention as showed in Table 1.

Table 1: General characteristics of MIRE, RE, MRE/RE and Control groups.

Group	Sex (M/F)	Age (yr)*	Duration of ulcer (month)*
MIRE group	3/7	60.00±5.07	5.50±1.58
RE group	5/5	58.70±4.11	5.70± 2.35
MIRE/RE group	5/5	59.70±5.43	5.90±1.44
Control group	6/4	60.00±4.94	6.70±1.41

* Mean ± S.D.

Ulcer surface area was measured at specific day intervals as explained in the Table 2 which showed that all treatment interventions used significantly reduced ulcer surface area as compared to control group, similarly all intervention groups showed a significant reduction in ulcer surface area at day 6 and day 12 in comparison with base line measurement at day 1, on the other hand, there was no significant difference between MIRE group and RE group at day 6 and 12, but there was a significant difference between MIRE/RE group and Mire group, RE group, and control group either at day 6 or 12.

Table 2: Comparison of ulcer surface area of MIRE, RE, MRE/RE with Control groups.

Days	Treatment groups			
	Control	MIRE	RE	MIRE/RE
Day 1	11.61± 1.05	12.33± 1.02	11.65± 1.76	11.61± 1.77
Day 6	8.67± 0.60^{B,C,D,†}	6.59± 0.68 ^{A,C,D,†}	6.69± 0.62 ^{A,B,D,†}	6.46± 1.76 ^{A,B,C,†}
Day 12	7.43± 0.56^{B,C,D,†}	4.11± 0.96^{A,D,†,‡}	4.55± 1.14^{A,D,†,‡}	1.89± 1.72^{A,B,C,†,‡}

Data were expressed as Means ± SD of 10 venous ulcer patients /group. C; Control group, MIRE; monochromatic infrared energy treated group, RE; resisted exercise treated group, MIRE/RE; monochromatic infrared plus resisted exercise treated group. ^{A}significantly different versus control group; ^{B}significantly different versus MIRE group; ^{C}significantly different versus RE group; ^{D} significantly different versus MIRE/RE group at $P \leq 0.05$. †significantly different versus Day 1; ‡significantly different versus Day 6; at $P \leq 0.05$. Significance was carried out by One-way ANOVA Tukey-Krammer test.

PUSH score was measured at specific day intervals as explained in the Table 3 which showed that all treatment interventions used significantly reduced in PUSH scale as compared to control group, similarly all intervention groups showed a significant reduction in PUSH scale at day 6 and day 12 in comparison with base line measurement at day 1, on the other hand, there was no significant difference between MIRE group and RE group at day 6 and 12, but there was a significant difference between MIRE/RE group and Mire group, RE group, and control group either at day 6 or 12.

Table 3: Comparison of PUSH score of MIRE, RE, MRE/RE with Control groups.

Days	Treatment groups			
	Control	MIRE	RE	MIRE/RE
Day 1	13.70± 1.16	13.20± 1.22	12.70± 1.25	12.60± 0.84
Day 6	8.67± 0.60^{B,C,D,†}	6.59± 0.68 ^{A,C,D,†}	6.69± 0.62 ^{A,B,D,†}	6.46± 1.76 ^{A,B,C,†}
Day 12	7.43± 0.56^{B,C,D,†}	4.11± 0.96^{A,D,†,‡}	4.55± 1.14^{A,D,†,‡}	1.89± 1.72^{A,B,C,†,‡}

Data were expressed as Means ± SD of 10 venous ulcer patients /group. C; Control group, MIRE; monochromatic infrared energy treated group, RE; resisted exercise treated group, MIRE/RE; monochromatic infrared plus resisted exercise treated group. ^{A}significantly different versus control group; ^{B}significantly different versus MIRE group; ^{C}significantly different versus RE group; ^{D} significantly different versus MIRE/RE group at $P \leq 0.05$. †significantly different versus Day 1; ‡significantly different versus Day 6; at $P \leq 0.05$. Significance was carried out by One-way ANOVA Tukey-Krammer test.

DISCUSSION

Leg ulceration is a debilitating condition characterized by long periods of ulceration and a high incidence of recurrence.[19] Venous ulcers cause significant social and economic impact due to their recurrent nature and long lasting course between onset and healing. When they are not properly managed, about 30% of the healed venous ulcers relapse within the first year, and that increases to 78% after two years. Thus, due to prolonged treatment, patients with venous ulcer need frequent health care delivered by physicians and other professionals, therefore,[20] The purpose of the current study is to elucidate a new physical therapy treatment program for the enhancement of venous leg ulcer healing.

The current study showed the 3 treatment group and control showed no significant difference regarding the ulcer size, duration of ulcer, and age of the patients, which indicate that the outcome measures either ulcer size or PUSH score are only in response of treatment interventions.

The result of the current study showed that there was a significant improvement in healing in the MIRE group compared to the control group, as measured by a reduction in ulcer area and PUSH scores. Possible reasons for improved healing rates in the MIRE group may be due to that MIRE technique had been shown to increase blood circulation by 400% over the baseline circulation after 30 minutes of application, as opposed to elevation of skin temperature to the same degree with heat therapy, which increases blood flow by only 40%.[13] Increased circulation possibly accounts for the reported increased healing rates after 12 weeks of MIRE application.

Another possible reason is that mono chromatic infrared energy modality increases nitric oxide (NO) in the blood and plasmas of normal adult subjects.[21] An elevation in nitric oxide (NO) has been suggested to be the basis of improved rates and quality of healing during L-arginine or nitroglycerin therapy in patients with wounds.[22] It has been proposed that through this NO-mediated process, MIRE might prove beneficial in patients with venous and diabetic ulcers and in patients who exhibits low rates of post amputation wound closure.[21]

On the other hand, the result of the current study showed that there was a significant improvement in healing in the RE group compared to the control group, as measured by a reduction in ulcer area and PUSH scores. Possible reasons for improved healing rates in the RE group may be due to that venous hemodynamic is maintained for up to 30 minutes after cessation of exercise.[23] Similarly, structured exercise programs are associated with improvements in calf muscle pump function.[11,12,24,25]

Based on the result of the current study, the third group which combined the beneficial effect of both MIRE and RE showed a significant decrease in the ulcer size and PUSH score when compared to control group or even to each treatment modality alone, which is quit logical.

CONCLUSION

It was concluded that the combination of MIRE and RE was highly effective in the enhancement of venous leg ulcer wound healing.

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Ethical approval: We certify that this study involving human subjects is in accordance with Helsinki declaration of 1975 as revised in 2000 and that it has been approved by the relevant ethical committee.

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ORIGINAL ARTICLE

Short-term therapeutic effects of 890-nanometer light therapy for chronic low back pain: a double-blind randomized placebo-controlled study

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Abstract We conducted a double-blind randomized placebo-controlled study to investigate the effects of short-term 890-nm light therapy in patients with chronic low back pain in a rehabilitation clinic. Thirty-eight women and 22 men with chronic low back pain (mean age, 60.3 years; range, 32–80 years) received 40-min sessions of hot-pack therapy combined with active or placebo 890-nm light therapy (wavelength=890 nm, radiant power output=6.24 W, power density=34.7 mW/cm^2 for 40 min, total energy=83.2 J/cm^2) over the lower back three times weekly for 2 weeks. Participants were assessed before and after treatment by using a range of motion measurements, a visual analog scale evaluation of pain, the Multidimensional Fatigue Inventory, the Biodex Stability System, the Fear-Avoidance Beliefs Questionnaire, repeated chair-rising times, the Frenchay Activity Index, the Oswestry Disability Questionnaire (ODQ), and the Osteoarthritis Quality of Life Questionnaire. The severity of disability based on the ODQ score was used as the primary clinical outcome measurement. Compared to the baseline measurements, participants in the treatment group reported significant reductions in fear-avoidance beliefs regarding physical activity (P=0.040) and work (P=0.007) and in the severity of disability (P=0.021). Treatment with hot-pack therapy and 890-nm light therapy was associated with reductions in the severity of disability and fear avoidance beliefs in patients with chronic low back pain.

Keywords Low back pain · Light therapy · Effects · Fear-avoidance · Disability

Introduction

Low back pain affects 60 to 80 % of adults during their lifetime, and is one of the most prevalent ailments in society [1]. Low back pain causes activity limitations and disability, and imposes a substantial financial burden on patients and health care systems [2], the majority of which stems from patients' disabilities, rather than treatment costs [3]. Although most patients with low back pain recover spontaneously within 1 to 3 months, regardless of the treatment or treatment type, 3 to 10 % develop chronic low back pain [4]. The etiology and underlying pathology of low back pain are often unclear, and may be multifactorial [5]. The psychological, occupational, and social impacts of chronic low back pain increase with the duration or severity of the condition [6].

Low back pain is a multifaceted phenomenon that causes psychological distress, physical impairment, and social limitations [7]. According to the International Classification of Functioning, Disability and Health (ICF), a functional health status consists of dynamic biopsychosocial interactions among the components of body functions and structures, activities, participation, and personal and environmental factors [8]. Therefore, the major goal in the management of low back pain is to enable patients to resume their daily activities and maintain an optimal functional health status [8, 9].

Physical modalities are common treatments for musculoskeletal disorders to ameliorate pain and improve functional performance. Light energy exerts biochemical, bioelectrical, bioenergetic, and biostimulatory effects [10]. Mechanisms by which light therapies have been shown to relieve pain

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include increases in microcirculation and nitric oxide synthesis, the enhanced release of endorphins, the modulation of nerve transmissions, and the modulation of key mediators of inflammation, such as inhibitory cyclooxygenase and prostaglandin E2 [11]. Because it promotes tissue healing and produces anti-inflammatory and analgesic effects, light therapy is commonly used to treat musculoskeletal conditions [12–15]. Light therapy has been shown to be an effective treatment for various musculoskeletal disorders, including lateral epicondylitis [16], temporomandibular joint pain [13], carpal tunnel syndrome [17], and delayed onset muscle soreness [12]. The use of 890-nm light therapy was approved by the United States Food and Drug Administration for the treatment of minor muscle and joint pain in 2002 [18]. Previous studies have shown that 890-nm light therapy reduces pain [19] without detrimental systemic cardiovascular effects [20].

However, to date, ICF health status criteria have not been evaluated in investigations of the therapeutic effects of light therapy for chronic low back pain [21–23]. Therefore, we conducted a double-blind randomized placebo-controlled study to examine the short-term therapeutic effects of 890-nm light therapy based on ICF-related outcome measures in patients with chronic low back pain. We hypothesized that short-term hot-pack therapy combined with 890-nm light therapy would improve assessment scores for body structures and functions, activities and participation, and health-related quality of life (QOL) for low back pain patients, compared to treatment with hot-pack therapy only.

Methods

Study design and participants

Our study was approved by the Institutional Review Board for the Protection of Human Subjects at Shin Kong Wu Ho-Su Memorial Hospital (SKWHS) (IRB number: 20121211R). Written informed consent was obtained from each participant. Patients with chronic low back pain were recruited from the clinic of the Department of Physical Medicine and Rehabilitation at SKWHS in Taipei, Taiwan.

The participants were selected based on the following inclusion criteria: (1) nonspecific chronic pain in the posterior torso, below the 12th rib and above the gluteal folds with or without radiating pain or numbness in the lower limb; (2) being 18 to 85 years of age; and (3) symptoms that are persisting for more than 12 weeks. Lumbar radiographic examination with anteroposterior and lateral views was performed for all the participants. Those meeting any of the following criteria were excluded (1) low back pain accompanied by specific pathological conditions, such as an infection, inflammation, rheumatoid arthritis, fracture, or tumor; (2) a self-reported history of malignancy, vertigo, stroke, or other condition that may impair postural stability; (3) a history of low back surgery with an implant; (4) pregnancy or plans to become pregnant during the course of the study; or (5) having received concurrent treatment for low back pain by another health care professional.

Participants were randomly assigned to either the treatment group (active light therapy) or the placebo group (inactive light therapy) by block randomization by using a block size of 4 through a computer-generated random number. Each participant's group assignment was initially concealed. An envelope was opened for each consecutive participant to reveal the participant's group assignment to an investigator at the beginning of the study. The group assignments were not revealed to the participants. The outcome measures were assessed both before and after the 2-week interventions were completed. The investigator who conducted the therapy was not blinded to the allocation of each participant.

Outcome measures

We evaluated participants according to ICF-related variables, such as impairment, limitation of functional performance, restriction of participation, and health-related QOL. The assessments were performed by an investigator who was blinded to the treatment group assignment of the participants.

Body functions and structures

Lumbar active range of motion assessments, including forward flexion, extension, and right and left rotations, were measured in degrees using a Back Range of Motion instrument [24].

A 100-mm visual analog scale (VAS) was used for low back pain assessment. The anchor terms of the VAS were 0 (*no pain*) and 10 (*maximal pain imaginable*). Higher VAS scores indicated greater pain intensity.

The Multidimensional Fatigue Inventory (MFI) was used to assess fatigue [25]. The MFI contains 20 visual 5-point Likert statements that cover different aspects of fatigue, including general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. A higher MFI score indicates greater fatigue.

The Fear-Avoidance Beliefs Questionnaire (FABQ) was used to measure fear-avoidance beliefs regarding physical activity and work [26]. The FABQ is a 16-item questionnaire with two subscales. The FABQ physical activity subscale contains four items that assess fears, avoidance attitudes, and beliefs regarding general physical activity. The FABQ work subscale contains seven items that assess fears, avoidance attitudes, and beliefs regarding occupational activity. Higher scores for the physical activity (range, 0–24) and work

(range, 0–42) subscale evaluations indicate greater fears, avoidance attitudes, and beliefs. The content of the work subscale was modified to reflect housework performance for unemployed participants.

Postural stability and dynamic balance were assessed using the Biodex Stability System (BSS) [27, 28]. The BSS uses an unstable platform to evaluate postural control. The BSS measures the degree of tilt of a platform on which the participant stands along the anteroposterior and mediolateral axes to obtain an overall stability index. Greater postural variability results in a higher overall stability index, which indicates reduced ability to balance on the platform.

The BSS evaluates dynamic balance through assessments of dynamic limits of stability that are demonstrated as the participant moves a cursor on a monitor screen back and forth from a centered box to peripheral boxes that appear successively in random order. Higher scores for the limits of stability indicate better control of dynamic balance. We used the most stable BSS resistance level (level 8) to measure participants' postural stability and dynamic balance. A bipedal stance was used on the platform, and the test was performed with bare feet and open eyes. The feet positions were recorded for each participant, to ensure an identical stance for both the stability and the dynamic balance evaluations. For each measurement, the participants were allowed one practice attempt, followed by one formal test.

Activities and participation

Chair-rising times were assessed by measuring the time required for participants to rise five times from a seated position in a standard chair to a standing position as quickly as possible, without using their arms for support [29]. Longer chair-rising times represented greater limitations of physical function.

The Frenchay Activities Index (FAI) was used to evaluate extended activities of daily living, such as indoor domestic activities, outdoor domestic activities, and outdoor social activities [30, 31]. The FAI contains 15 items, with overall scores ranging from 0 to 45. Higher overall FAI scores indicate higher activity levels.

The Oswestry Disability Questionnaire (ODQ) was used to evaluate the degree to which low back pain affected the participants' ability to manage daily activities [32]. The ODQ contains ten questionnaires, with overall scores ranging from 0 to 100. Considering that certain cultural differences may be inherent in a questionnaire that was originally developed for a Western population, the severity of the ODQ was classified into five categories in our study, according to a previous study on chronic low back pain conducted on a Taiwanese population [33]. The severity of disability was obtained by separating the total scores into the following five categories: minimal disability (0–11), moderate disability (12–22), severe disability (23–32), crippled (33–43), and bed bound (≥44) [33].

The Osteoarthritis Quality of Life Questionnaire (OA-QOLQ) was used to assess the impact of osteoarthritis (OA) on QOL [34]. The OA-QOLQ consists of a 22-item one-dimensional questionnaire that evaluates a patient's psychological characteristics, including their sense of frustration, fear, loss of independence, the impact of their OA on others, and their level of annoyance regarding living with their disorder. A higher OA-QOLQ score indicates a greater impact of OA on QOL.

Personal factors

Age, sex, education level, marital status, work status, smoking and drinking habits, and comorbidities were recorded for all participants, and their body mass index was calculated.

Interventions

Each participant was positioned supine on a standard bed with clothes removed. A moist heating pad (14×27 in.) was placed under light-emitting pads of the Anodyne Therapy Professional System 480 (Anodyne, Tampa, FL, USA), and were positioned at the lower back (Fig. 1). The light therapy device used eight flexible therapy pads that were held in place with neoprene straps. Each pad consisted of 60 superluminous gallium-aluminum-arsenide diodes (13 mW per diode per 22.5 cm^2 pad) that emitted 890-nm light energy with 780 mW of power (radiant power output=6.24 W, power density=34.7 mW/cm^2 for 40 min, total energy=83.2 J/cm^2). All participants received three 40-min hot-pack treatments weekly for 2 weeks. The light device was used for all the participants, but electrical power was supplied to the Anodyne unit for the treatment group only. Six 40-min sessions of hot-pack therapy were conducted for 2 weeks at the end of the study for the placebo group.

An investigator blinded to the participants' group assignments evaluated the ICF-related variables before and after the 2-week treatment was completed (Fig. 2). Neither the participants receiving the treatment nor the investigator were aware of the operating status of the light-therapy unit during the treatment and data collection periods of the study. Disability severity measured using the ODQ was used as the primary outcome measurement, and fear-avoidance beliefs measured using the FABQ were used as the secondary outcome measurements.

Sample size

We required 22 participants in each arm to detect the mean difference in score between the two groups; the mean scores were 12.2 for the treatment group, and 17.9 for the placebo group [33]. The pooled standard deviation was 6.7 in a

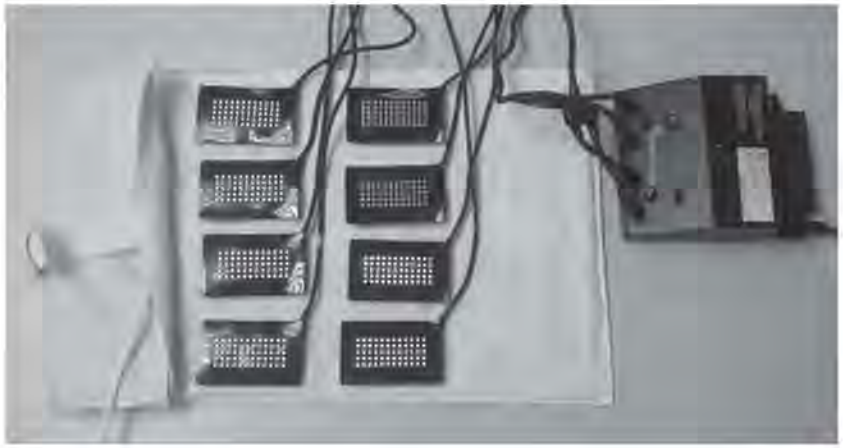

Fig. 1 A moist heating pad was placed under eight flexible light-emitting pads of the Anodyne unit, which was held in place with neoprene straps at the lower back of supine participants

previous study [33], with a significance level of 5 % (two-tailed) and a statistical power of 80 %.

Statistical methods

The results of our evaluations are expressed as the mean ± standard deviation. Chi-squared tests or *t* tests were used to compare the differences in the data between the treatment and placebo groups according to demographic and baseline variables. Paired *t* tests were used to compare the intervention effects based on the primary and secondary outcome measures within and between the study groups. The level of statistical significance was set to $P < 0.05$.

Results

Each group initially comprised 35 participants. However, of the 70 participants selected, 7 declined to participate because of unavailability, and 3 declined for unstated personal reasons before the start of the assessment and intervention. Excluding the declining participants, the treatment group included 33 participants, and the placebo group included 27 participants. Thirty-eight women and 22 men were enrolled, aged from 32 to 80 years, with a mean age of 60.3 years. No statistically significant differences in age, sex, education level, marital status, occupation, comorbidity, smoking and drinking habits, or body mass index

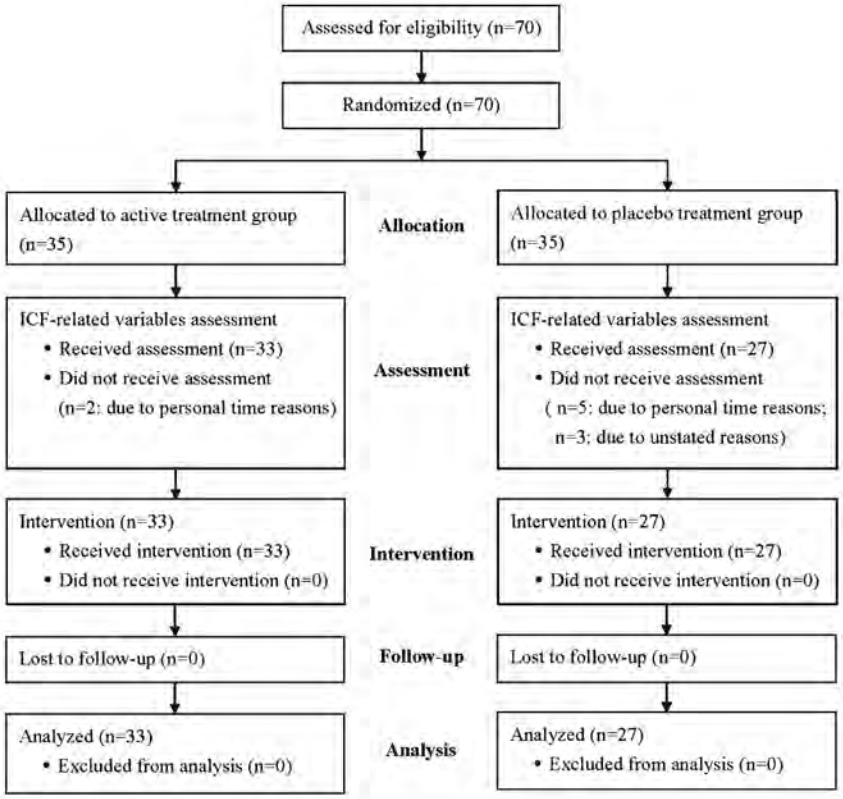

Fig. 2 Trial profile. *ICF* International Classification of Functioning, Disability and Health

were observed between the treatment and placebo groups (Table 1).

The scores at each time point for each group for each outcome measure and the means between the group differences based on 95 % confidence intervals are summarized in Table 2. No significant differences in baseline scores for lumbar active range of motion, VAS, MFI, FAI, ODQ, physical activity (repeated chair-rising), postural stability and dynamic balance (limits of stability), or OA-QOLQ were observed between the study groups. All participants completed the entire course of treatment (Table 2).

Compared with the results of the baseline assessments, significant reductions were observed in the treatment group for fear-avoidance beliefs for physical activity (P=0.040) and work (P=0.007), as measured using the FABQ. Significant reductions were also observed in the treatment group for the severity of disability, as assessed using the ODQ (P=0.021). However, compared with the baseline measurements, no significant effect was observed between the groups at the 2-week follow-up assessments for the other variables assessed (Table 2). No systemic or local side effects were noted during or after treatment.

Table 1 Demographic data of study participants

	Treatment group (n=33)	Control group (n=27)	P value
Sex			
Female	19 (58)	19 (70)	0.306
Male	14 (42)	8 (30)	
Age (years)	60.1±14.2	58.5±10.6	0.635
Weight (kg)	62.6±8.7	62.0±11.2	0.814
Height (cm)	161.6±8.1	160.3±6.9	0.529
BMI (kg/m^2)	23.9±2.7	24.0±4.1	0.914
Married			
Yes	27 (82)	22 (81)	0.973
Education level			
Below 9th grade	17 (52)	14 (52)	0.979
Above 9th grade	16 (48)	13 (48)	
Employed			
Yes	10 (30)	6 (22)	0.481
Smoker			
Yes	3 (9)	4 (15)	0.492
Drinker			
Yes	3 (9)	1 (4)	0.405
Comorbidity			
None	17 (52)	10 (37)	0.369
≤2	8 (24)	11 (40)	
≥3	8 (24)	6 (22)	
Pain radiation in lower limb			
Yes	23 (70)	21 (78)	0.481

Values are n (%), except for age, weight, height and BMI, where values are mean ± SD

BMI body mass index.

Discussion

First demonstrated by Mester et al. in 1968 [35], the clinical application of light therapy has become popular. In recent years, a trend among practitioners has emerged toward the use of light-therapy devices with light-emitting diodes because of the lower costs associated with the irradiation of large-surface areas, compared with treatments using laser-based light-therapy devices [11, 29, 36]. We evaluated the short-term effect of hot-pack therapy combined with light therapy by using an 890-nm light-emitting diode-based device on chronic low back pain by using a double-blind randomized placebo-controlled study. Our results showed that the 890-nm light therapy group experienced statistically significant reductions in the severity of disability and fear-avoidance beliefs for physical activity and work compared with the placebo group. The results of our study indicate that short-term 890-nm light therapy and hot-pack treatment reduced chronic low back pain, as evidenced by improvements in body functions and participation, according to the ICF criteria.

Infrared wavelengths of light penetrate human skin more efficiently than red wavelengths do [36], and previous research showed a significant increase in microcirculation following 20 min of light therapy [37]. Our previous study indicated that 40 min of light therapy using light-emitting diodes produces no detrimental systemic cardiovascular effects [20]. We used the 890-nm light-emitting diodes for the 40-min light therapy in this study, and no adverse effects were observed following the short-term treatments. Most patients with chronic low back pain who require medication for pain relief are likely to be middle-aged or older, and are at high risk for both adverse gastrointestinal and cardiovascular effects [38]. Therefore, the observed reductions in fear-avoidance beliefs and the severity of disability, with no accompanying detrimental effects on systemic cardiovascular health or other adverse effects, indicate that 890-nm light therapy is a safe treatment for chronic low back pain in middle-aged and older patients, despite the presence of cardiovascular comorbidities.

A growing consensus indicates that psychological factors, such as catastrophizing and fear-avoidance beliefs, play greater roles in the transition from acute to chronic low back pain than the severity of the pain [39]. Such observations indicate that the process of chronicity is triggered by catastrophizing perceptions of pain that initiate a cycle of fear regarding re-injury and the onset of additional pain associated with safety-seeking behaviors, such as hypervigilance and avoidance [40]. Fear-avoidance beliefs in patients with

Table 2 Comparison of changes of scores in body function, activities, participation, and quality of life for study participants

	Before treatment			Changes after treatment			
	Treatment group	Placebo group	*P* value	Treatment group	Placebo group	Mean difference between groups (95 % confidence interval)	*P* value
Body functions							
Range of motion							
Flexion	25.0±9.2	26.0±8.9	0.674	0.6±5.4	−2.6±9.0	−3.1 (−7.0, 0.7)	0.133
Extension	12.1±5.6	11.3±5.4	0.623	−0.1±4.5	1.0±4.5	1.1 (−1.3, 3.5)	0.382
Rotation (R)	28.4±12.9	29.3±10.9	0.776	−0.3±6.4	−1.1±8.7	−0.8 (−4.8, 3.2)	0.677
Rotation(L)	27.5±11.7	27.5±11.7	0.964	−2.4±8.4	−1.1±11.6	1.3 (−4.0, 6.6)	0.629
Visual analog scale	7.8±2.4	7.9±1.7	0.929	0.73±1.4	0.4±1.1	−0.3 (−1.0, 0.3)	0.295
Multi-fatigue inventory							
General fatigue	10.3±3.7	11.7±3.4	0.144	−0.2±1.9	−0.2±2.3	0.1 (−1.0, 1.1)	0.927
Physical fatigue	12.1±3.3	13.2±3.6	0.255	−0.4±1.3	−0.0±1.2	0.4 (−0.3, 1.0)	0.274
Reduced activity	9.8±2.2	11.1±3.0	0.054	0.3±1.1	0.1±1.4	−0.3 (−0.9, 0.4)	0.443
Reduced motivation	10.7±1.8	10.9±1.7	0.626	−0.5±1.3	0.01±1.2	−0.5 (−1.1, 0.2)	0.141
Mental fatigue	10.6±1.7	11.4±2.2	0.152	−0.1±1.3	−0.4±1.1	−0.3 (−1.0, 0.3)	0.293
Biodex stability system							
Postural stability	0.5±0.2	0.5±0.5	0.846	0.2±0.7	−0.1±0.4	−0.3 (−0.6,0.02)	0.068
Dynamic limit of stability	41.1±11.2	39.6±11.2	0.698	2.2±16.8	1.0±12.4	−1.1 (−9.0, 6.7)	0.773
Fear-avoidance behavior questionnaire							
Physical activity	12.4±5.7	11.5±6.3	0.583	−1.0±4.3	1.0±3.0	2.1 (0.1, 4.1)	0.040*
Work	9.8±7.7	9.0±9.3	0.746	−1.7±4.6	1.9±5.4	3.7 (1.0, 6.3)	0.007**
Activities and participation							
5 repeated chair-rising times	15.9±3.6	16.8±5.1	0.430	−0.3±3.4	−1.5±3.8	−1.2 (−3.1, 0.7)	0.212
Frenchay activities index	32.2±10.5	33.5±10.5	0.628	1.9±6.1	1.5±5.5	−0.4 (−3.4, 2.6)	0.782
Oswestry disability questionnaire	2.3±1.0	2.6±1.2	0.245	−0.4±0.7	−0.1±0.3	−0.3 (−0.6, −0.1)	0.021*
Osteoarthritis quality of life	3.8±6.2	5.9±7.2	0.234	−0.5±3.0	−0.6±1.6	−0.1 (−1.4, 1.1)	0.814

Values are expressed as mean ± SD or mean (95 % confidence interval).

*P <0.05; **P <0.01

chronic low back pain have been shown to be associated with weakened muscle strength, decreased walking speed, diminished physical task performance, and increased disability [41], which have in turn been shown to significantly affect occupational performance, treatment outcomes, health-related QOL, and patients' return to work following functional rehabilitation programs [42, 43].

Our findings represent the first report of the effectiveness of short-term light therapy for the reduction of fear-avoidance beliefs and the severity of disability. However, the reason for this reduction in fear beliefs is unclear. The possible mechanisms for the reduction of pain following light therapy include the following: (1) increased endogenous opioid neurotransmitter production [43]; (2) enhanced thermal pain threshold [44] and local blood circulation [45]; (3) increased oxygen consumption [46] and ATP production [47] at the cellular level; and (4) anti-inflammatory effects [48]. The attentional and interpretive processes of pain and nociceptive input to the cerebral cortex are complex, and are related to the subjective experience of pain [49]. Therefore, our participants felt possibly less pain upon moving after light therapy, thereby becoming less afraid of moving afterward. Alternatively, expectations generated after light therapy through cortical responses specifically related to pain processing [50] may have diminished their subsequent perception of pain.

The effects of phototherapy are time-dependent [51]. Light therapy initiates the release of nitric oxide, with subsequent subcellular and cellular biochemical and physiological changes [52]. Multiple variables affect the clinical therapeutic effects of light therapy, such as the light source, the wavelength of light, total energy, power, energy density, the size of the exposure area, the method of application (contact mode or non-contact mode), the total number of treatment sessions, the frequency of treatment, and the duration of each treatment session [11, 53, 54]. We used a higher dose of total energy (83.2 J/cm^2) per treatment in this study compared with previous studies that have used doses of 4 to 36 J/cm^2

[21–23]. At this higher energy level, ICF-related components of body function and participation, such as fear-avoidance beliefs and the severity of disability, improved in the treatment group compared with the placebo group. In addition, we administered a higher dose of photo energy over a shorter total duration of treatment compared with previous studies (2 vs 4 to12 weeks, respectively) [21–23]. We also conducted fewer treatment sessions, compared with previous studies (6 vs 10 to 20 sessions) [21–23]. Further studies on light therapy for chronic low back pain should ideally investigate the use of longer treatment durations and different energy levels, treatment frequencies, wavelengths of infrared light, and placements of the light therapy pads, in addition to combinations of treatments using other therapeutic modalities, such as exercise.

This study used reliable, valid, patient-centered measurements based on the ICF model, including self-reported and functional performance-based assessments [55]. Self-reported assessments, such as the FABQ, the FAI, the ODQ, and the OA-QOLQ, represent the gold standard for the measurement of perceived health status and health-related QOL. Indices and questionnaires used in this study each have justification [24, 25, 28, 31, 34]. We also used functional assessments to objectively measure activity, such as repeated chair-rising times, and body functions such as the lumbar range of motion, postural stability, and dynamic balance. These assessments, which have demonstrated acceptable validity and reproducibility [56], are well suited for measuring the functions of disabled and elderly patients, and are not influenced by cultural and demographic factors. We recruited relatively middle-aged to old participants. For safety reasons, we used the most stable resistance level (level 8) to measure their postural stability and dynamic balance by using the BBS.

Our findings are subject to several limitations. First, we applied light therapy for 2 weeks only. Whether longer durations of treatment would produce the same results remains uncertain. Second, most conservative treatment approaches for chronic low back pain use multiple treatment modalities involving some form of exercise. Our use of hot-pack therapy combined with light therapy as the sole treatment for our study may not be clinically plausible. Further studies comparing the effects of co-interventions, such as light therapy combined with exercise, are warranted. Third, we did not include an evaluation of environmental factors, as recommended under the ICF structure, which may have affected our findings. Finally, because light therapy produces tangible heat, participants in our light therapy group may have perceived an additional sensation of heat during treatment. We concede that any perceived increase in heat by the participants in the treatment group may have confounded our results. Treatment with superficial heat, such as the use of heat wraps or heated blankets, has been shown to be effective for short-term pain relief and back-related functional performance [57]. We added the simultaneous hot-pack treatment to the intervention for our study to avoid the potential confounding thermal effects of blinded light monotherapy, but thermal effects clearly resulted from the light therapy dose used in our study. Thus, the limits of current light-emitting diode technology prevented the precise evaluation of the effects of light therapy alone. However, the possible synergistic effects of light therapy-induced heat and hot-pack treatment may have some relevance for clinical care. Our findings should motivate future studies with alternative designs for the evaluation of light therapy for chronic low back pain.

In conclusion, the combination of short-term 890-nm light therapy and hot-pack treatment reduced chronic low back pain, compared with hot-pack treatment combined with placebo light therapy. The reductions in chronic low back pain were associated with reductions in the severity of disability and fear avoidance beliefs.

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MR-01800 Rev W 11/06/2013

Anodyne® Therapy Professional System

Model 480

Important Safety Information and Instructions

Read Entire Booklet Before Operating

Table of Contents

The Anodyne® Therapy System is a noninvasive, drug-free medical device that delivers Monochromatic Infrared Energy (MIRE™) through infrared light-emitting diodes, with a wavelength of 890 nm, that are mounted in flexible therapy pads. The FDA has cleared this device for use in the United States with indicated uses for temporarily increasing local circulation and reducing pain, stiffness and muscle spasm.

Please review this manual in its entirety prior to using this system. If you have any questions, comments or concerns, please call Anodyne Therapy, LLC at 800-521-6664 or visit *www.anodynetherapy.com*.

Contraindications

Anodyne® Therapy should not be used directly over or near the womb during **pregnancy** or directly over **an active cancer**. The effects of this device with these types of conditions are unknown.

Adverse Reactions

- Some patients with extremely poor circulation may experience some discomfort or hypersensitivity initially. This usually resolves with 3-6 treatments.
- Potential for superficial burns.
- Potential for hypoglycemia due to increased patient activity.

Warnings and Precautions

WARNING: Use carefully. May cause serious burns. Do not use over sensitive areas or in the presence of poor circulation. The unattended use of the Model 480 by children or incapacitated persons may be dangerous.

To minimize the risks of burns, please read and follow these important precautions

Treatment Time	• Never treat a patient for more than 45 minutes per treated area. • If the patient's skin is very dry, thin, necrotic or sensitive, treat for the minimum times listed in the *Instructions for Use*. • Check the treatment area every 10 minutes for burns. • If there is evidence of a burn, discontinue treatment and call Anodyne Therapy at 1-800-521-6664 to report the incident. • It is recommended to utilize a timer when administering treatments as this will help to prevent over treatment
Therapy Pad Placement	• Use caution when treating over bony areas such as ankles, knees, elbows shins and tops of feet and hands. These areas have less tissue and are more susceptible to burns.
Therapy Pad Pressure	• Do not have a patient lie on top of or put pressure on the Therapy Pads during treatment. • Place pads lightly on the skin. Excessive pressure may cause burning.
Therapy Pad Warmth	• It is normal for patients to experience warmth during treatment. If a patient feels that the therapy is too hot for comfort, discontinue treatment and reference Device Troubleshooting on page 13 of this manual. • If you feel that your system is too hot, discontinue use and call Anodyne Therapy at 1-800-521-6664.
Skin Color Changes	• It is normal for the treated area to be slightly pink after treatment. This is a sign of increased circulation in the area and should go away within a few hours. If area is red and redness persists, stop treatment. Then reduce therapy time or decrease the energy dial setting in subsequent treatments thereafter.
Energy Setting	• 6-8 bars when treating patients with compromised skin integrity, circulatory compromise, insensate areas; or an open wound in the treatment area. • 8-10 bars for patients with good skin integrity.
Topical Heating Agents	• Do not use Therapy Pads over pain patches, or residual of; or over topical heating lotions or gels.
Other	• Do not saturate, soak, or immerse components in water or liquid.

Warnings and Precautions

NORMAL ENVIRONMENTAL CONDITIONS

- An ambient temperature range of +10 degrees C to +40 degrees C (50° F to 104° F).
- A relative humidity range of 30% to 75%.
- An atmospheric pressure range of 500 hPa to 1060 hPa.

ENVIRONMENTAL CONDITIONS FOR TRANSPORTATION AND STORAGE

- An ambient temperature range of -40 degrees C to 70 degrees C (-40° F to 158° F).
- A relative humidity range of 10 to 100RH including condensation. Be sure not to store in excessively damp location.
- An atmospheric pressure range of 500 hPa to 1060 hPa.
- Device is packaged to maintain cleanliness and minimize egress of water.

CAUTION: THIS IS AN ELECTRICAL DEVICE AND CAN CAUSE ELECTRICAL SHOCK.

Electrical Precautions

- To avoid risk of electrical shock, this equipment must only be connected to a supply mains with protective earth.
- This equipment is intended for use with Anodyne® Therapy pad cables only.
- The Anodyne® Therapy System needs to be installed and put into service according to the information supplied with this Instruction Manual.
- No modification of this equipment is allowed.
- Use only the supplied attachment straps, paper tape, gravity or applicators approved in this manual to maintain the Therapy pad position. Do not use pins or other metallic materials as a means of attachment.
- Do not use a portable electric generator as a power source.
- The Anodyne® Therapy System is an electronic device in which a portion of the electronics may be hazardous. As such, the device should be disposed of in an environmentally responsible manner. The device should be disposed of in a hazardous waste management facility in your local area at the end of its useful life.
- ***Avoid using this system in water, near water or while the device or user is wet. This may cause burn or electrical shock.***

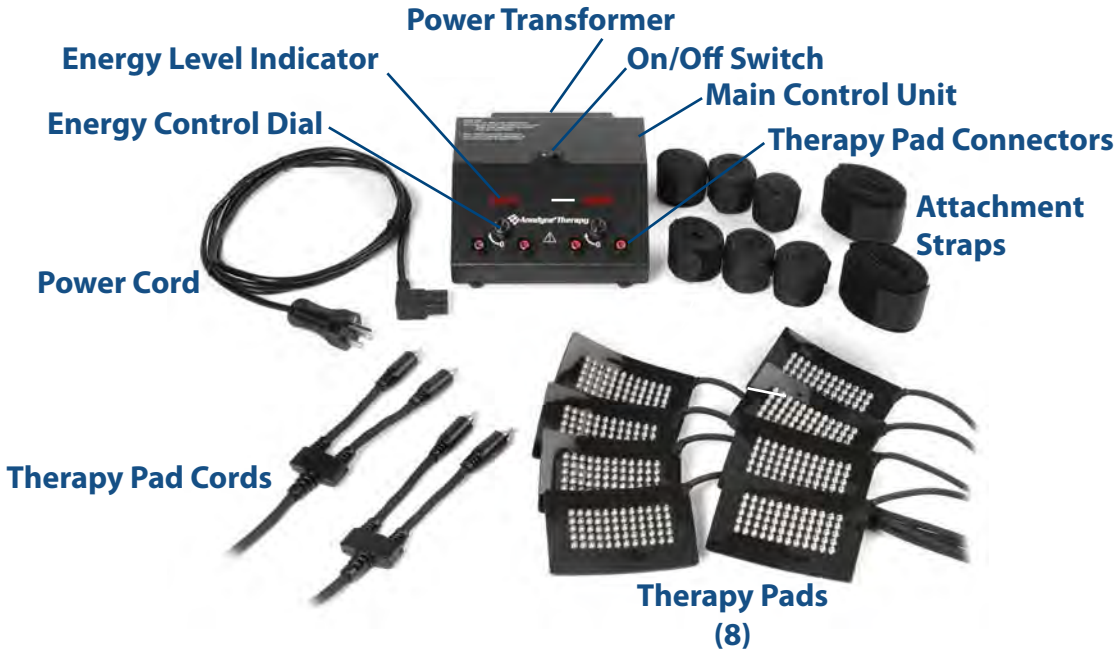
Markings and Symbols

	Consult Accompanying Documents	O	Off (power: disconnection from the mains)		Separate Collection for Electrical and Electronic Equipment
	Alternating Current	I	On (power: connection to the mains)		Type B Applied Part
	Direct Current	CE 0120	Conforms to essential health and safety requirements set out by European Directives - CE MARK	EC REP	Authorized Representative in the European Community
ISO 13485	Compliant to the ISO 13485 Standard				

Instructions For Use

Components

The Anodyne® Therapy System, Model 480 consists of the Main Control Unit, Therapy Pads, Attachment Straps, Velcro Strips and the Carrying Case.



Setting up the Anodyne® Therapy System

Step 1: Place the Main Control Unit securely on a table or cart to prevent it from falling and endangering the patient. Be sure there is an electrical outlet close to the System.

Step 2: Do not position the equipment in such a manner that it makes it difficult to operate the disconnection device when an appliance coupler or separable plug is used as an isolation means.

Step 3: Visually inspect both the power cord and the Therapy Pads to ensure that no exposed wires are present, as exposed wires may be unsafe and can cause electrical shock. If exposed wires exist, discontinue use and reference Device Troubleshooting on page 13 of this manual.

Step 4: Plug the cord into the power transformer on the back of the System and into an active electrical wall outlet. Be sure the electricity to the outlet is turned on.

Step 5: Plug the ends of the cords of the Therapy Pads into the Therapy Pad Connectors on the front of the Control Unit. Be sure they are inserted firmly into the Connectors.

Step 6: Turn on the Control Unit using the On/Off Switch on the top of the System.

Step 7: Turn the Energy Control Dials all the way to the right. The Energy Control Indicators should show 10 energy bars on each side when all Therapy Pads are properly connected. If all 10 bars do not illuminate, wait a few minutes and retry. If the bars still do not illuminate, discontinue use and reference Device Troubleshooting on page 13 of this manual.

Step 8: The System is now ready to be used with patients. Place the Therapy Pads on the area to be treated, being sure to place a clear plastic barrier between the Pads and the patient's skin. Specific treatment protocols are located on pages 9-11 of this manual.

Step 9: Always turn this System OFF between each session using the On/Off Switch.

Instructions For Use

Treatment Guidelines and Precautions

The recommendations appearing on the subsequent pages are meant only to be guidelines. Every patient is different and may have different experiences and results with Anodyne® Therapy treatment. Please address questions to these guidelines to Anodyne Therapy at 1-800-521-6664.

- Review all the *Warnings and Precautions* before using this device to prevent burns or electrical shocks.
- Prior to starting each treatment session, always ensure all 10 energy bars are lit when both Energy Dials have been turned all the way to the right.
- Prior to starting each therapy session, ensure the Energy Dials are adjusted to the appropriate setting for each patient.
- Prior to starting each therapy session, always completely remove topical heating or cooling agents and pain patches.
- Ensure that there is nothing between the Therapy Pads and the patient's skin except for a clear plastic barrier.
    - ☑ Ensure there are no socks or any other type of clothing between the Therapy Pads and the patient's skin.
    - ☑ Do not place the Therapy Pads over a bandage, dressing, or cast.
- For maximum effectiveness, ensure all of the diodes of the Therapy Pads are in light contact with the skin.
- Do not use if System materials cause skin irritation.
- This System may be safely used over metal implants, pins and screws and with people with pacemakers and defibrillators.
- This System may be used adjunctively with other therapeutic modalities.
- Always separate Anodyne® Therapy sessions by a minimum of four hours.
- Do not leave this System unattended around small children or pets.
- Do not saturate, soak or immerse components in water or liquid.

Normal Physiological Responses

- Patients may feel a therapeutic warmth during an treatment session.
- Patients with impaired circulation in the extremities, may experience tingling and pulsing as circulation returns to the area. *If this causes discomfort:*
    - Reduce treatment time
    - Increase frequency of treatments
    - Move Therapy Pads further up on legs or arms
- Patients may experience re-growth of hair or toenails as this is an indication of increased micro circulation in the legs and feet.
- Treated area may be slightly pink after a treatment session.
- As circulation increases, it is normal for lesions near the treatment area to increase amount of exudate after a treatment session.
- As circulation increases, it is normal for dry and necrotic skin near the treatment area to peel or slough off exposing new skin below.

Instructions For Use

Treatment of impaired circulation, pain, stiffness or muscle spasm in the extremities

Therapy Pad Placement	***Feet and Legs:*** - Place two Therapy Pads in a "T" shape on the bottom of each foot as shown below. - Place an additional Therapy Pad on the lateral and medial side of each calf where symptoms begin as shown below. - Move Therapy Pads proximal to distal as symptoms improve ***Hands and Arms:*** - Place one to two Therapy Pads on the palm of the hand - Place one to two Therapy Pads on the lateral and medial sides proximally on the arm where symptoms begin.
Energy Control Setting	6-8 bars Do *not treat patients with compromised skin integrity at 9 or 10 energy bars.*
Clinical Treatment Frequency	3 times per week for 12 treatments, or until condition improves. **NOTE:** *Treatment with Anodyne® Therapy is not a cure for patients exhibiting impaired circulation and extremity pain due to a chronic condition. Ongoing symptomatic relief can be obtained from either periodic additional treatment in a clinical setting or through patient self-treatment with an Anodyne home system.*
Clinical Treatment Time	30-40 minutes - check treated area every 10 minutes for burns.

THERAPY PAD PLACEMENT

Therapy Pads should be placed on each side of the calf and on the bottom of the foot in a "T" formation.

Additional Treatment Notes:

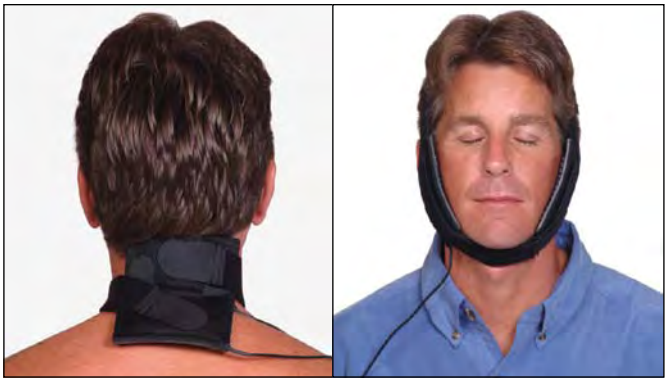
- Tingling and pulsing may be felt by the patient as circulation returns to the area. *If this causes discomfort:*
  - Reduce treatment time
  - Increase frequency of treatments
  - Move Therapy Pads further up legs or arms
- Tight blood glucose control for diabetics is always recommended for optimal results.
- Diabetic patients should monitor their blood glucose levels regularly due to increased activity.

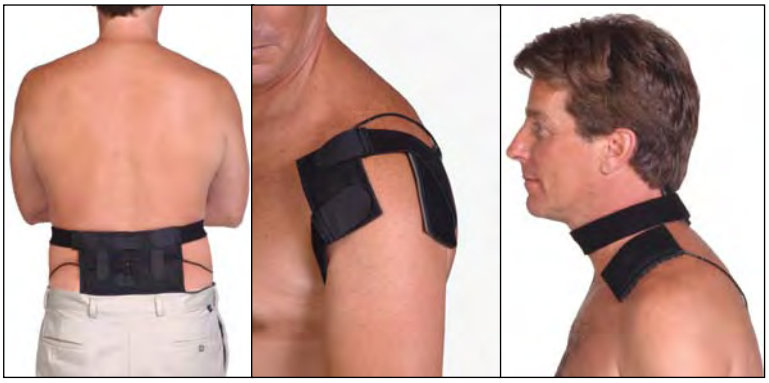
Instructions For Use

Treatment of painful soft tissue injuries, muscle spasm or stiffness

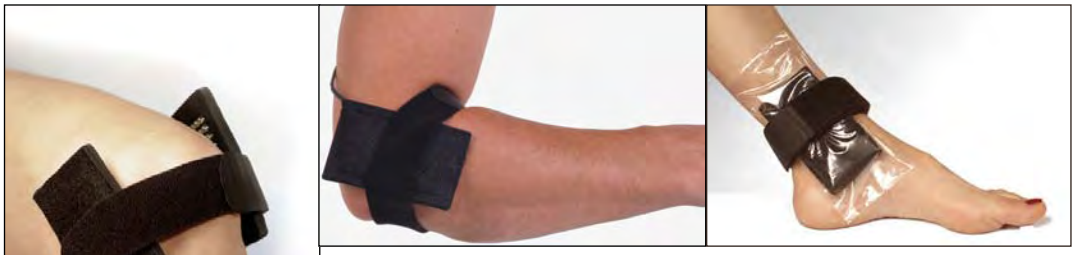
Therapy Pad Placement	Place a minimum of two Therapy Pads directly over the painful area (i.e., knee, elbow, neck, back, etc). If placement of Therapy Pads causes increased pain, place the Therapy Pads proximal, lateral and medial to the injured site. In patients suffering from referred pain - ensure to treat the origin of the pain.
Energy Control Setting	8-10 bars for patients with good skin integrity. 6-8 bars for patients with poor skin integrity. Do *not treat patients with compromised skin integrity at 9 or 10 energy bars.*
Clinical Treatment Frequency	Daily if possible, but at least 3 times per week until symptoms resolve. May be used up to 3 times per day; separate treatments by 4 hours. ***NOTE:*** *Clinical treatment may be stopped when condition resolves. If symptoms are a result of an overuse injury biomechanical issues must also be addressed to prevent reinjury.*
Clinical Treatment Time	20-45 minutes

THERAPY PAD PLACEMENT EXAMPLES





The Therapy Pads can be arranged to fit any area of the body where the patient could benefit from an increase in local circulation, reduction of pain, stiffness or muscle spasm.



If there is an open wound in the treatment area, and/or if this system is being shared by more than one user;

Cover the Therapy Pads or the patient's skin with a clear plastic barrier to avoid the spread of bacteria, viruses and other microorganisms from one person to another.

Instructions For Use

Treatment of impaired circulation and or pain with an open lesion in/near the treatment area.

Therapy Pad Placement	To increase local circulation - place one or two Therapy Pads proximal to the treatment site. To reduce pain - place a minimum of two Therapy Pads directly over the affected area. *If tolerate direct contact is not well tolerated, place the Therapy Pads lateral, medial, proximal and distal of the affected area - until pain lessens.*
Energy Control Setting	5-8 bars Use lower end of range if patients: - Are hypersensitive to heat or light - Exhibit compromised skin integrity Use higher end of range if patients do not exhibit any of the above. *Do not treat patients with compromised skin integrity at 9 or 10 energy bars.*
Clinical Treatment Frequency	Daily if possible, but at least 3 times per week until symptoms resolve. May be used up to 3 times per day; separate treatments by 4 hours.
Clinical Treatment Time	20-30 minutes

Additional Treatment Notes:

- Do not treat directly over a bandage, dressing or an opaque cream - remove all non-clear dressings prior to treatment.
- As circulation increases, it is normal for lesions near the treatment area to increase amount of exudate after a session.
- As circulation increases, it is normal for dry and necrotic skin near the treatment area to peel or slough off exposing new skin below.

Care and Maintenance

The Anodyne® Therapy System is a sophisticated medical device. The following care and maintenance will extend the life of your unit:

- Be careful not to drop the System as this could damage the circuitry.
- Never pull the Therapy Pads out of the Control Unit by the cords.
- Never wrap cords around the Therapy Pads. This may cause the Therapy Pads to separate.
- Never carry the Therapy Pads or the Control Unit by the cords.
- Gently remove Velcro Straps when removing them from the Therapy Pad tops, to avoid pulling the Therapy Pads apart.
- To clean attachment straps, hand wash in cold water with a mild detergent, rinse, and air dry.
- Equipment is factory-calibrated and does not require adjustment on site. There are no field serviceable components. Contact Anodyne Therapy, LLC at 1-800-521-6664 for product servicing.

Infection Control

- If you are treating multiple patients or treating over an open wound/lesion, always cover the Therapy Pads or the patient's skin with a clear plastic barrier.
- Always change the plastic barrier between patients to protect them from cross-contamination and discard the plastic barrier after each use.
- Keep the Therapy Pads and Control Unit clean with a hospital-grade disinfectant, as per facility protocol.
  - Spray lightly and wipe with a clean cloth only when unit is powered off.
- Do not saturate, soak, or autoclave the Therapy Pads or Control Unit when disinfecting, as per facility protocol. This may cause corrosion to the components which may increase the risk of burns or cause electrical shock.

Warranty

Anodyne Therapy, LLC ("Manufacturer") warrants the Anodyne® Therapy System ("The Product") to the immediate purchaser as follows:

Limited Warranty
Manufacturer warrants that The Product sold hereunder will be free from defects in material and workmanship for a period of either: two (2) years (New Systems) or one (1) year (Reburbished Systems) from the date of purchase with normal use. If the defects are of such type and nature as to be covered by this warranty, Manufacturer shall, at its option, either repair or replace the damaged product at its expense, however consumer is responsible for any international shipping charges that may apply.

This warranty does not cover any Products that have been abused, misused, or tampered with in any way. This warranty does not cover Products damaged in natural disaster or flood; nor does it cover theft. This limited warranty is not transferable, and only applies to purchases direct from Anodyne Therapy LLC, or its authorized distributors.

THIS WARRANTY IS IN LIEU OF OTHER WARRANTIES, INCLUDING WITHOUT LIMITATION, WARRANTIES OF MERCHANTABILITY AND FITNESS FOR PARTICULAR USE, WHICH ARE HEREBY SPECIFICALLY DISCLAIMED.

This limited warranty gives you specific legal rights. You may have other rights, which vary from state to state. To the extent allowed by applicable law, in no event shall manufacturer be liable for any incidental, consequential, special, indirect, punitive or exemplary damages or lost profits from any breach of warranty.

Device Troubleshooting and Servicing

Problem	Troubleshooting
1a. All 10 Energy Bars do not illuminate	• Ensure Therapy Pads are plugged firmly into the jack on the Control Unit. • If you switch the Therapy Pads to the opposite jack, does the problem still occur? • Check the Therapy Pads with a digital camera - are some of the lights on the Therapy Pad illuminated while others are not? • Do the Energy Bars stay at a fixed setting of 5 or 6 or do they flicker or jump? Press on dial 'potentiometer' for visual confirmation. (If Yes, see 1b) • Manipulate the Therapy Pad wires, does this cause the Energy Bar reading to increase or decrease? • If manipulation of the Therapy Pads alone causes the bars to flicker, the problem likely exists in the Therapy Pads and not the Control Unit. • ***Discontinue System use and call Anodyne Therapy at 1-800-521-6664 to arrange for service.***
1b. Energy Bars flicker or do not stay at level set	• Ensure Therapy Pads are plugged firmly into the jack on the Control Unit. • Perform the following actions - without touching the Therapy Pads: - Press on dial 'potentiometer' to see if flickering occurs. - Turn the dial 'potentiometer' slowly to see if flickering occurs. • If touching 'potentiometer' causes bars to flicker, the problem likely exists in the Control Unit. • ***Discontinue System use and call Anodyne Therapy at 1-800-521-6664 to arrange for service.***
2. Therapy Pad array cords are damaged	• Wires exposed or Therapy Pads separating. • ***Discontinue System use and call Anodyne Therapy at 1-800-521-6664 to arrange for service.***
3. Therapy Pads or Control Unit getting too hot	• A therapeutic warmth is normal, however, not a significant heat. • Turn the unit off in between patients, do not let it run continuously. • Have healthcare staff member confirm heat, as patient may be heat sensitive. • ***If problem persists, discontinue System use and call Anodyne Therapy at 1-800-521-6664 to arrange for service.***

Returning A Unit For Repair

To send a unit to Anodyne Therapy, LLC for repair, you must first call 1-800-521-6664 and obtain a return authorization (RA). The following information must be supplied to Anodyne Therapy, LLC before an RA number can be issued:

1) User name and address
2) Device serial number
3) A description of the problem with the unit.

Place return items in a closed plastic bag; place bagged items in a shipping box. DO NOT RETURN straps, velcro attachment tabs, soft shoes or carrying case.

Declaration - Electromagnetic Immunity

The Anodyne® Therapy System, Model 480 is intended for use in the electromagnetic environment specified below. The user of this product should assure that it is used in such an environment.

Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment - Guidance
Electrostatic discharge (ESD) IEC 61000-4-2	+ - 6 kV contact + - 8 kV air	+ - 6 kV contact + - 8 kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.
Electrical fast transient/ burst IEC 61000-4-5	+ - 2 kV for power supply lines + - 1 kV for i/o lines	+ - 2 kV for power supply lines + - 1 kV for i/o lines	Main power quality should be that of a typical commercial or hospital environment.
Surge IEC 61000-4-5	+ - 1 kV differential mode + - 2 kV common mode	+ - 1 kV differential mode + - 2 kV common mode	Main power should be that of a typical commercial or hospital environment.
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	<5% Ut (>95% dip in UT) for 0.5 cycle 40% UT (60% dip in UT) for 5 cycles 70% UT (30% dip in UT) <5% UT (>95% dip in UT) for 5 s	<5% Ut (>95% dip in UT) for 0.5 cycle 40% UT (60% dip in UT) for 5 cycles 70% UT (30% dip in UT) <5% UT (>95% dip in UT) for 5 s	Main power quality should be that of a typical commercial or hospital environment.
Power frequency (50/60 Hz) magnetic field. ISO 61000-4-8	3 A/m	0.3 A/m	If image distortion occurs, it may be necessary to position Model 480 further from the sources of power frequency magnetic fields or to install magnetic shielding. The power frequency magnetic field should be measured in the intended installation location to assure that it is sufficiently low.
NOTE: UT is the a.c. main voltage prior to application of the test level.			

Declaration - Electromagnetic Emissions

The Anodyne® Therapy System, Model 480, is intended for use in the electromagnetic environment specified below. The user of the Model 480 should assure that it is used in such an environment.

Emissions Test	Compliance	Electromagnetic Environment - Guidance
RF emissions	Group 1	The Model 480 uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.
RF emissions	Class B	The Model 480 is suitable for use in all establishments including domestic establishments and those directly connected to the public low-voltage power supply network that supply buildings used for domestic purposes.
Harmonic emissions IEC 61000-3-2	Not Applicable	
Voltage Fluctuations/Flicker emissions IEC 61000-3-3	Complies	

Declaration - Photo Biological Emissions

Each Therapy Pad contains 60 - 890 nm light emitting diodes (LEDs) that emit infrared energy at a maximum radiant intensity of 19.7 mW/sr. Based upon the supplier's LED specifications, the photo biological emissions from the Anodyne Therapy System Model 480 meet the eye safety guidelines of the IEC60825-1- Class 1, IEC62471-Exempt, and the EU Directive 2006/25/EC.

NOTES

Anodyne® Therapy
The Trusted Name in Light Therapy

Manufacturer:
Anodyne Therapy, LLC
Address: 14105 McCormick Drive
Tampa, FL 33626
Tel: 1-800-521-6664
Fax: 1-800-835-4581
Website: www.anodynetherapy.com

EC REP

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CE
0120

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Zion, IL 60099

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web cancercenter.com

Dr. David Phillips
CEO and Founder
Rebuilder Medical

RE: ReBuilder System®

On behalf of the Oncology Rehabilitation team and the Medical Staff at Midwestern Regional Medical Center, I want to personally thank you for inventing and developing the ReBuilder System, a fabulous medical device to help alleviate the symptoms of Peripheral Neuropathy. In the past, we have used traditional physical therapy electrical stimulation devices such as traditional TENS and Interferential Current (IFC), but the ReBuilder System provided our patients with Chemotherapy Induced Peripheral Neuropathy (CIPN) the best and longest lasting pain relief while undergoing chemotherapy treatment.

From 2005 to 2007 we treated 124 cancer patients with CIPN who were actively undergoing chemotherapy treatment at Midwestern Regional Medical Center of which 40% reported a 30% to 50% reduction in their pain scale, 53% reporting 10% to 20% reduction in their Pain scale, and 3% reporting 50% or more reduction in their pain scale, and only 4% reported no change.

With these remarkable results (96% success rate) the ReBuilder System is now being used across all four CTCA sites in Tulsa, Phoenix, Philadelphia and Chicago – touching and helping more oncology patients relieve their CIPN symptoms. This calendar year alone, between all four sites, we have treated over 300 patients successfully.

We believe in your product's ability to alleviate CIPN symptoms for cancer patients receiving chemotherapy. Patients have reduced or stopped taking pain medicine such as Gabapentin and Lyrica for CIPN.

At CTCA…

"It is only… and always will be…..about the patient." Richard Stephenson, Chairman of the Board at of Cancer Treatment Centers of America

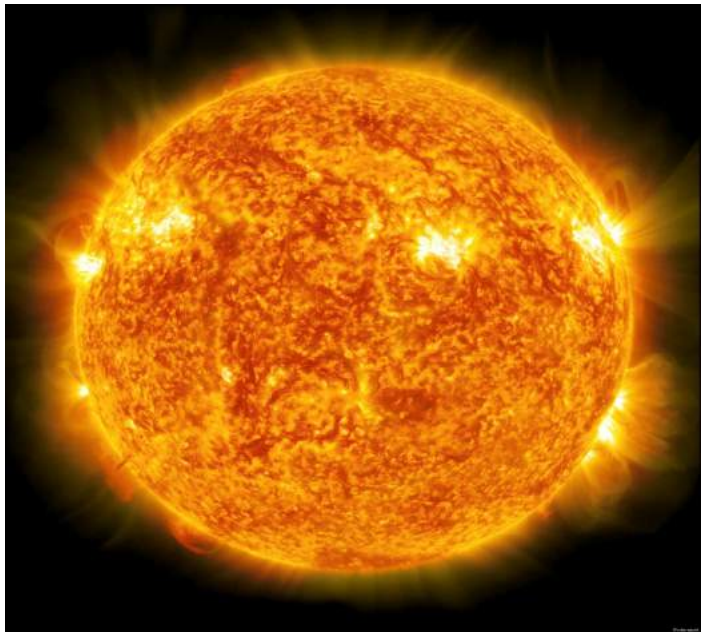
Respectfully Yours,

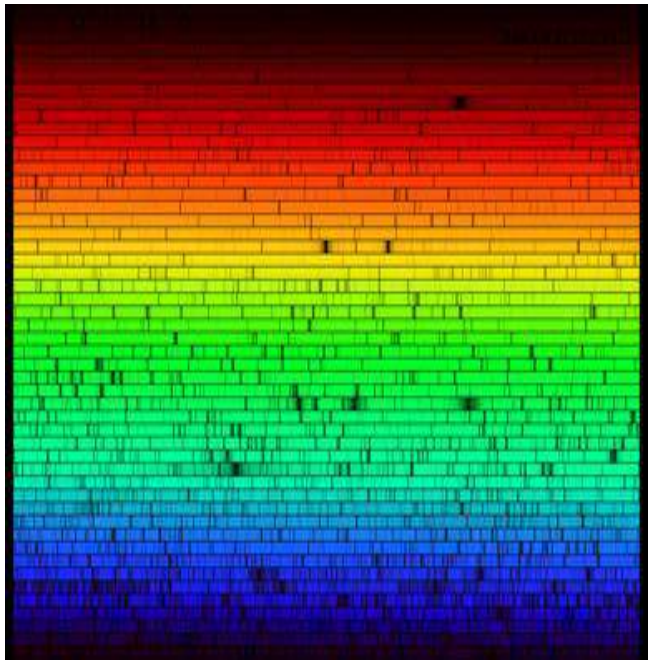
Stanislav Maravilla, PT
Director of Rehabilitation Services
Cancer Treatment Centers of America @
Midwestern Regional Medical Center

Synergistic Effects of Light Therapy and Nutrition

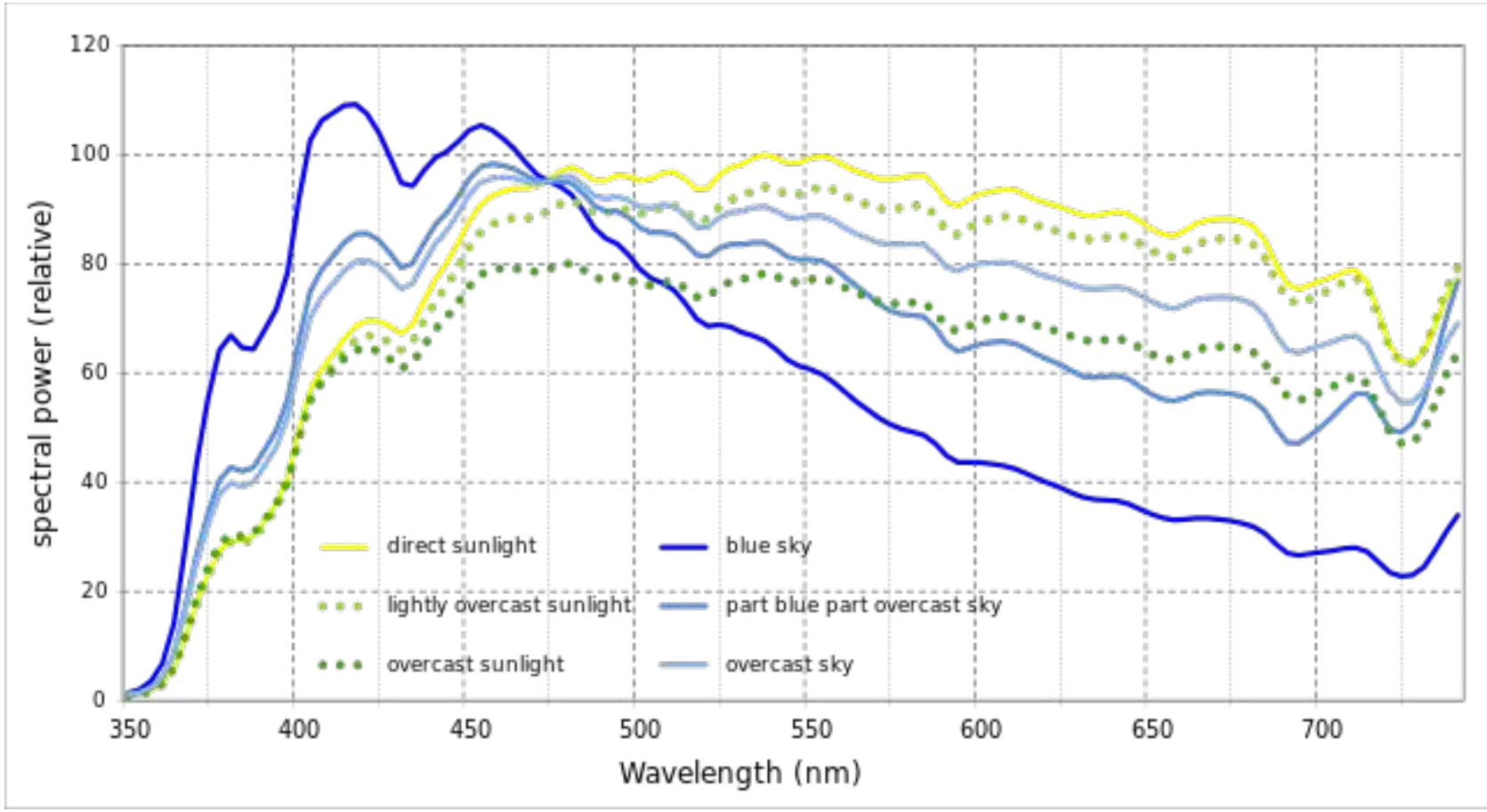
Kyl Smith, DC

Sunlight is a portion of the electromagnetic radiation given off by the *Sun*





Synergistic Effects of Light Therapy and Nutrition



Yellow line = the spectrum of direct illumination under optimal conditions

Synergistic Effects of Light Therapy and Nutrition

- **Although cells in vitro are responsive to a variety of wavelengths in the electromagnetic spectrum, *beneficial responses in vivo are observed within a narrow wavelength range*.**
- Lower wavelengths such as violet and ultraviolet penetrate less, whereas ***those in the red and infrared range have higher penetration*.**
- Energy at wavelengths shorter than 600nm are generally scattered in biological tissues in vivo and are absorbed by melanin, whereas water significantly absorbs energy at wavelengths higher than 1150nm.
- **For clinical purposes = *the in vivo therapeutic "optical window" strongly corresponds to red and near-infrared wavelengths*.**

Synergistic Effects of Light Therapy and Nutrition

Low-Level-Laser (Light) Therapy (LLLT) involves exposing cells or tissue to low levels of red and near infrared (NIR) light, and is referred to as "low level" because of its use of light at energy densities that are low compared to other forms of laser therapy that are used for ablation, cutting, and thermally coagulating tissue.

LLLT is also known as "cold laser" therapy as the power densities used are lower than those needed to produce heating of tissue. It was originally believed that LLLT or **photobiomodulation** required the use of coherent laser light, but more recently, **light emitting diodes (LEDs)** have been proposed as a cheaper alternative.

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The Nuts and Bolts of Low-level Laser (Light) Therapy

Hoon Chung,[1,2] Tianhong Dai,[1,2] Sulbha K. Sharma,[1] Ying-Ying Huang,[1,2,3] James D. Carroll,[4] and Michael R. Hamblin[1,2,5]

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Abstract

Soon after the discovery of lasers in the 1960s it was realized that laser therapy had the potential to improve wound healing and reduce pain, inflammation and swelling. In recent years the field sometimes known as photobiomodulation has broadened to include light-emitting diodes and other light sources, and the range of wavelengths used now includes many in the red and near infrared. The term "low level laser therapy" or LLLT has become widely recognized and implies the existence of the biphasic dose response or the Arndt-Schulz curve. This review will cover the mechanisms of action of LLLT at a cellular and at a tissular level and will summarize the various light sources and principles of dosimetry that are employed in clinical practice. The range of diseases, injuries, and conditions that can be benefited by LLLT will be summarized with an emphasis on those that have reported randomized controlled clinical trials. Serious life-threatening diseases such as stroke, heart attack, spinal cord injury, and traumatic brain injury may soon be amenable to LLLT therapy.

Keywords: Low level laser therapy, Photobiomodulation, Mitochondria, Tissue optics, Wound healing,

Synergistic Effects of Light Therapy and Nutrition

Light Therapy has now developed into a therapeutic procedure that is science-based, well-substantiated, and utilized in three main ways:

1. ***to reduce inflammation, edema, and chronic joint disorders;***
2. ***to promote healing of wounds, deeper tissues, and nerves;***
3. ***and to treat neurological disorders and pain.***

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Keywords: Low level laser therapy, Photobiomodulation, Mitochondria, Tissue optics, Wound healing,

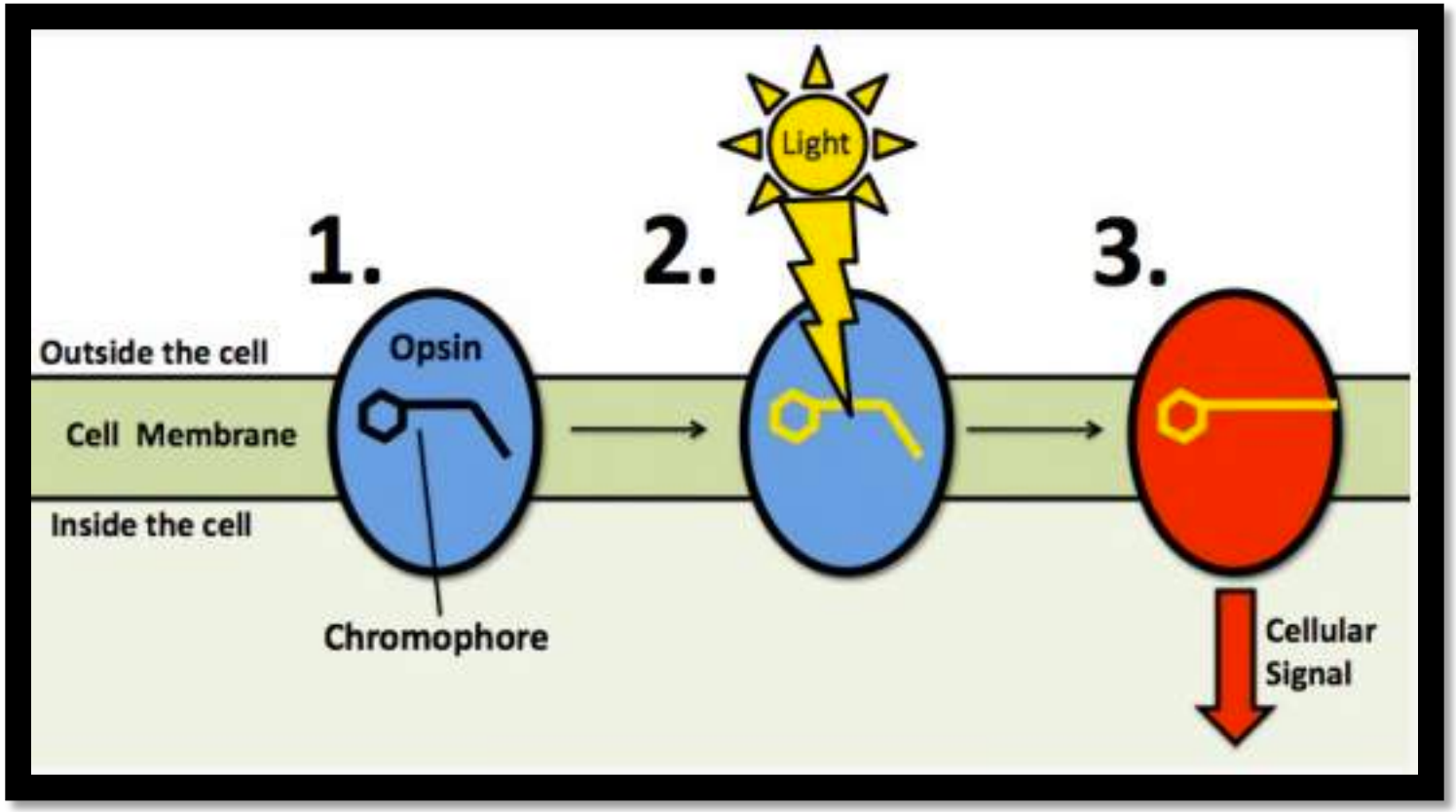
Synergistic Effects of Light Therapy and Nutrition

Photochemical reaction = Biostimulation = Photobiomodulation

A **chromophore** is the part of a molecule responsible for its color.[1]

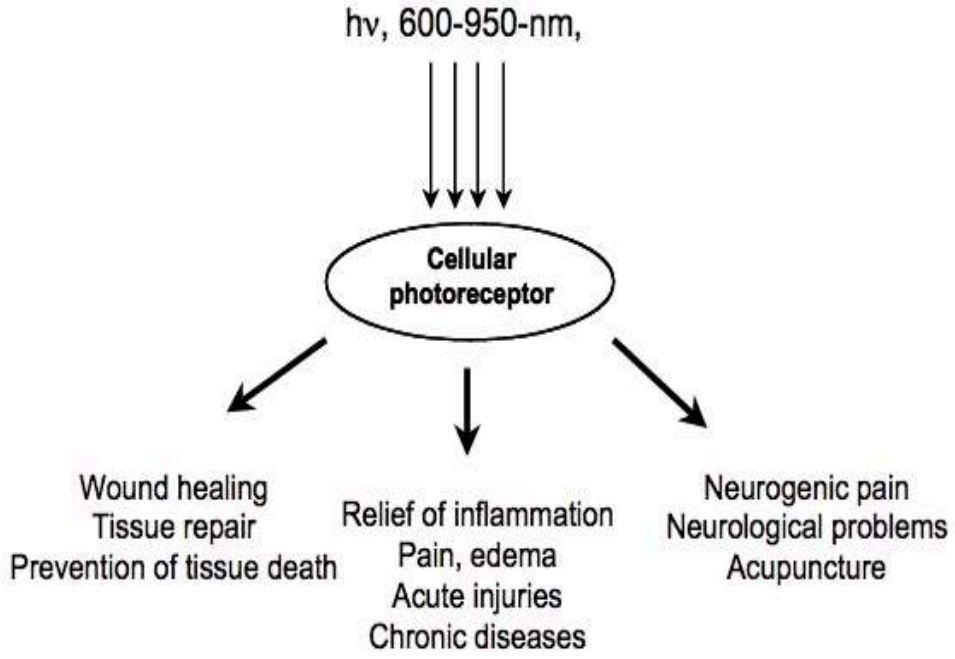
The color arises when a molecule absorbs certain wavelengths of visible light and transmits or reflects others.

Visible light that hits the chromophore can thus be absorbed by exciting an electron from its ground state into an excited state.



Synergistic Effects of Light Therapy and Nutrition

Chromophore within Mitochondria = Initial Target of LLLT



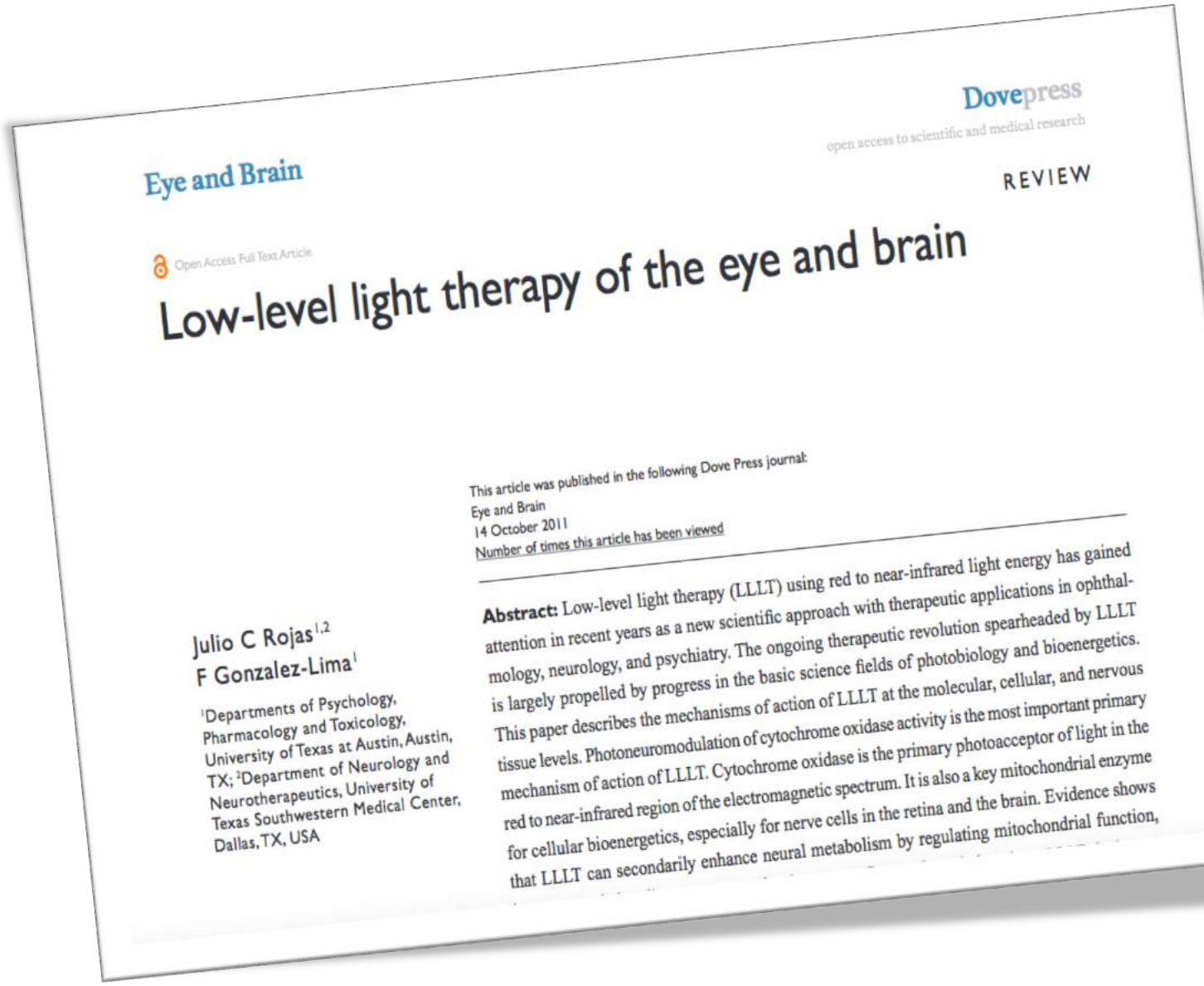
Mitochondria are stimulated, leading to increased ATP production, modulation of reactive oxygen species, and induction of transcription factors.

Patient Benefits Include:

- **Increased healing of chronic wounds**
- **Improvements in sports injuries and carpal tunnel syndrome**
- **Pain reduction in arthritis and neuropathies**
- **Amelioration of damage after heart attacks, stroke, and nerve injury**

Synergistic Effects of Light Therapy and Nutrition

"Photoneuromodulation of cytochrome oxidase activity is the most important primary mechanism of action of LLLT. Cytochrome oxidase is the primary photoacceptor of light in the red to near-infrared region of the electromagnetic spectrum. It is also a key mitochondrial enzyme for cellular bioenergetics, especially for nerve cells in the retina and the brain. Evidence shows that LLLT can secondarily enhance neural metabolism by regulating mitochondrial function, intraneuronal signaling systems, and redox states."



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Eye and Brain

REVIEW

Open Access Full Text Article

Low-level light therapy of the eye and brain

This article was published in the following Dove Press journal:
Eye and Brain
14 October 2011
Number of times this article has been viewed

Julio C Rojas[1,2]
F Gonzalez-Lima[1]

[1]Departments of Psychology, Pharmacology and Toxicology, University of Texas at Austin, Austin, TX; [2]Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX, USA

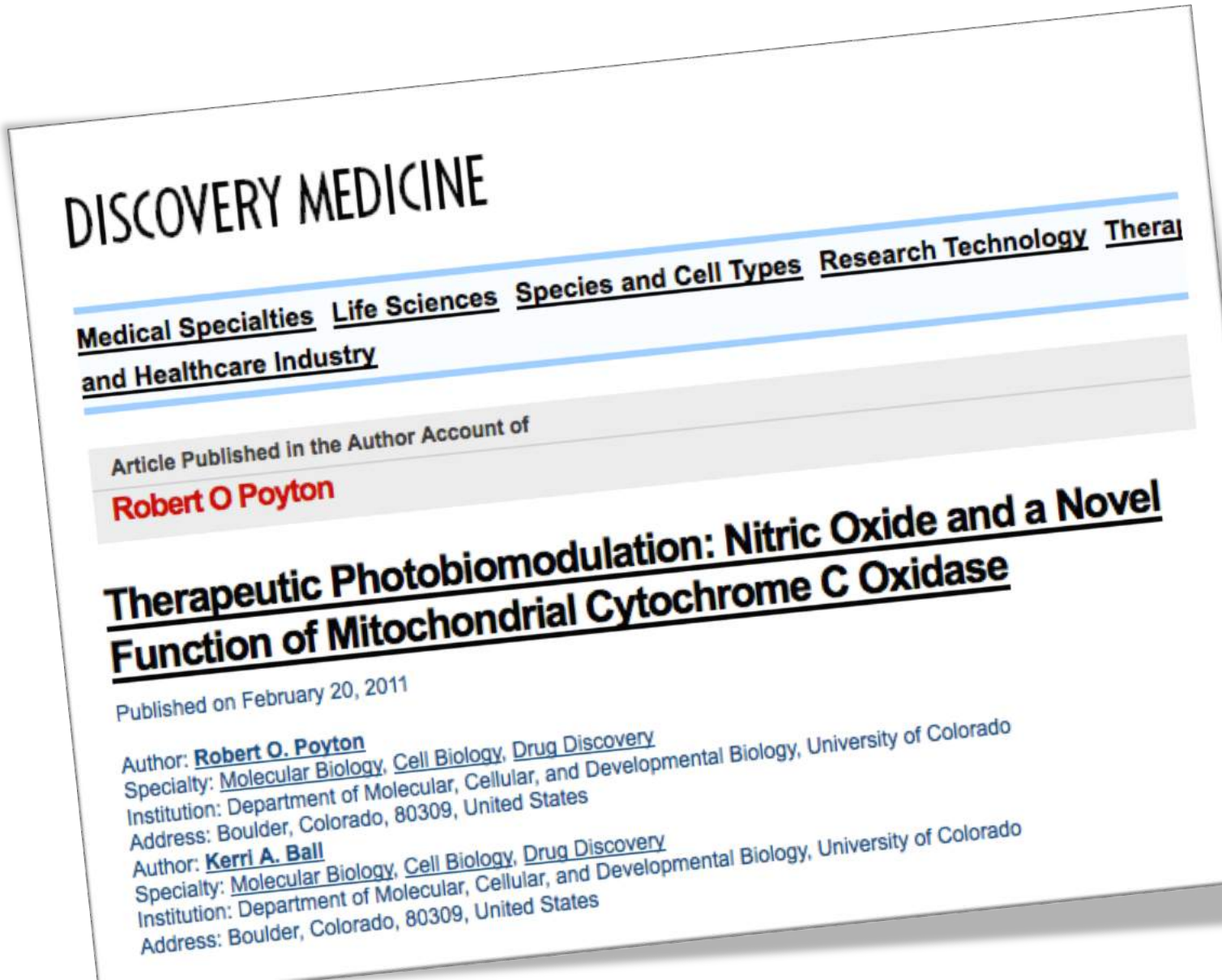
Abstract: Low-level light therapy (LLLT) using red to near-infrared light energy has gained attention in recent years as a new scientific approach with therapeutic applications in ophthalmology, neurology, and psychiatry. The ongoing therapeutic revolution spearheaded by LLLT is largely propelled by progress in the basic science fields of photobiology and bioenergetics. This paper describes the mechanisms of action of LLLT at the molecular, cellular, and nervous tissue levels. Photoneuromodulation of cytochrome oxidase activity is the most important primary mechanism of action of LLLT. Cytochrome oxidase is the primary photoacceptor of light in the red to near-infrared region of the electromagnetic spectrum. It is also a key mitochondrial enzyme for cellular bioenergetics, especially for nerve cells in the retina and the brain. Evidence shows that LLLT can secondarily enhance neural metabolism by regulating mitochondrial function,

Synergistic Effects of Light Therapy and Nutrition

Cytochrome c oxidase has been shown to have a new enzymatic activity----*the reduction of nitrite to nitric oxide*.

Low intensity light enhances nitric oxide synthesis by cytochrome c oxidase without altering its ability to reduce oxygen.

From these findings, we propose that cytochrome c oxidase functions in photobiomodulation by producing nitric oxide, a signaling molecule which can then function in both intra- and extracellular signaling pathways.



DISCOVERY MEDICINE

Medical Specialties Life Sciences Species and Cell Types Research Technology Therap
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Article Published in the Author Account of

Robert O Poyton

Therapeutic Photobiomodulation: Nitric Oxide and a Novel Function of Mitochondrial Cytochrome C Oxidase

Published on February 20, 2011

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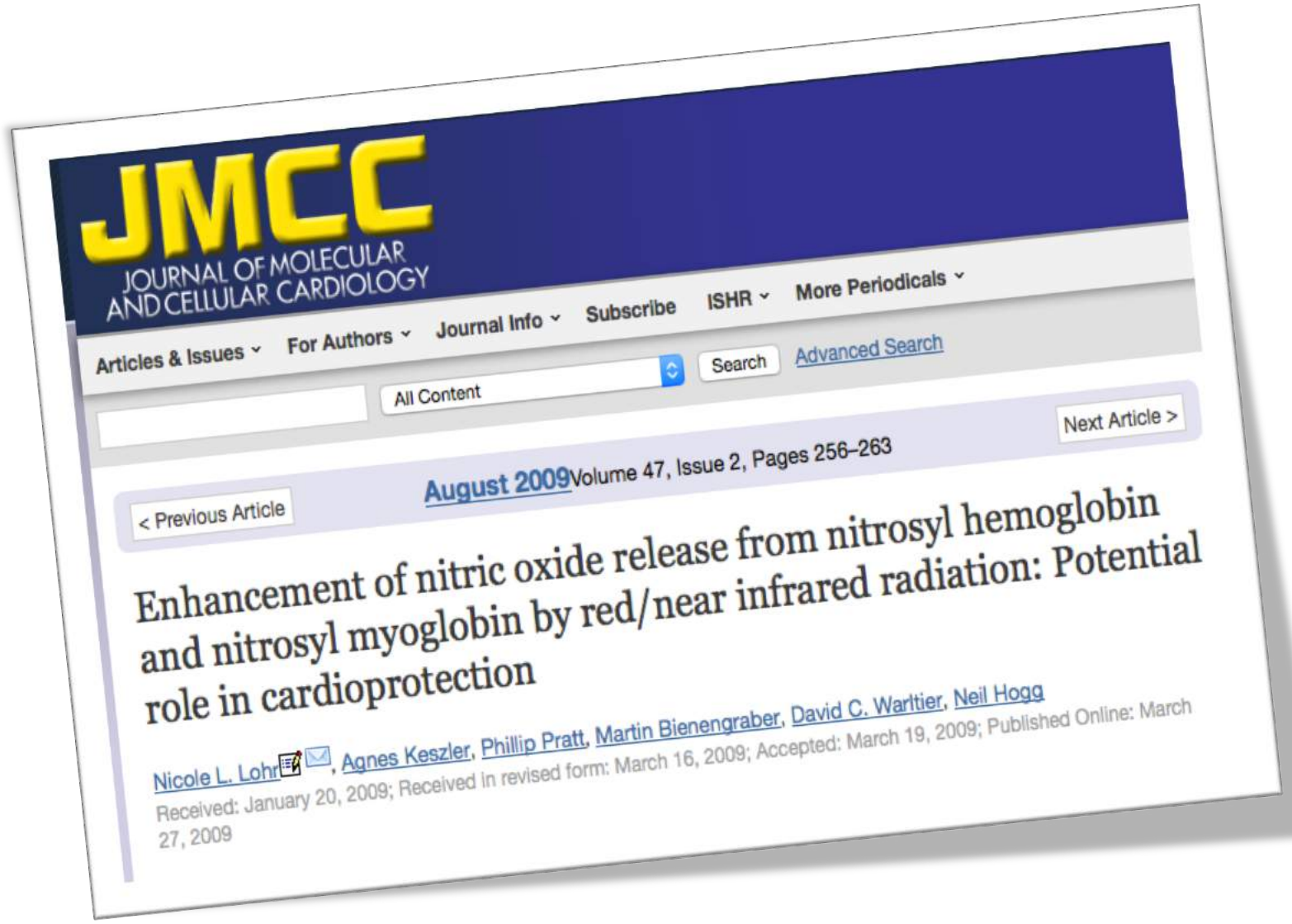
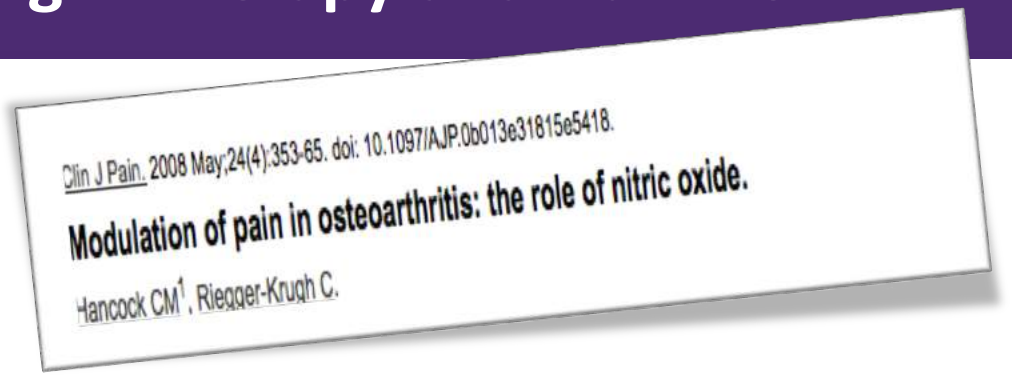
Synergistic Effects of Light Therapy and Nutrition

"We show both in purified systems and in myocardium that R/NIR light can decay nitrosyl hemes and release NO, and that this released NO may enhance the cardioprotective effects of nitrite. ***Thus, the photodissociation to NO and its synergistic effect with sodium nitrite may represent a noninvasive and site-specific means for increasing NO bioavailability.***"



Synergistic Effects of Light Therapy and Nutrition



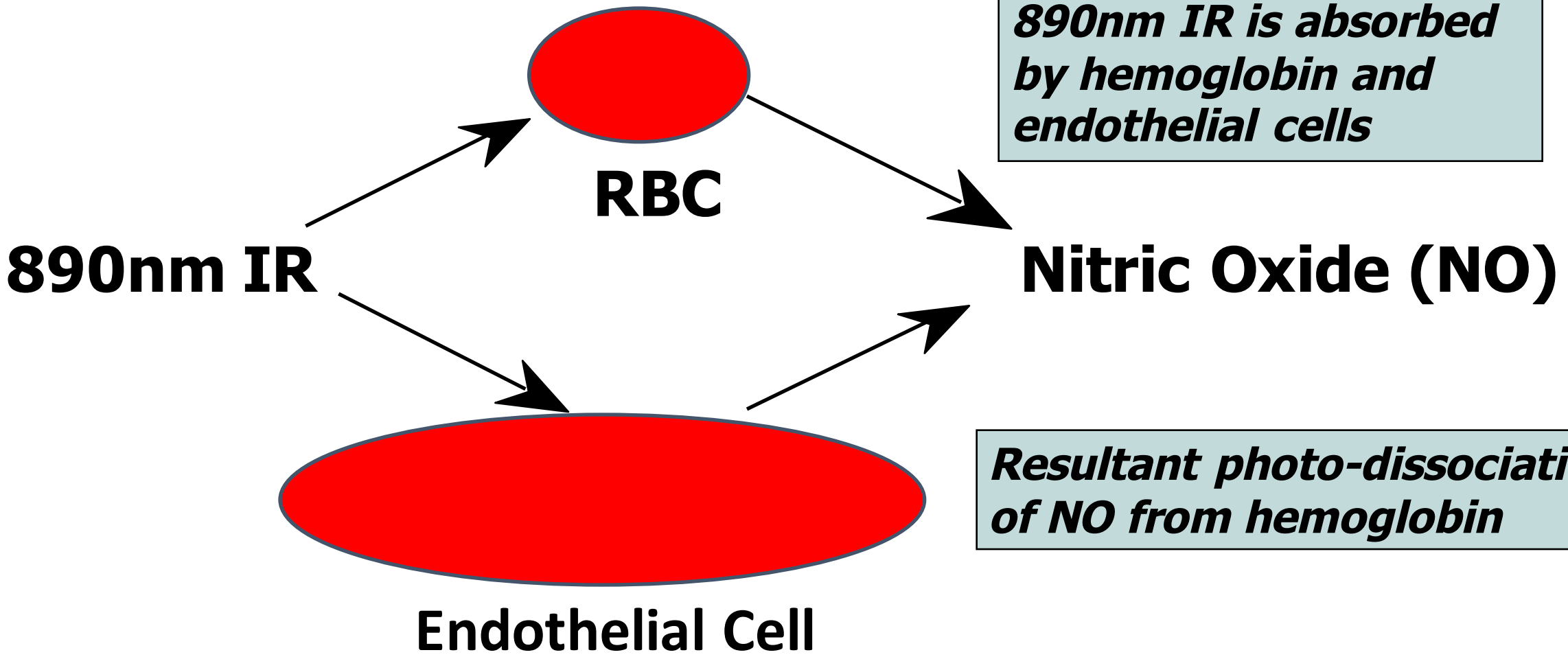
(1) NO via the beneficial cNOS pathway is decreased in joint structures exposed to chronic load-induced stresses and biochemical change-induced stresses,

(2) Monochromatic infrared light energy at an 890 nm wavelength, applied at the skin surface, is absorbed into blood vessels and stimulates production of NO in joints by the beneficial cNOS pathway,

(3) NO from the cNOS pathway may help decrease the detrimental effects of NO induced by iNOS and produced in OA pathology, and

(4) NO-based intervention may produce substantial pain relief without undesirable side effects by increasing circulation, decreasing nerve irritation, and decreasing inflammation in joints.

Synergistic Effects of Light Therapy and Nutrition

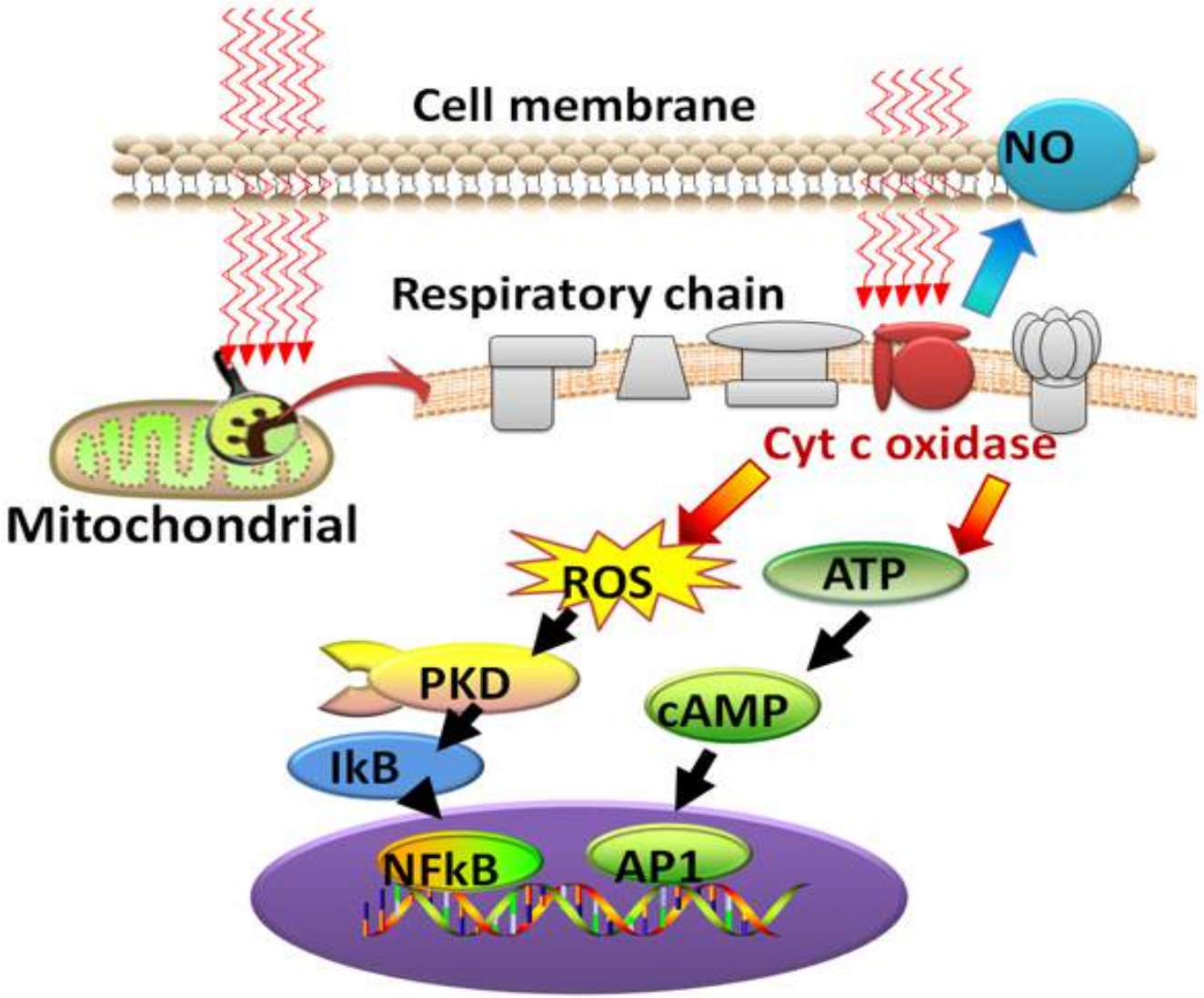


890nm (IR) causes the photo-dissociation of NO from hemoglobin in the red blood cells (and possibly from the endothelial cells as well) allowing NO to be free (locally) to do its work.

Synergistic Effects of Light Therapy and Nutrition

NO Release From Tissue or Blood:

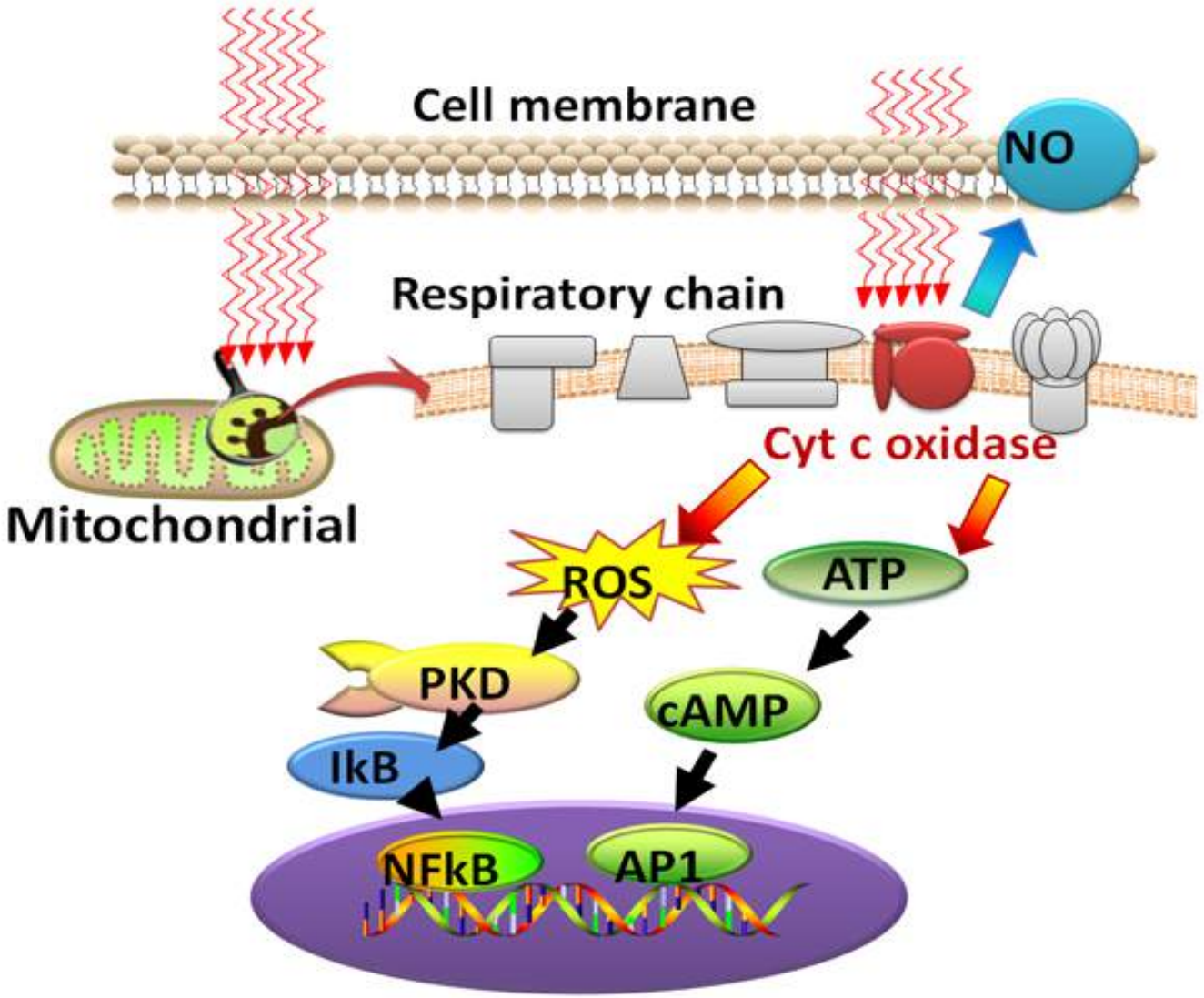
- **Significantly Improves circulation**
  (via vasodilation)
- **Reduces inflammation**
- **Decreases pain**
- **Increases angiogenesis**
  - Builds new vessels
- **Increases lymphatic activity**
  - Decreases swelling



Synergistic Effects of Light Therapy and Nutrition

NO Release From Tissue or Blood:

- **Increases cell regeneration** (wound healing)
  - Stimulates tissue granulation & connective tissue
- **Increases bone mineralization**
  - Reduces osteoporosis
- **Increases phagocytosis** (immune response)
- **Increases RNA-DNA synthesis** (cell building)



Synergistic Effects of Light Therapy and Nutrition

- **Certain vegetables possess a high nitrate content representing a potential source of vasoprotective nitric oxide via bioactivation.**
- In healthy volunteers, approximately 3 hours after ingestion of a dietary nitrate load (beetroot juice 500 mL), BP was substantially reduced (max 10.4/8 mm Hg); an effect that correlated with peak increases in plasma nitrite concentration.

CME Available

Nitric Oxide, Oxidative Stress

Acute Blood Pressure Lowering, Vasoprotective, and Antiplatelet Properties of Dietary Nitrate via Bioconversion to Nitrite

Andrew J. Webb, Nakul Patel, Stavros Loukogeorgakis, Mike Okorie, Zainab Aboud, Shivani Misra, Rahim Rashid, Philip Miall, John Deanfield, Nigel Benjamin, Raymond MacAllister, Adrian J. Hobbs, Amrita Ahluwalia

Abstract—Diets rich in fruits and vegetables reduce blood pressure (BP) and the risk of adverse cardiovascular events. However, the mechanisms of this effect have not been elucidated. Certain vegetables possess a high nitrate content, and we hypothesized that this might represent a source of vasoprotective nitric oxide via bioactivation. In healthy volunteers, approximately 3 hours after ingestion of a dietary nitrate load (beetroot juice 500 mL), BP was substantially reduced (Δ_{max} −10.4/8 mm Hg); an effect that correlated with peak increases in plasma nitrite concentration. The dietary nitrate load also prevented endothelial dysfunction induced by an acute ischemic insult in the human forearm and significantly attenuated ex vivo platelet aggregation in response to collagen and ADP. Interruption of the enterosalivary conversion of nitrate to nitrite (facilitated by bacterial anaerobes situated on the surface of the tongue) prevented the rise in plasma nitrite, blocked the decrease in BP, and abolished the inhibitory effects on platelet aggregation, confirming that these vasoprotective effects were attributable to the activity of nitrite converted from the ingested nitrate. These findings suggest that dietary nitrate underlies the beneficial effects of a vegetable-rich diet and highlights the potential of a "natural" low cost approach for the treatment of cardiovascular disease. (***Hypertension***. 2008;51:784-790.)

Key Words: diet ■ nitric oxide ■ blood pressure ■ hypertension ■ ischemia/reperfusion ■ platelets ■ endothelium

Perhaps the largest public health initiative in the Western world has focused on improvement of diet, particularly in those with a high risk of cardiovascular disease. Trials have shown that diets rich in fruits and vegetables reduce blood pressure (BP; Dietary Approaches to Stop Hypertension; DASH, Vegetarian Diet and BP)[1,2] and adverse cardiovascular events.[3–7] These protective effects have previously been attributed to the high antioxidant vitamin content, yet large clinical trials have failed to provide evidence in support of this thesis.[8,9] The greatest protection against coronary heart disease afforded by a change in diet is that associated with the consumption of green leafy vegetables (eg, spinach, lettuce).[6] Such vegetables, also including beetroot, commonly have a high inorganic nitrate (NO_3^-) content.[10,11] In humans, after absorption through the stomach wall, ≈25% of consumed nitrate enters the enterosalivary circulation where it is reduced to nitrite (NO_2^-) by bacterial nitrate reductases from facultative anaerobes on the dorsal surface of the tongue.[12–14] This nitrite is swallowed and in the acidic environment of the stomach is reduced to nitric oxide (NO) or re-enters the circulation as nitrite. Indeed, it has been hypothesized that dietary nitrate represents an intravascular source of the pleiotropic, vasoprotective molecule NO, which supplements conventional NO generation by NO synthases (NOS).[15]

Endothelium-derived NO is a potent dilator, governs systemic BP, and retards atherogenesis (NO inhibits inflammatory cell recruitment and platelet aggregation).[16] Consequently, numerous cardiovascular pathologies (including prehypertension,[17] hypertension,[18] atherosclerosis,[19] and stroke[20]) are associated with endothelial dysfunction and diminished NO bioactivity. Recently, studies have demonstrated that nitrite confers marked protection against ischemia/reperfusion (I/R) injury in the myocardial, hepatic, renal, pulmonary, and cerebral vasculature.[21,22] This cytoprotective effect has been attributed to reduction of nitrite to NO during ischemia or hypoxemia (conditions that inactivate endothelial NOS, the

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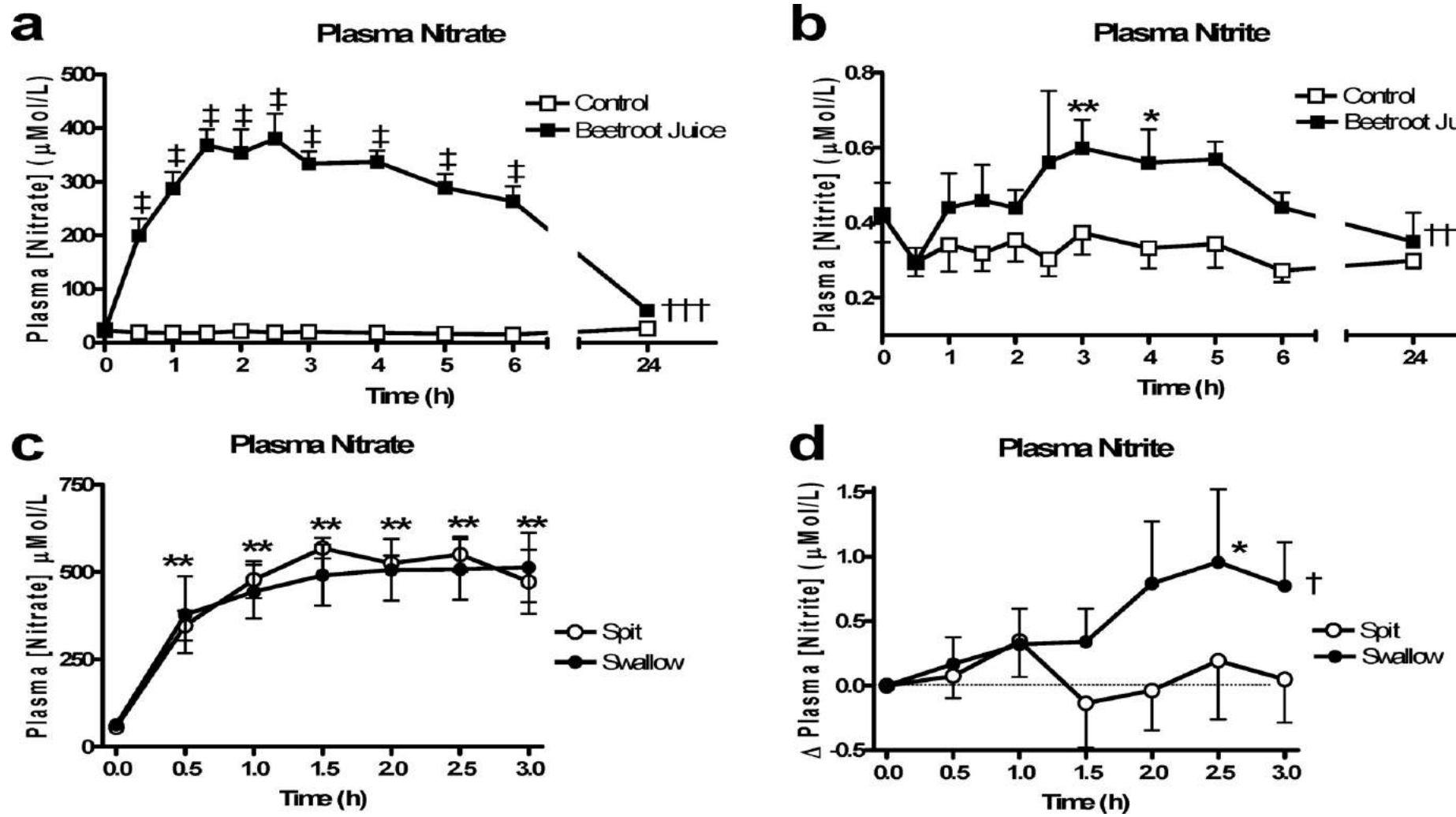
Correspondence to Professor Amrita Ahluwalia, Clinical Pharmacology, William Harvey Research Institute, Barts & the London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK. E-mail a.ahluwalia@qmul.ac.uk

Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.107.103523**

Figure 1. The effect of beetroot juice on the plasma concentrations of (a) nitrate and (b) nitrite and the effects of spitting vs swallowing of saliva on plasma concentrations of (c) nitrate and (d) nitrite.

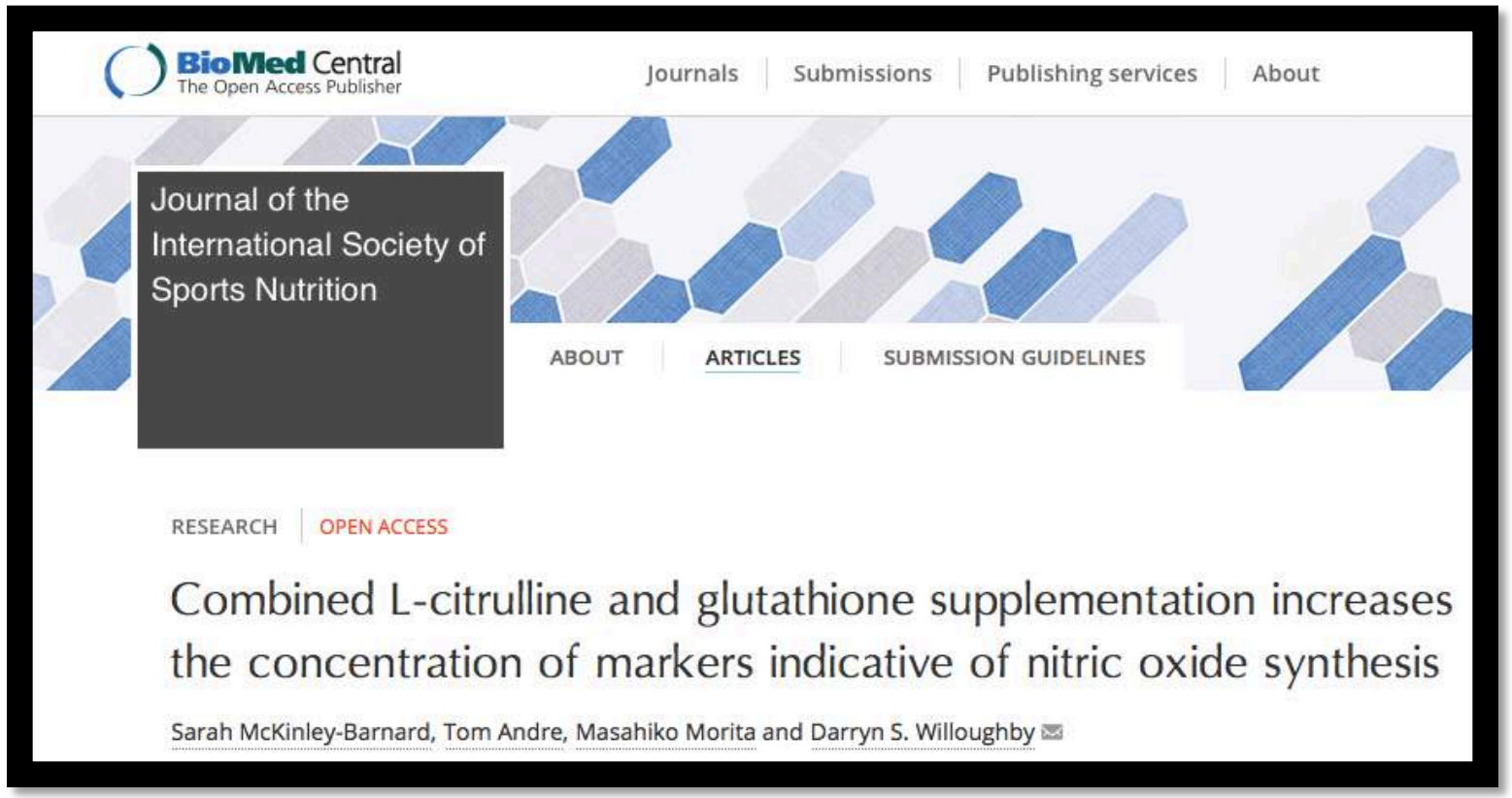


Andrew J. Webb et al. Hypertension. 2008;51:784-790

Synergistic Effects of Light Therapy and Nutrition

Classification of vegetables according to nitrate content[1]	
Nitrate content (mg/100 g fresh weight)	Vegetable varieties
Very low, <20	Artichoke, asparagus, broad bean, eggplant, garlic, onion, green bean, mushroom, pea, pepper, potato, summer squash, sweet potato, tomato, watermelon
Low, 20 to <50	Broccoli, carrot, cauliflower, cucumber, pumpkin, chicory
Middle, 50 to <100	Cabbage, dill, turnip, savoy cabbage
High, 100 to <250	Celeriac, Chinese cabbage, endive, fennel, kohlrabi, leek, parsley
Very high, >250	Celery, cress, chervil, lettuce, red beetroot, spinach, rocket (rucola)

Synergistic Effects of Light Therapy and Nutrition



➔ Nitrite levels in cells treated with L-citrulline and GSH were significantly greater than control ($p < 0.05$).

➔ Plasma NOx with L-citrulline + GSH was significantly greater than control and L-citrulline ($p < 0.05$).

➔ Nitrite and NOx for L-citrulline + GSH were significantly greater at 30 min post-exercise when compared to placebo ($p < 0.05$).

Conclusion:

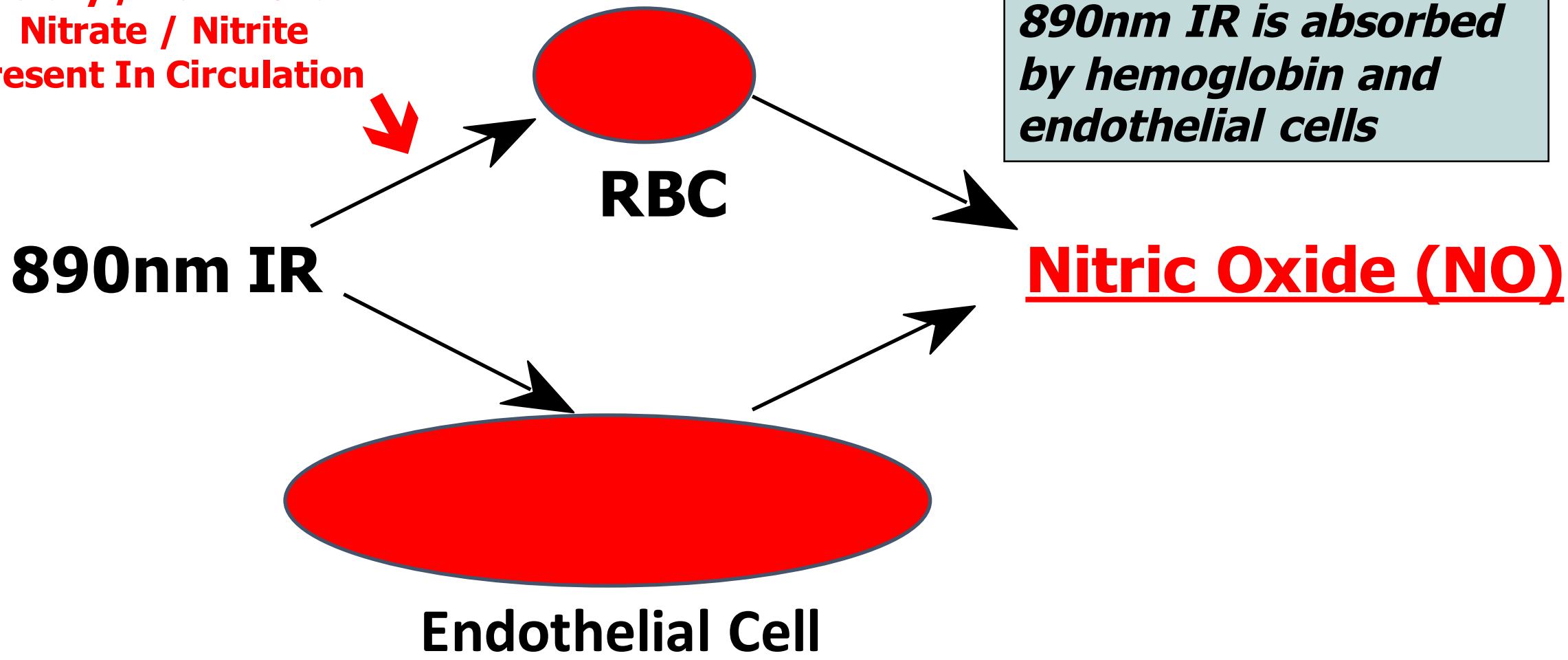
Combining L-citrulline with GSH augments increases in nitrite and NOx levels during *in vitro* and *in vivo* conditions.

McKinley S, Andrew T, Morita M, Willoughby D. *Journal of the International Society of Sports Nutrition*. 2015, 12:27

Synergistic Effects of Light Therapy and Nutrition

Dietary / Nutritional Nitrate / Nitrite Present In Circulation

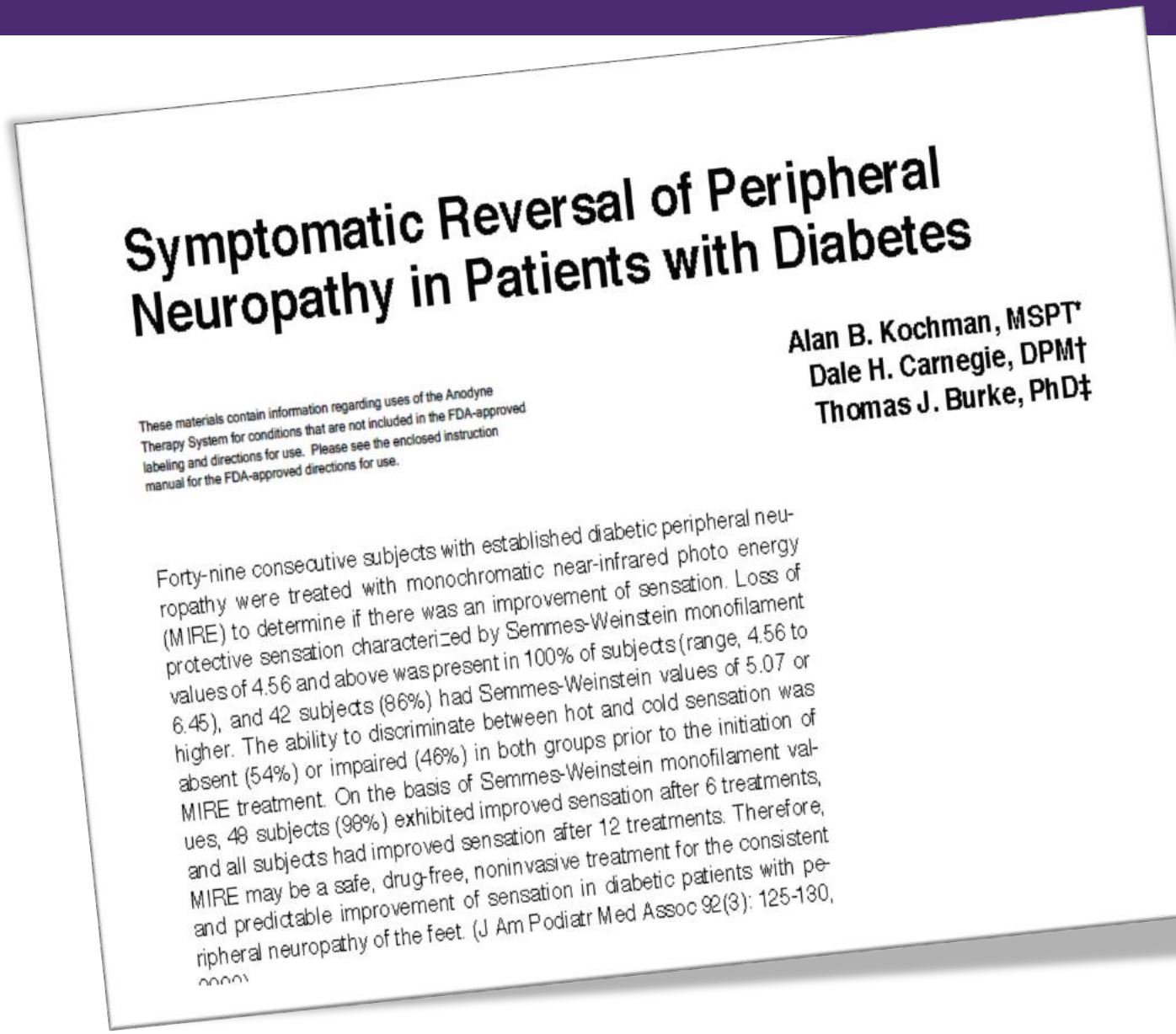
890nm IR is absorbed by hemoglobin and endothelial cells



Synergistic Effects of Light Therapy and Nutrition

Forty-nine subjects with established diabetic peripheral neuropathy were treated with monochromatic near-infrared photo energy (MIRE) to determine if there was an improvement of sensation.

Loss of protective sensation characterized by Semmes-Weinstein monofilament values of 4.56 and above was present in 100% of subjects (range, 4.56 to 6.45), and 42 subjects (86%) had Semmes-Weinstein values of 5.07 or higher.



Symptomatic Reversal of Peripheral Neuropathy in Patients with Diabetes

Alan B. Kochman, MSPT*
Dale H. Carnegie, DPM†
Thomas J. Burke, PhD‡

These materials contain information regarding uses of the Anodyne Therapy System for conditions that are not included in the FDA-approved labeling and directions for use. Please see the enclosed instruction manual for the FDA-approved directions for use.

Forty-nine consecutive subjects with established diabetic peripheral neuropathy were treated with monochromatic near-infrared photo energy (MIRE) to determine if there was an improvement of sensation. Loss of protective sensation characterized by Semmes-Weinstein monofilament values of 4.56 and above was present in 100% of subjects (range, 4.56 to 6.45), and 42 subjects (86%) had Semmes-Weinstein values of 5.07 or higher. The ability to discriminate between hot and cold sensation was absent (54%) or impaired (46%) in both groups prior to the initiation of MIRE treatment. On the basis of Semmes-Weinstein monofilament values, 48 subjects (98%) exhibited improved sensation after 6 treatments, and all subjects had improved sensation after 12 treatments. Therefore, MIRE may be a safe, drug-free, noninvasive treatment for the consistent and predictable improvement of sensation in diabetic patients with peripheral neuropathy of the feet. (J Am Podiatr Med Assoc 92(3): 125-130,

Synergistic Effects of Light Therapy and Nutrition

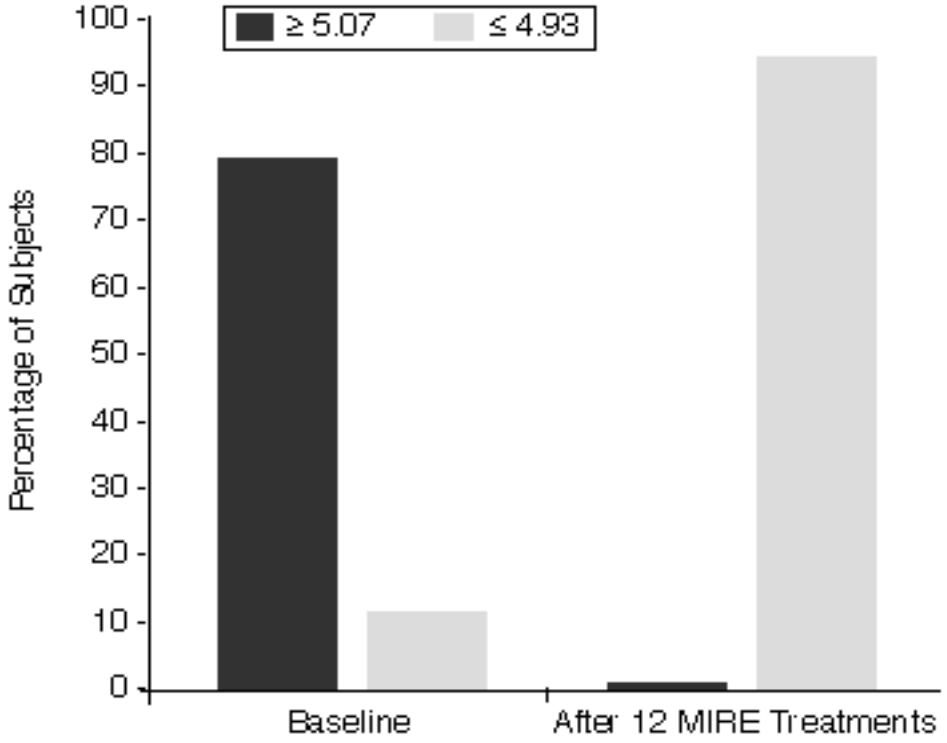


Figure 1. Percentage distribution of patients with type 1 diabetes (N = 25) with Semmes-Weinstein monofilament values ≥ 5.07 and ≤ 4.93 before (left) and after (right) 12 MIRE treatments.

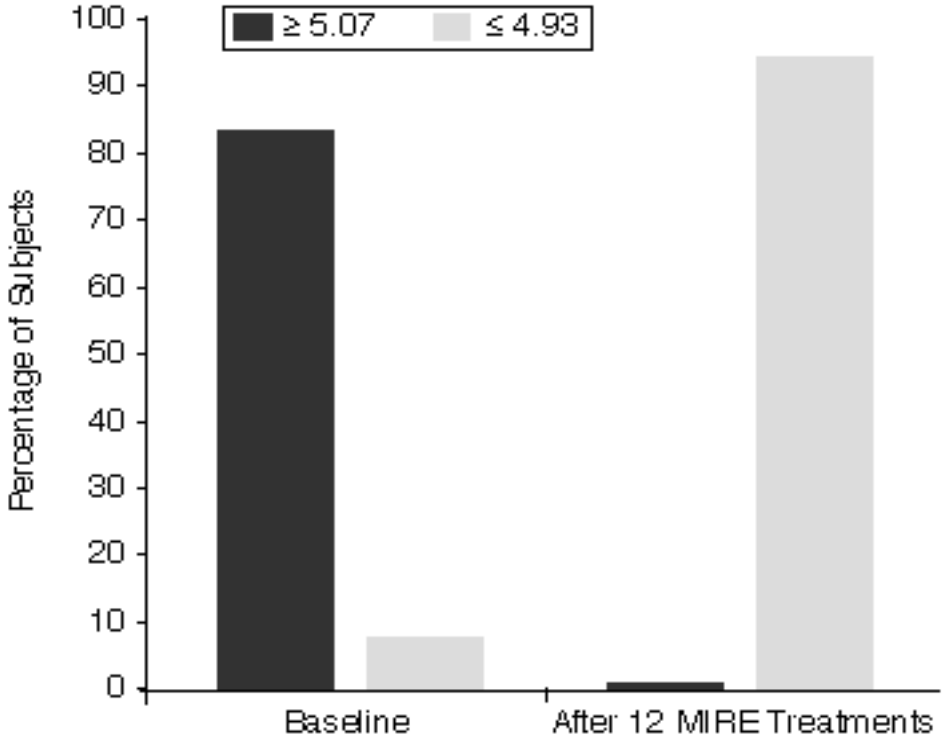


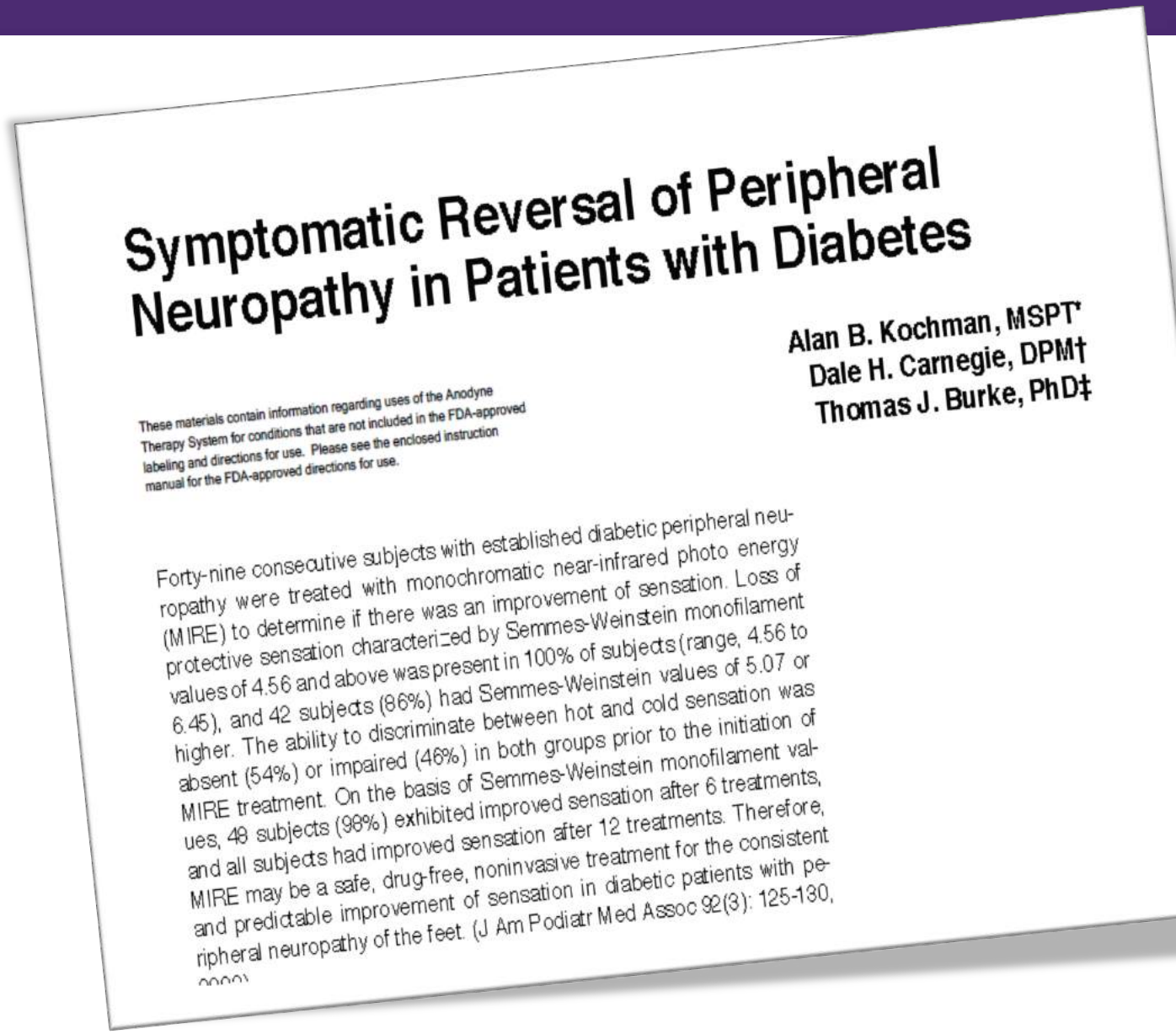
Figure 2. Percentage distribution of patients with type 2 diabetes (N = 24) with Semmes-Weinstein monofilament values ≥ 5.07 and ≤ 4.93 before (left) and after (right) 12 MIRE treatments.

Synergistic Effects of Light Therapy and Nutrition

The ability to discriminate between hot and cold sensation was absent (54%) or impaired (46%) in both groups prior to the initiation of MIRE treatment.

<u>48 subjects (98%) exhibited improved sensation after 6 treatments, and all subjects had improved sensation after 12 treatments</u>.

Therefore, MIRE may be a safe, drug-free, noninvasive treatment for the consistent and predictable improvement of sensation in diabetic patients with peripheral neuropathy of the feet. (*J Am Podiatr Med Assoc* 92(3): 125-130, 2002)



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Forty-nine consecutive subjects with established diabetic peripheral neuropathy were treated with monochromatic near-infrared photo energy (MIRE) to determine if there was an improvement of sensation. Loss of protective sensation characterized by Semmes-Weinstein monofilament values of 4.56 and above was present in 100% of subjects (range, 4.56 to 6.45), and 42 subjects (86%) had Semmes-Weinstein values of 5.07 or higher. The ability to discriminate between hot and cold sensation was absent (54%) or impaired (46%) in both groups prior to the initiation of MIRE treatment. On the basis of Semmes-Weinstein monofilament values, 48 subjects (98%) exhibited improved sensation after 6 treatments, and all subjects had improved sensation after 12 treatments. Therefore, MIRE may be a safe, drug-free, noninvasive treatment for the consistent and predictable improvement of sensation in diabetic patients with peripheral neuropathy of the feet. (J Am Podiatr Med Assoc 92(3): 125-130,

Synergistic Effects of Light Therapy and Nutrition

27 patients with peripheral neuropathy received treatment with monochromatic near-infrared photoenergy (890 nm).

Methods: All enrolled patients exhibited abnormal sensory perception (either hyperesthesia or hypoesthesia) based on a qualifying examination with the Neurometer CPT (current perception threshold) (baseline CPT). The patients received 10 treatments (each lasting 40 minutes) during a 2-week period and then underwent CPT retesting to determine the extent of improvement of sensory impairment in myelinated and unmyelinated sensory fibers of the peroneal nerve.

labeling and directions for use. Please see the enclosed instruction manual for the FDA-approved directions for use.

Original Article

IMPROVEMENT OF SENSORY IMPAIRMENT IN PATIENTS WITH PERIPHERAL NEUROPATHY

J. Joseph Prendergast, MD, Galdina Miranda, MA, and Manuel Sanchez, MA

ABSTRACT

Objective: To report the findings in 27 patients with peripheral neuropathy (21 with lower extremity sensory impairment associated with diabetic peripheral neuropathy and 6 with other causes), who received treatment with monochromatic near-infrared photoenergy (890 nm) delivered by the Anodyne Therapy System (ATS).

Methods: All enrolled patients exhibited abnormal sensory perception (either hyperesthesia or hypoesthesia) based on a qualifying examination with the Neurometer CPT (current perception threshold) (baseline CPT). The patients received 10 ATS treatments (each lasting 40 minutes) during a 2-week period and then underwent CPT retesting to determine the extent of improvement of sensory impairment in myelinated and unmyelinated sensory fibers of the peroneal nerve.

Results: All patients obtained improvement in sensory impairment in comparison with baseline CPT measures, and 16 of the 27 patients achieved normal sensory

INTRODUCTION

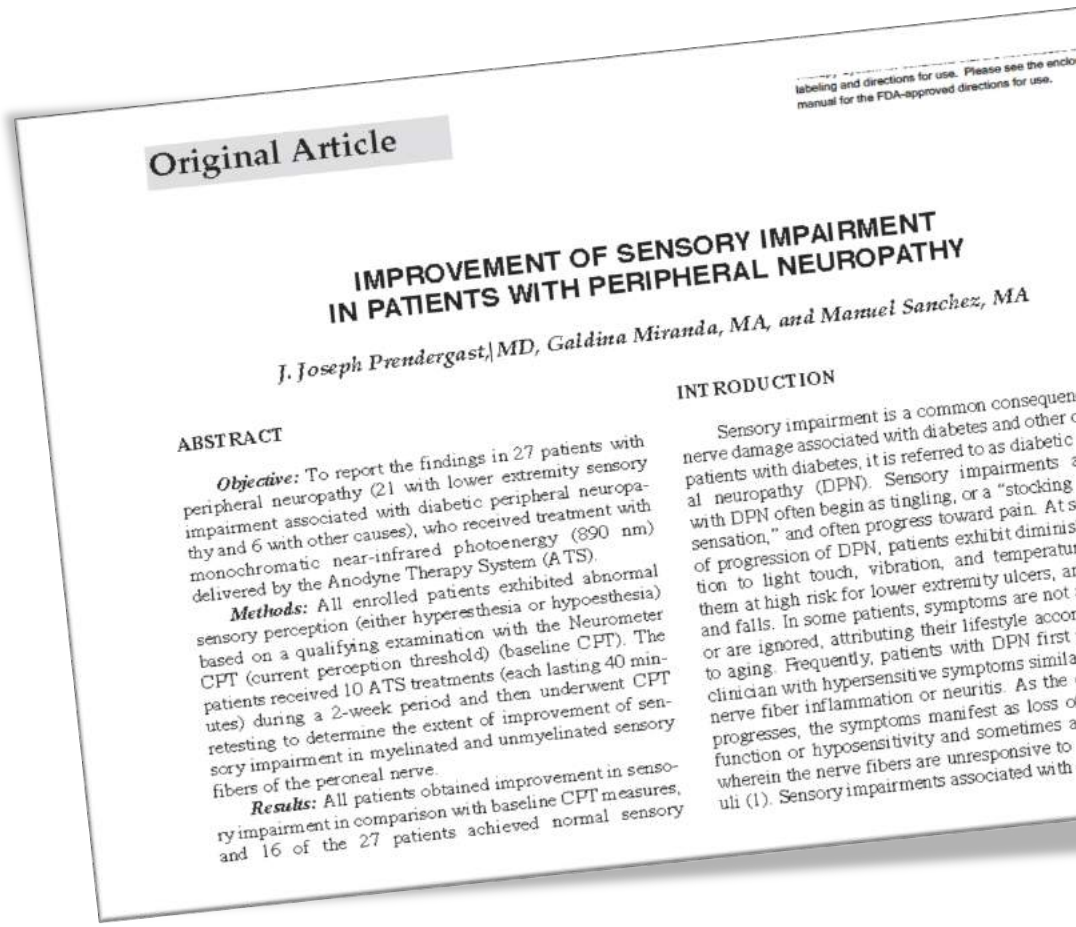
Sensory impairment is a common consequence of the nerve damage associated with diabetes and other causes. In patients with diabetes, it is referred to as diabetic peripheral neuropathy (DPN). Sensory impairments associated with DPN often begin as tingling, or a "stocking and glove sensation," and often progress toward pain. At some stage of progression of DPN, patients exhibit diminished sensation to light touch, vibration, and temperature, placing them at high risk for lower extremity ulcers, amputations, and falls. In some patients, symptoms are not appreciated or are ignored, attributing their lifestyle accommodations to aging. Frequently, patients with DPN first present to a clinician with hypersensitive symptoms similar to those in nerve fiber inflammation or neuritis. As the disease state progresses, the symptoms manifest as loss of nerve fiber function or hyposensitivity and sometimes as anesthesia, wherein the nerve fibers are unresponsive to various stimuli (1). Sensory impairments associated with diabetes have

Synergistic Effects of Light Therapy and Nutrition

Results: All patients obtained improvement in sensory impairment in comparison with baseline CPT measures, and 16 of the 27 patients achieved normal sensory responses in all nerve fiber subpopulations.

Ten patients had been tested previously (initial CPT) and did not exhibit spontaneous improvement in sensory impairment during a mean period of 27 months before baseline CPT. After receiving the ATS treatments, however, this group of patients showed improvement in comparison with both initial CPT results and baseline CPT.

Conclusion: On the basis of the data from this study, the ATS seems to be a safe and effective treatment to improve sensory impairment associated with peripheral neuropathy due to diabetes and other causes. (*Endocr Pract*. 2004;10:24-30)



Original Article

IMPROVEMENT OF SENSORY IMPAIRMENT IN PATIENTS WITH PERIPHERAL NEUROPATHY

J. Joseph Prendergast, MD, Galdina Miranda, MA, and Manuel Sanchez, MA

ABSTRACT

INTRODUCTION

Synergistic Effects of Light Therapy and Nutrition

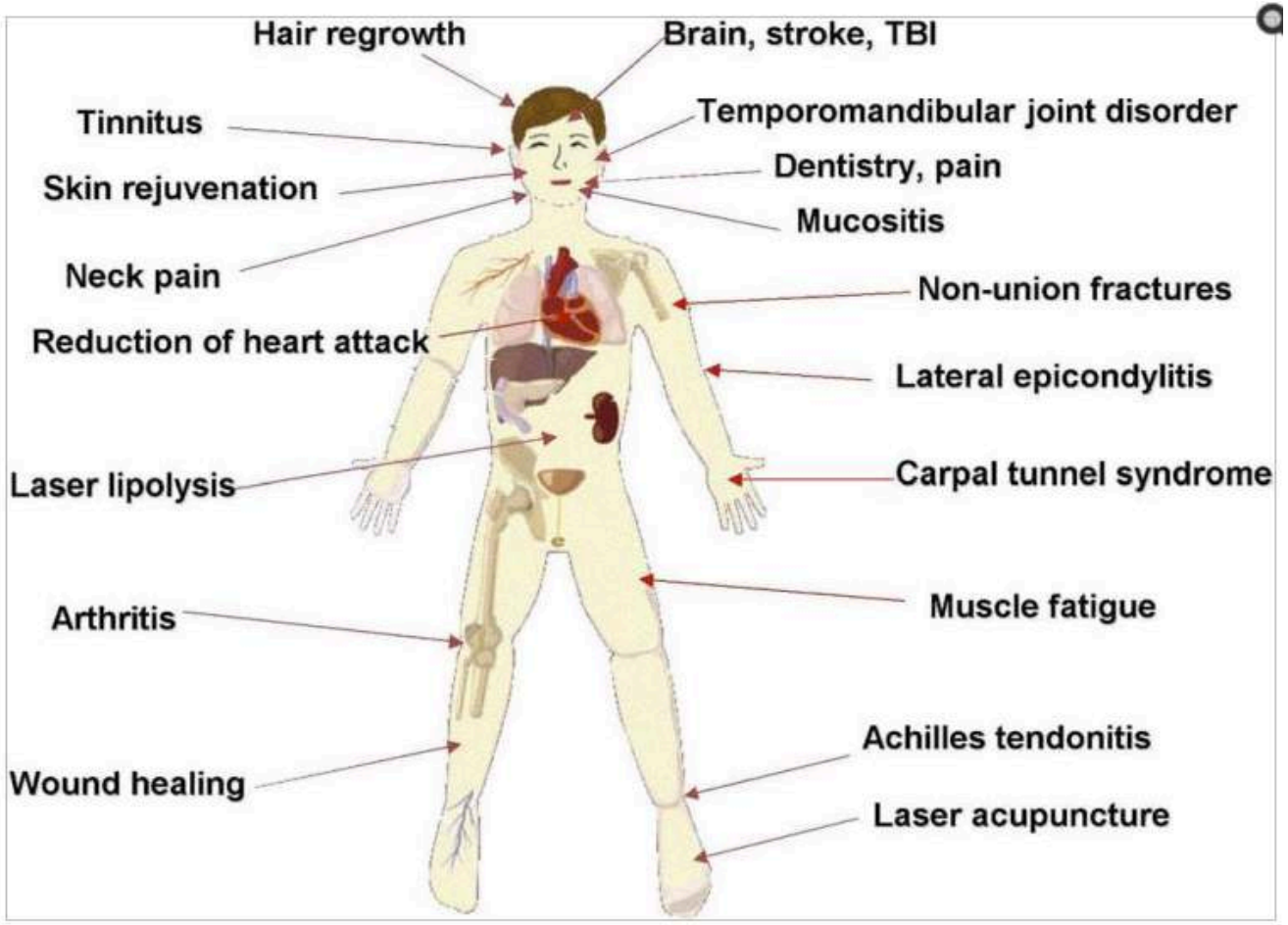


Diagram of the various medical applications of low-level light therapy.

THANK YOU!

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RESEARCH Open Access

Combined L-citrulline and glutathione supplementation increases the concentration of markers indicative of nitric oxide synthesis

Sarah McKinley-Barnard[1], Tom Andre[1], Masahiko Morita[2] and Darryn S. Willoughby[1*]

Abstract

Background: Nitric oxide (NO) is endogenously synthesized from L-arginine and L-citrulline. Due to its effects on nitric oxide synthase (NOS), reduced glutathione (GSH) may protect against the oxidative reduction of NO. The present study determined the effectiveness of L-citrulline and/or GSH on markers indicative of NO synthesis in *in vivo* conditions with rodents and humans and also in an *in vitro* condition.

Methods: In phase one, human umbilical vein endothelial cells (HUVECs) were treated with either 0.3 mM L-citrulline, 1 mM GSH (Setria®) or a combination of each at 0.3 mM. In phase two, Sprague–Dawley rats (8 weeks old) were randomly assigned to 3 groups and received either purified water, L-citrulline (500 mg/kg/day), or a combination of L-citrulline (500 mg/kg/day) and GSH (50 mg/kg/day) by oral gavage for 3 days. Blood samples were collected and plasma NOx (nitrite + nitrate) assessed. In phase three, resistance-trained males were randomly assigned to orally ingest either cellulose placebo (2.52 g/day), L-citrulline (2 g/day), GSH (1 g/day), or L-citrulline (2 g/day) + GSH (200 mg/day) for 7 days, and then perform a resistance exercise session involving 3 sets of 10-RM involving the elbow flexors. Venous blood was obtained and used to assess plasma cGMP, nitrite, and NOx.

Results: In phase one, nitrite levels in cells treated with L-citrulline and GSH were significantly greater than control ($p < 0.05$). In phase two, plasma NOx with L-citrulline + GSH was significantly greater than control and L-citrulline ($p < 0.05$). In phase three, plasma cGMP was increased, but not significantly ($p > 0.05$). However, nitrite and NOx for L-citrulline + GSH were significantly greater at 30 min post-exercise when compared to placebo ($p < 0.05$).

Conclusions: Combining L-citrulline with GSH augments increases in nitrite and NOx levels during *in vitro* and *in vivo* conditions.

Keywords: Nitric oxide, L-citrulline, L-arginine, Glutathione, Resistance exercise

Introduction

Also known as endothelium-derived relaxing factor (EDRF), nitric oxide (NO) is biosynthesized endogenously from L-arginine and oxygen, by various nitric oxide synthase (NOS) enzymes and by reduction of inorganic nitrate [1]. Cell types containing NOS have been demonstrated to be able to reutilize L-citrulline, the byproduct of NO synthesis, to L-arginine by the arginine-citrulline cycle [2]. Nitric oxide is a gaseous signaling molecule which activates soluble guanylate cyclase (sGC) in smooth muscle cells, thereby catalyzing cyclic guanosine monophosphate (cGMP) synthesis. Intracellular cGMP serves as a cellular messenger and plays a role in a variety of biological processes, and in human blood vessels, results in vasodilation [3]. Cell types containing NOS have been demonstrated to be able to reutilize L-citrulline, the byproduct of NO synthesis, to L-arginine by the arginine-citrulline cycle [2]. An elevation in plasma L-arginine has been shown to improve endothelial function because the vascular endothelium uses NO to signal the surrounding smooth muscle to relax, thus resulting in vasodilation and increasing blood flow [4]. During exercise, vasodilation occurs as a result of various intracellular events, including the production and release of NO. However, it has recently been shown that

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seven days of oral L-arginine supplementation at 12 g/day, while effective in elevating plasma L-arginine and NO metabolites nitrite and nitrate (NOx) after exercise, was ineffective at increasing blood flow during exercise [5].

L-citrulline has been indicated to be a second NO donor in the NOS-dependent pathway, since it can be converted to L-arginine [6]. Dietary L-citrulline supplementation has shown conflicting results regarding its effectiveness at improving exercise performance [7, 8]. Moreover, results showing favorable effects in exercise performance [8] did not assess NO status; therefore, this response cannot be related to an improvement in exercise performance. The importance of L-citrulline towards ergogenic support is based on the premise that L-citrulline is not subject to pre-systemic elimination and, consequently, could be a more efficient way to elevate extracellular levels of L-arginine. L-Citrulline can perhaps improve the effects on nitrate elimination during the course of recovery from exhaustive muscular exercise, and also serves as an effective precursor of L-arginine. It has been shown that three grams daily of oral L-citrulline supplementation for seven days elevated plasma L-arginine concentration and augmented NO-dependent signaling [9].

Glutathione is a low molecular weight, water-soluble tripeptide composed of the amino acids cysteine, glutamic acid, and glycine. Glutathione is an important antioxidant and plays a major role in the detoxification of endogenous metabolic products, including lipid peroxides. Intracellular glutathione exists in both the oxidized disulfide form (GSSG) or in reduced (GSH) state; the ratio between GSH and GSSG is held in dynamic balance depending on many factors including the tissue of interest, intracellular demand for conjugation reactions, intracellular demand for reducing power, and extracellular demand for reducing potential. In some cell types, GSH appears to be necessary for NO synthesis and NO has been shown to be correlated with intracellular GSH [10]. GSH stimulates total L-arginine turnover and, in the presence of GSH, NOS activity is increased [11]. This suggests that GSH may play an important role in protection against oxidative reaction of NO, thus contributing to the sustained release of NO. Therefore, combining L-citrulline with GSH may augment the production of NO. However, the effectiveness for oral GSH supplementation in humans, particularly in combination with L-citrulline has not been clearly delineated.

Using *in vitro* (cell culture) and *in vivo* approaches in rodents and humans, the overall purpose of this study was to determine the efficacy of L-citrulline and/or GSH supplementation towards increasing the levels of cGMP, nitrite, and NOx. We hypothesized that the combination of L-citrulline and GSH would preferentially increase the concentrations of cGMP, nitrite, and NOx levels when compared to control conditions.

Methods and procedures

L-citrulline and GSH (Setria®) used in each phase were obtained from KYOWA HAKKO BIO CO., LTD (Tokyo, Japan).

Phase 1 (*in vitro* efficacy study)

Human umbilical vein endothelial cells (HUVECs) were purchased from Clonetics (San Diego, CA, USA) and cultured in EGM-2 Bullet Kit medium (Clonetics) supplemented with 2 % fetal bovine serum (FBS) and complete endothelial growth factors at 37 ° C in humidified 5 % CO_2. The cells were seeded into twenty-four well plates 5000 cells/cm2, and sub-confluent cell monolayers were used for experiments. A subset of sub-confluent HUVECs were used as controls and the remainder were treated with either 0.3 mM L-citrulline, 1 mM GSH, or a combination of each at 0.3 mM, and incubated for 24 h. To measure nitrite production by HUVECs, the culture medium was collected and centrifuged to remove any precipitated materials. Four wells for each condition were used and nitrite concentrations of supernatants from each well were determined by high performance liquid chromatography (HPLC) (ENO-20; Eicom, Kyoto, Japan) using our previous approach [12].

Phase 2 (rodent efficacy study)

This phase of the study was conducted in accordance with the guidelines for the Institutional Animal Care and Use Committee of KYOWA HAKKO BIO CO., LTD. Twenty-three male Sprague–Dawley rats (8 weeks old; Japan SLC, Hamamatsu, Japan) were given free access to standard rat chow (CE-2, CLEA JAPAN Inc., Tokyo, Japan) and tap water in a room with controlled temperature (22 ± 2 ° C), humidity (55 ± 5 %) and a 12-h light/dark cycle. After the rats had been anesthetized with pentobarbital sodium (30 mg/kg, i.p.), a catheter was inserted into the carotid artery. Following 3 days of acclimation, the rats were randomly assigned to 3 groups and received either purified water (CON) (n = 7), L-citrulline (500 mg/kg/day) (n = 8), or a combination of L-citrulline (500 mg/kg/day) plus GSH (50 mg/kg/day) (n = 8) by oral gavage for 3 days. Blood samples were collected from the catheter at baseline and at 0, 0.25, 0.5, 1, 2, and 4 h after the last administration on Day 3. Plasma NOx (nitrite + nitrate) was measured by HPLC (ENO-20; Eicom, Kyoto, Japan) using our previous approach [12].

Phase 3 (human efficacy study)

Participants

Sixty-six apparently healthy, resistance trained [regular, consistent resistance training (i.e., thrice weekly) for at least one year prior to the onset of the study], males between the ages of 18–30 and a body mass index

between 18.5–30 kg/m^2 volunteered to participate in the double-blind, randomized, placebo-controlled, parallel-groups study. Enrollment was open to men of all ethnicities. During the course of the study, six dropped out due to reasons unrelated to the study. As a result, 60 participants completed the study. The age, height, and body mass of participants in each of the four groups can be seen in Table 1. Only participants considered as low risk for cardiovascular disease and with no contraindications to exercise as outlined by the American College of Sports Medicine (ACSM) and who had not consumed any nutritional supplements (excluding multi-vitamins) one month prior to the study were allowed to participate. All participants provided written informed consent and were cleared for participation by passing a mandatory medical screening. All eligible subjects signed university-approved informed consent documents and approval was granted by the Baylor University Institutional Review Board for the Protection of Human Subjects in Research. Additionally, all experimental procedures involved in the study conformed to the ethical consideration of the Declaration of Helsinki.

Entry and familiarization session (visit 1)

Individuals expressing interest in participating in the study were interviewed on the telephone and/or e-mail to determine whether they appeared to qualify to participate in the study. Participants believed to meet eligibility criteria were then invited to attend an entry/familiarization session (visit 1). Once reporting to the lab, individuals were familiarized to the study protocol via a verbal and written explanation outlining the study design and signed an informed consent document. At this point, participants completed a medical history questionnaire and underwent a general physical examination to determine whether they met eligibility criteria. Participants also performed a muscle strength test of the elbow flexors (biceps), and were then given an appointment time to report to the laboratory for a baseline blood sample (visit 2). At this time, participants were instructed to refrain from exercise for 48 h and fast for 8 h prior to baseline blood sampling (visit 2) and post-supplementation testing at day 7 (visit 3).

Table 1 Age, height, and body mass of participants in each of the four groups

Group	Age (yrs)	Height (cm)	Body mass (kg)
PLC (n = 15)	21.80 ± 0.92	179.52 ± 2.10	83.92 ± 6.65
GSH (n = 15)	22.67 ± 0.97	179.90 ± 1.71	83.42 ± 2.92
CIT (n = 15)	21.07 ± 0.67	177.17 ± 1.55	80.46 ± 3.17
CIT + GSH (n = 15)	21.67 ± 0.56	179.03 ± 2.34	83.06 ± 2.79

Data are expressed as means ± SEM

Assessment of elbow flexor muscle strength (visit 1)

In order to determine maximum muscular strength of the elbow flexors, participants performed a one-repetition maximum (1-RM) test on the same elbow flexor machine used in the resistance exercise session based on our previous study [5]. Participants warmed up by completing 5 to 10 repetitions at approximately 50 % of the estimated 1-RM. The participant rested for 1 min, and then completed 3 to 5 repetitions at approximately 70 % of the estimated 1-RM. The weight was then increased conservatively, and the participant attempted to lift the weight for one repetition. If the lift was successful, the participant rested for 2 min before attempting the next weight increment. This procedure was continued until the participant failed to complete the lift. The 1-RM was recorded as the maximum weight that the participant was able to lift for one repetition.

Resistance exercise protocol (visit 3, day 7)

Based on our previous study [5], on day 7 participants reported to the Exercise and Biochemical Nutrition Lab at approximately 2:00 pm and performed 3 sets of 15 repetitions with as much weight as they could lift per set (typically 70–75 % of 1RM) involving the elbow flexion exercise on a selectorized weight machine (Body Master, Rayne, LA). Rest periods between sets were timed and lasted exactly 10 s. The resistance exercise session was performed under the direct supervision of study personnel.

Venous blood sampling (visit 2, day 0 and visit 3, day 7)

Venous blood samples were obtained from the antecubital vein into 10 ml serum and plasma collection tubes using a standard vacutainer apparatus. Blood samples were allowed to stand at room temperature for 10 min and then centrifuged. The serum and plasma was removed and frozen at −80 °C for later analysis. One baseline blood sample was obtained at visit 2 and 3 samples were obtained at visit 3 (for a total of 4 blood samples). At visit 3 on day 7, the first sample was obtained immediately before ingesting the supplement, the second sample was obtained immediately after resistance exercise, and the third sample 30 min following exercise (Fig. 1).

Supplementation protocol

In a randomized, double-blind fashion participants were randomly assigned to one of four groups (n = 15 per group) involving 7 days of the oral ingestion of four capsules containing a total daily dose of either: cellulose placebo (2.52 g/day), L-citrulline (2 g/day), GSH (1 g/day), or L-citrulline (2 g/day) + GSH (200 mg/day). The total weight of the four capsules for each group was the same. Each participant ingested all four capsules containing their respective daily supplement dose each evening for six consecutive days. At Visit 3 (Day 7), participants

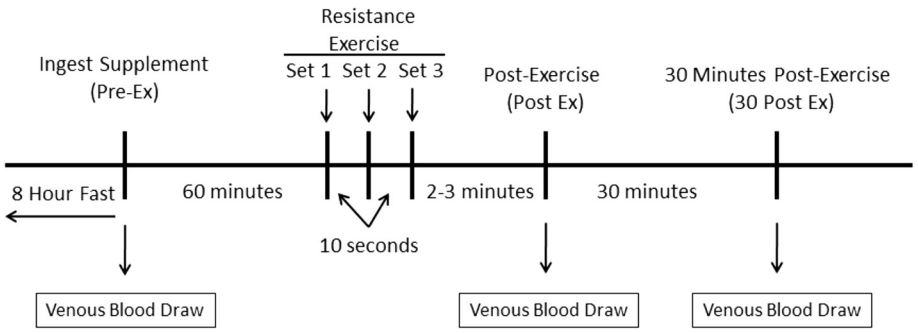

Fig. 1 An illustration of the experimental protocol for the testing session at visit 3, following seven days of L-citrulline and/or GSH supplementation

were provided the final daily dose of their respective supplement ingested one hour prior to performing the resistance exercise. Supplementation compliance was monitored by participants returning empty containers of their supplement on day 7, and also by completing a supplement compliance questionnaire.

Assessment of blood variables (L-citrulline and L-arginine)

To determine plasma L-citrulline and L-arginine concentrations, the plasma was de-proteinated by mixing equal volumes of plasma and trichloroacetic acid (TCA) (6.0 % wt/vol). The samples were vortexed and centrifuged for 15 min at 12,000 × g. Amino acids in the supernatant were analyzed with an amino acid analyzer (L-8900, Hitachi, Japan).

Assessment of plasma cGMP and nitrite

From the blood samples obtained at visit 2 (day 0) and visit 3 (day 7), using commercially-available enzyme-linked immunoabsorbent assay (ELISA) kits (Cayman Chemical, Ann Arbor, MI, USA), plasma cGMP, nitrite, and NOx were determined. Assays were analyzed in duplicate and absorbances for each variable were determined at a wavelength of 450 nm using a microplate reader (iMark, Bio-Rad, Hercules, CA). A set of standards of known concentrations for each variable utilized to construct standard curves and concentrations were determined using data reduction software (Microplate Manager, Bio-Rad, Hercules, CA).

Statistical analysis

For *in vitro* (phase 1), rodent (phase 2), and the human (phase 3) efficacy studies, results were expressed as mean ± SEM. Delta values (differences between the baseline and sequential values) were analyzed using Bonferroni's test following one-way ANOVA. For multiple comparisons to identify the statistical differences among treatments, the Bonferroni correction or Dunnett's multiple test following a comparison of the data by non-repeated ANOVA was employed. Statistical significance was considered as a p-value ≤ 0.05. Statistical analysis was performed using Statcel software for Windows (Version 2, OMS Publishing, Inc., Saitama, Japan) and the Systat 2000 Statistical Program File (Igaku Tosho Shuppan, Tokyo, Japan).

Results

Phase 1 (*in-vitro* cell culture study)

Results demonstrated no significant differences between the control condition and cells treated with L-citrulline and GSH ($p > 0.05$) for nitrite concentration. However, cells treated with L-citrulline and GSH were significantly greater than control-treated cells ($p < 0.05$) (Fig. 2).

Phase 2 (rodent efficacy study)

For plasma NOx delta values, results demonstrated that L-citrulline + GSH was significantly greater than control and L-citrulline at one hr post-supplement infusion ($p < 0.05$) (Fig. 3).

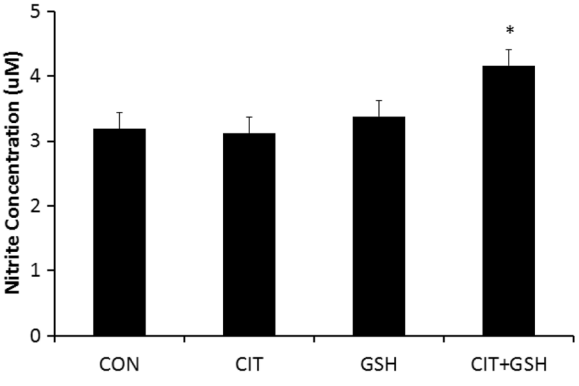

Fig. 2 From phase one, an illustration of nitrite concentration in HUVECs following supplementation with L-citrulline and/or GSH. The symbol * indicates that cells supplemented with a combination of L-citrulline (CIT) and GSH underwent significant increases in nitrite formation compared to cells supplemented with phosphate buffered saline (CON) ($p < 0.05$)

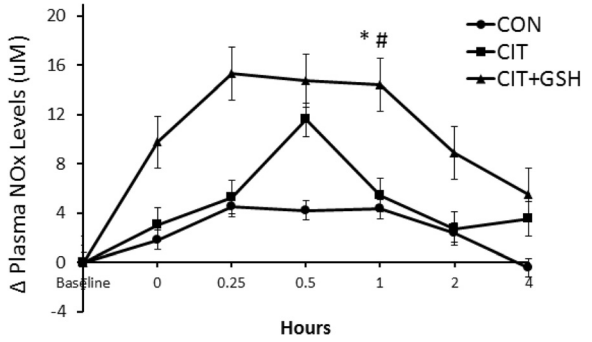

Fig. 3 From phase two, an illustration of plasma NOx levels in rats following supplementation with L-citrulline and/or GSH. The symbols * and # indicate that combined L-citrulline (CIT) and GSH-supplemented rats underwent significant increases in plasma NOx at one hr following supplement infusion compared to animals supplemented with water (CON) and CIT, respectively ($p < 0.05$)

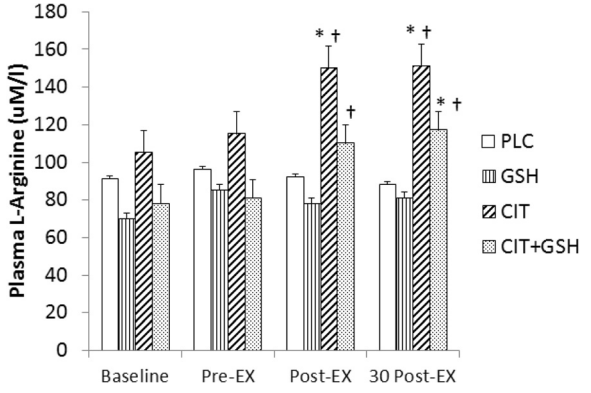

Fig. 4 From phase three, an illustration of plasma arginine levels in humans following seven days of supplementation with L-citrulline and/or GSH. Results indicated that L-citrulline (CIT) and a combination of CIT + GSH produced significant increases in plasma arginine immediately after and 30 min post-exercise compared to groups supplemented with cellulose (PLC) and GSH. The symbol * indicates a significant increase compared to PLC and the symbol † indicates a significant increase compared to GSH ($p < 0.05$)

Phase 3 (human efficacy study)

Plasma L-arginine and L-citrulline

Since no supplementation was involved at the baseline testing session, as expected, no significant differences between groups or time points ($p > 0.05$) for plasma L-citrulline and L-arginine were observed. However, at the follow-up testing session following seven 7 days of supplementation significant increases for plasma L-arginine and L-citrulline were noted. For L-arginine, no significant differences occurred between placebo and GSH at any time points ($p > 0.05$). However, at the immediate post-exercise time point L-citrulline was significantly greater than placebo and GSH, whereas L-citrulline + GSH was greater than GSH ($p < 0.05$). In addition, at 30 min post-exercise L-citrulline and L-citrulline + GSH were both significantly greater than placebo and GSH ($p < 0.05$) (Fig. 4). For plasma L-citrulline, L-citrulline and L-citrulline + GSH were both significantly greater than placebo and GSH immediately post-exercise and at 30 min post-exercise ($p < 0.05$) (Fig. 5).

Plasma cGMP, nitrite, and NOx

The delta values for the plasma levels of cGMP, nitrite, and NOx can be seen in Figs. 6, 7 and 8, respectively. For cGMP (Fig. 6), L-citrulline + GSH was elevated compared to the other three groups, but there were no significant differences between groups and time points observed ($P > 0.05$). For nitrite (Fig. 7) and NOx (Fig. 8), L-citrulline + GSH was significantly greater than placebo at 30 min post-exercise ($P < 0.05$).

Discussion

In the present study, we sought to determine the effectiveness of L-citrulline and/or GSH in increasing NO synthesis during *in vivo* conditions with rodents and humans and also in an *in vitro* condition using HUVEC. Collectively, in phase one and three of the study we observed combining L-citrulline with GSH to be more effective at increasing the concentrations of nitrite and/or NOx than with control/placebo in HUVEC and humans, respectively. In phase two, we observed L-citrulline combined with GSH to be more effective at increasing plasma NOx.

L-citrulline is a ubiquitous amino acid in mammals [13], and in the kidneys, vascular endothelium, and other tissues can be readily converted to L-arginine thus

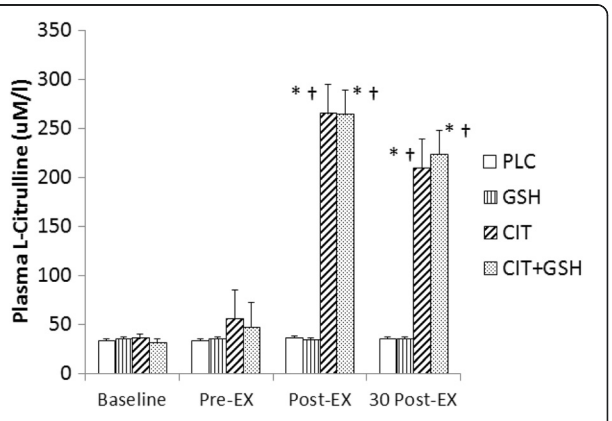

Fig. 5 From phase three, an illustration of plasma citrulline levels in humans following seven days of supplementation with L-citrulline and/or GSH. Results indicated that L-citrulline (CIT) and a combination of CIT + GSH produced significant increases in plasma CIT immediately after and 30 min post-exercise compared to groups supplemented with cellulose (PLC) and GSH. The symbol * indicates a significant increase compared to PLC and the symbol † indicates a significant increase compared to GSH ($p < 0.05$)

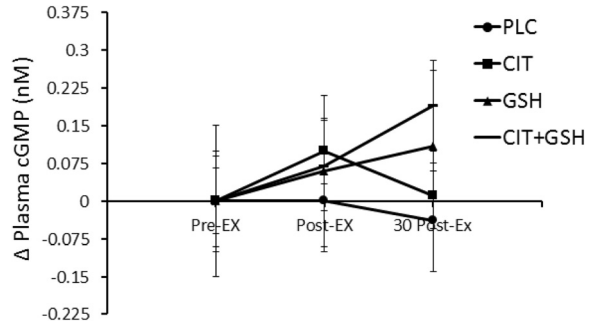

Fig. 6 From phase three, an illustration of plasma cGMP levels in humans following seven days of supplementation with L-citrulline and/or GSH. Results indicated no significant differences between any of the groups at any of the assessed time points ($p > 0.05$)

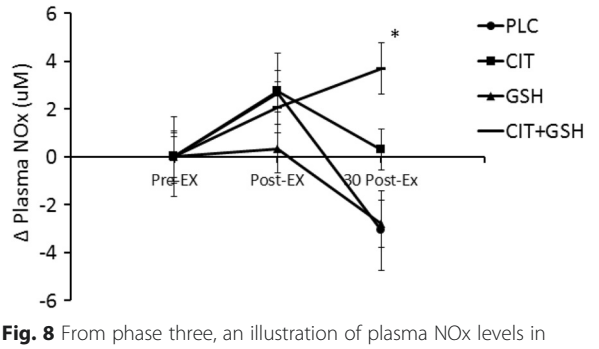

Fig. 8 From phase three, an illustration of plasma NOx levels in humans following seven days of supplementation with L-citrulline and/or GSH. The symbol * indicates that a combination of L-citrulline (CIT) and GSH produced significant increases in plasma NOx at 30 min post-exercise compared to the group supplemented with cellulose placebo (PLC) ($p < 0.05$)

raising plasma and tissue levels of L-arginine which increases NOS synthesis and subsequent NO production [14]. Additionally, L-citrulline has been indicated to be a secondary NO donor in the NOS-dependent pathway, since it can be converted to L-arginine. Nitrate and nitrite are the main substrates to produce NO via the NOS-independent pathway. These anions can be reduced *in vivo* to NO and other bioactive nitrogen oxides.

Previous studies have reported that L-citrulline could increase plasma L-arginine concentration by the L-citrulline-NO cycle [15]. Fu et al. [16] showed that pre-treatment with L-citrulline in rodents for seven days at doses of 300, 600, and 900 mg/kg increased the NO content. Since L-citrulline can be readily converted to L-arginine, it provides a recycling pathway for the conversion of L-citrulline to NO via L-arginine [14, 17]. In phase three of the present study, we observed seven days of L-citrulline supplementation, with and without GSH, to result in significant increases in the levels of plasma citrulline and arginine. Our present data support

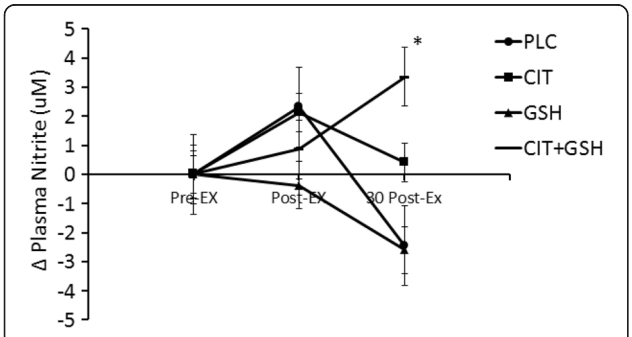

Fig. 7 From phase three, an illustration of plasma nitrite levels in humans following seven days of supplementation with L-citrulline and/or GSH. The symbol * indicates that a combination of L-citrulline (CIT) and GSH produced significant increases in plasma nitrite at 30 min post-exercise compared to the group supplemented with cellulose placebo (PLC) ($p < 0.05$)

previous results [18] showing that a 10-g oral bolus of L-citrulline significantly enhanced plasma citrulline and arginine levels compared with placebo. Therefore, our present observations indicate that L-citrulline is indeed a precursor to L-arginine formation which subsequently increases circulating levels of NOx, and that recycling of L-citrulline to L-arginine may maintain substrate concentration in favor of NO synthesis [19].

It has been shown in some mammalian cell types, that GSH and NO activity are linked [20]. Furthermore, results suggest that GSH is necessary in HUVEC for NO synthesis rather than for the NO-related effect on guanylate cyclase, because when cells were depleted of GSH, citrulline synthesis and cGMP production were inhibited in a concentration-dependent manner [21]. This may be explained based on the premise that the synthesis of NO, detected as L-citrulline production, in HUVEC and murine endothelial cells has been shown to be correlated with intracellular GSH [10]. A previous study suggested that in some cell types, the activity of NO is influenced by the endogenous antioxidant GSH [22]. It is conceivable that GSH activity may be augmented by L-citrulline as it has been shown that pre-treatment with L-citrulline in rodents for seven consecutive days lead to an elevation in the level of GSH [23].

Furthermore, in phase one of the present study, we showed that combining L-citrulline and GSH effectively increased nitrite concentration in HUVEC cells compared to control; although, both L-citrulline and GSH alone had no effect on nitrite. However, in phase two, the combined L-citrulline and GSH provided to rodents resulted in a significant increase in plasma NOx one hr following ingestion compared to control and L-citrulline. Moreover, we observed a similar response in phase three compared to phase one, where combining L-citrulline and GSH effectively increased plasma nitrite and NOx concentration in humans compared to placebo.

Oral supplementation with L-arginine can increase plasma L-arginine levels; although, oral supplementation with L-citrulline, a precursor for arginine biosynthesis, has been shown to be more efficient than oral L-arginine in increasing plasma L-arginine [9], due to splanchnic catabolism of ingested L-Arginine [24]. NO synthesis is primarily dependent upon intracellular arginine availability and is affected by: 1) the transport of extracellular arginine; 2) intracellular synthesis of arginine from citrulline, which is dependent on citrulline availability; and 3) the activity of arginase [17]. Moreover, this latter point can be further supported based on the data demonstrating increased arginine availability in cultured cell model or by supplementation *in vivo* was able to overcome the effects of arginase and to enhance NO synthesis [25]. Based on results from all three phases of the present study, it is evident that L-citrulline supplementation impacted extracellular arginine concentration and the subsequent intracellular arginine synthesis based on the responses we observed in nitrite and NOx concentrations.

In phase 3 of the present study, we were also interested to determine if increased plasma arginine availability and subsequent NO synthesis due to oral L-citrulline and/or GSH supplementation was effected by resistance exercise. Interestingly, we observed increases in plasma NOx in all four groups immediately following resistance exercise, which indicates this response in plasma NOx to be particularly due to the stimulus of resistance exercise. These results are similar to our previous study where resistance exercise increased plasma NOx, independent of increased plasma arginine, due to seven days of L-arginine supplementation [5]. In the same way as NOx, plasma cGMP levels were increased by the combination of L-citrulline and GSH; however, this increase was not significantly different. Nevertheless, this suggests a possible synergistic effect from GSH that may be partially mediated by the formation of the NO-GSH complex. However, in the present study, significantly different increases in NOx occurred 30 min following resistance exercise, and only for the L-citrulline + GSH group. This suggests that a resistance exercise-related mechanism of inducing plasma NO, perhaps due to increased shear stress that triggered an up-regulation in NO-cGMP signaling, is a conceivable candidate for this response.

Consequently, there are possible physiological benefits of having high NO levels at 30 min post-exercise relative to its impact on muscle protein metabolism and possible muscle performance in response to resistance exercise training. It has been shown that NOS activity is necessary for calcium-induced activation of the Akt pathway (involved in translation initiation and thus muscle protein synthesis), and that NO is sufficient to elevate Akt activity in primary myotubes. Nitric oxide appears to influence Akt signaling though a cGMP/PI3K-dependent pathway [26], which is the primary pathway for up-regulating translation initiation and protein synthesis in skeletal muscle. Additionally, nitrite has been shown to enhance the proliferation and mTOR activity of myoblasts [27]. Similarly, NO seems to influence skeletal muscle function through effects on excitation-contraction coupling, myofibrillar function, perfusion, and metabolism. Another study showed that by using an agent to inhibit phosphodiesterase-5, that the augmentation of NO-cGMP signaling increased protein synthesis and reduced fatigue in human skeletal muscle [28]. In the present study, L-citrulline + GSH showed an improvement in cGMP activity suggesting that this outcome could likely play a role in muscle protein synthesis and muscle performance when combined with resistance training.

Our present data suggest that the oral supplementation of L-citrulline combined with GSH provides an augmenting effect on plasma NOx. Based on results from recent studies, this may be explained based on the premise that in some cell types, the activity of NO is influenced by the endogenous antioxidant, GSH [10]. Therefore, GSH may play an important role in protection against oxidative reaction of NO, thus contributing to the sustained release of NO.

Conclusions

Herein, we have presented *in vitro* and *in vivo* data demonstrating the efficacy of combining L-citrulline and GSH and the subsequent effects on NO synthesis and, collectively, we conclude that the combination of L-citrulline and GSH increases the levels of cGMP, nitrite, and NOx.

Competing interests

Masahiko Morita is an employee of KYOWA HAKKO BIO CO., LTD. The other co-authors declare no conflicts of interest.

Authors' contributions

SM served as the study coordinator and was involved in participant recruitment, testing, laboratory analyses, and assisted in manuscript preparation. TA was involved in testing and laboratory analyses. MM was involved in conducting the phase 1 and 2 portions of this study, in performing the plasma L-citrulline and L-arginine analyses in phase 3, and was involved in manuscript preparation. DSW was the principal investigator and, was responsible for securing grant funding and developing the experimental design. He was also involved in training and mentoring for laboratory analyses, provided primary oversight during the course of the study, and supervised manuscript preparation. All authors read and approved the final manuscript.

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