Symptomatic reversal of peripheral neuropathy in diabetic patients

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Running head: Reversal of peripheral neuropathy

Word count 3264:

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Abstract:

Objective: There is no therapy which reverses peripheral neuropathy (PN) in most diabetic patients. We hypothesized that a FDA cleared medical device, which emits monochromatic near infrared (890 nm) photo energy (MIRE) would improve neural function lost during diabetes. Research Design arid Methods: 49 consecutive diabetic subjects (Type 1. n=25: Type II, n=24). with established neuropathy received MIRE treatment to determine if there was an improvement of sensation. All had PN classified as either absent. diminished, or impaired protective sensation assessed by the Semmes-Weinstein *(SW)* monofilament test or hot/cold (H/C) sensation impairment. Impaired protective sensation, (4.56 or above) was present in 100% of subjects (range: 4.56-6.45) and 42 of 49 subjects had SW values exceeding 5.07. reported to be one of the most sensitive predictors of eventual diabetic foot ulceration. H/C sensation was absent (54%) or impaired (46%) prior to initiating treatment. The MIRE diode array was placed in contact with the skin on the lower leg/foot for 30 min./day, 3X/week for one month. SW and H/C tests were repeated at two and four weeks.

Results: After 6 treatments, most subjects exhibited improved sensation. After 12 treatments, no subject continued to experience absent sensation to HC: all had improved sensation based on SW.

Remarkably. 65% of subjects exhibited restoration of protective sensation (4.17 or below) and no subject had a SW value above 4.93.

Conclusions: MIRE may be a very safe, drug free, non-invasive treatment for the consistent and predictable improvement of sensation in diabetic subjects with PN of the feet.

Introduction:

Diabetic peripheral neuropathy is a consequence of diabetes-mediated impairment in blood flow to. and resultant hypoxia of. nerves (1). There is no treatment for reversing the neurologic deficit of this disease manifestation although some treatments, such as capsaicin cream, tricyclic antidepressants and valproic acid are efficacious in diminishing pain (2). Other studies have demonstrated some increase in conduction with use of aldose reductase inhibitors and insulin pumps or pancreas transplantation (3). With each of these approaches there have been notable problems in feasibility, logistics, and efficacy so that additional research into preventing/treating diabetic neuropathy has become a major research focus of the Juvenile Diabetes Foundation and the National Institutes of Health.

Impaired sensation in the feet becomes evident to the patient and clinician several years after the onset of diabetes (4) and, importantly, does not spontaneously regress: in other words, diabetic peripheral neuropathy is considered to be a progressive disease. Ultimately the loss of feeling can result in one or more ulcerations of the foot or feet. If the degree of sensory impairment reaches a level of 5.07, using the Semmes-Weinstein monofilament test, there is a very high likelihood of ulceration, followed by amputation (5). Thus, other approaches to improving blood flow in the feet of diabetic patients could be advantageous in the restoration of sensation: restoration of adequate circulation might delay the onset of ulcerations that often lead to amputations.

We have treated many diabetic and other subjects with MIRE in a protocol designed to heal otherwise recalcitrant ulcers, including venous stasis and diabetic ulcers, on the lower leg (6). The device is

FDA cleared for increasing circulation and reducing, pain. In many instances, subjects reported feeling a sensation of warmth, several days after beginning treatment, although they had not been able to discern differences in temperature prior to MIRE treatment.

To investigate if, indeed, sensation was returning to the lower, we performed a prospective study in diabetic subjects with neuropathy. The results demonstrate that all 49 subjects had partial restoration of feeling in their feet at the end of the 30-day trial. To our knowledge this is the first, highly successful, non-invasive drug free maneuver, which restores, at least temporarily, neural sensation in diabetic subjects.

Methods and Materials:

All subjects were treated at The Medical Center of Aurora, a Healthone facility, Aurora, CO in the Physical Therapy Department. The subjects ranged in age from 35 to 80 years old; 25 were Type I diabetic patients and 24 were Type IT diabetic patients. All had peripheral neuropathy based on the Semmes-Weinstein (SW) monofilament test. In addition the ability to detect hot *vs.* cold was also absent or impaired in each patient. No novel treatments or pharmaceuticals that would have uniquely modified circulation in the lower extremities were employed during the 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, and exercise. The SW test is often used as an adjunct to gait testing analysis in a PT department. Such information guides the therapist in his or her efforts to reeducate the muscles of the lower leg (7). The study was initiated in diabetic subject 1 in December 1999 and we treated the next 48 diabetic subjects whose SW. H/C, and gait analysis values were abnormal.

Procedure:

MIRE is delivered from a series of 60 GaAlAs diodes in a flexible pad (diode array) placed on the feet and/or lower leg. Four diode arrays (60 diodes in each pad) were used during the treatment. Each

application was for 30 minutes. One diode array was placed on the distal posterior aspect of the tibia in an effort to altercirculation the posterior tibial artery and another diode array was placed over the anterior distal tibia in an effort to affect the dorsalis pedis artery. On array was placed on the dorsal and another on the ventral surface of the foot This was done to each foot. An alternate pad placement was used specifically at the plantar aspect of each foot if the posterior tibia region was uncomfortable for some subjects.

Several sizes of SW monofilaments were applied to at least three areas of the plantar side of the feet. As far as possible, the same locations were tested at each visit. The filament was applied until it began to bend, it was held in place for approximately 1.5 seconds. Each site was tested three times. Care was taken to test areas that had the least thickness of the keratin layer. The test sites were the great toe, plantar arch region, and the fourth toe. The response to the filament testing was based on the subjective response from the patient of "NO W" when the patient could feel the filament. Hot/cold testing was also done at the same test sites. Response to the hot/cold testing was determined from subjective reports of whether the patient could sense the hot or cold bar. These were graded as absent, impaired, or intact.

Statistics:

The data for Type I and Type II diabetic patients were grouped and analyzed by repeated measures analysis; values reported are means ± SD. Significance was accepted as $P<0.05$.

Results:

The ages of subjects, Type of diabetes (I or II), SW values, and hot/cold (H/C) detection ability prior to beginning the study and after MIRE treatment are shown in Table 1. Type I diabetic patients (60.4 ± 12.8 yo) were approximately 12 years younger than the Type II diabetic subjects (72.5± 5.5 yo).

Baseline SW deficits were virtually identical in the Type I (mean ± SD: 5.49 ± 0.52) and Type II (5.44 ± 0.47) (Table 1; Figures 1 and 2L Thirteen Type I diabetic subjects and 13 Type II diabetic subjects had absent sensation to H/C prior to treatment (Table I).

Eighty-eight percent of the Type I subjects exhibited diminished or protective sensation using the SW test (4.26 ± 0.34) after 12 MIRE treatments (Table I and Figure 1). Figure 2 documents a similar response to MIRE treatment in Type II diabetic subjects. Specifically, after 12 treatments with MIRE 62% of the Type II subjects had diminished or protective sensation (4.45 ± *0.32)* where none had this ability prior to treatment (5.44 ± 0.47). The mean (± SD) SW values before and after 12 treatments with MIRE for all diabetic subjects are shown in Figure 3, Whereas 42/49 subjects had values above 5.07 prior to initiating the study. by week 4 (12 treatments) all subjects had improved sensation as assessed by the SW test and no patient had a value above 4.93.

After 12 treatments with MIRE nine of twelve Type I subjects converted from impaired H/C sensation to an intact ability to discriminate hot from cold (Table 1). Four of eleven Type II diabetic patients were now able to discriminate hot vs. cold after 12 treatments with the MIRE (Table 1).

Discussion:

Several products expected to improve the neurologic deficit of diabetic neuropathy, including nerve growth factor and aldose reductase inhibitors have failed, in large clinical trials, to meet full expectations of clinicians or patients (8,9). At this time there is no effective therapy currently available that will reverse diabetic. PN. For this reason the Juvenile Diabetes Foundation and the National Institutes of Health have made finding treatments for diabetic PN a major research priority.

The present pilot study shows that treatment with monochromatic near infrared photo energy can reverse, to some degree, the symptoms in all diabetic subjects treated so far. Admittedly the trial was small but, importantly. no restrictions as to patient selection were made. In addition, we recognize that no placebo was used in these studies. However, double blind clinical studies are planned at three additional sites and there is a placebo device that will be used in those

studies. It is a diode array that does not emit MIRE and it is indistinguishable from the active diode array. Therefore, neither the patient nor the healthcare professional can ascertain which diode array is active and which is a placebo. This is because the eye cannot detect MIRE, i.e., photo energy just beyond the visible spectrum of light. We have previously used active and placebo diode arrays in patients with venous stasis ulcers (6). Healing rate and quality of the remodeled tissues was improved with the use of active diode arrays but no improvement in venous stasis ulcer wound healing rate was observed in subjects treated with placebo diode arrays (6).

The physiologic basis of this improvement in neural function may be related, in part, to an improved circulation related to the localized release of nitric oxide (NO). While it is well recognized that photo energy can modulate circulation, as evidenced by the early work of Nobel laureate Robert Furchgott (10), the precise effects of MIRE are less well understood. Experimental studies in rats showed that 890nm near infrared photo energy increases blood flow in part through an eNOS mediated effect; the vasodilation was sustained even after the photo energy was removed (11). We have measured increases in microcapillary circulation after treatment with MIRE, using a scanning laser Doppler (Moor Instruments), in normal subjects and in subjects with diabetes (unpublished data). An increase in microcirculation, measured at the skin surface, begins within minutes of MIRE exposure arid is significant (10-fold increase) after 20-30 mm. treatment with the ATS. The increased circulation persists for upwards of one hour.

Photo energy mediated vasodilation may be due in part to the localized release of nitric oxide (NO) from the red blood cells (RB C) continuously passing through vessels exposed to the MIRE (12). RBC are able to store large amounts of NO (13). partly in the form of nitrosothiols (14) and the absorption of this wavelength (890 nm) of photo energy by hemoglobin is well documented (15).

We have measured NO release from rat RBC (assessed as NOx using a chemiluminescent detection system) into the suspension saline after treatment with the MIRE in vitro (12). RBC ghosts devoid of hemoglobin, fail to release NO. We have also measured NOx elevations in serum from humans and horses treated with MIRE and have documented that placebo units do not cause an elevation in circulating NOx in vivo (12). If blood flow does not change in response to placebo treatment and if blood flow and plasma NOx increase only from treatment with an active MIRE device, then the beneficial effects may be related to a NO mediated increase in circulation. NO activates

guanylate cyclase in smooth muscle cells and, after formation of cGMP, phosphorylation of myosin occurs (14). This latter event is the primary cause of NO mediated vascular smooth muscle cell relaxation and the parallel increase in circulation.

Diabetic patients cannot form NO at the same rate or to the same degree as normal subjects (16,17). Not only is the activity of the enzyme that generates NO from L-arginine defective (16. 17) (possibly due to metabolic acidosis (18) that attends diabetes), but glycosylated hemoglobin, characteristic of diabetes, avidly binds any NO that is formed (19). The latter constraint suggests that even the small amounts of NO produced in diabetes may not be easily released from RBC at microcirculatory sites. In addition, glucose binds NO and therefore the hyperglycemia of diabetes would also be expected to constrain NO bioavailability at the microcirculatory level (20). Diabetic subjects may not be able to produce or release normal amounts of NO. Impaired regulation of local blood flow and the accompanying reduction in nutrition and oxygenation of peripheral tissues, including nerves, might be partly responsible for the symptoms of diabetic peripheral neuropathy. Because circulatory integrity is well recognized as being compromised in diabetic patients (21), it is riot surprising that wounds do not heal well and abnormal neural function develops and progresses.

NO, which causes vasodilation via. guanylate cyclase activation and subsequent phosphorylation of myosin through cGMP also phosphorylates the potassium channel via cGMP (22). Modulation of locally available NO may account for the photo relaxation of vascular smooth muscle induced by various wavelengths of photo energy (23). It may be that nerves may benefit from the localized availability of N), INDIRECTLY from the vasodilation (and improved oxygenation of neural tissue and increased ATP generation), and DIRECTLY via phosphorylation of the K+ channel which may help restore membrane potential.

In summary, previous studies demonstrated that short term treatment with MIRE accelerated the rate and quality of wound healing (6); the present study documents that improved neural function in diabetic subjects is also a consistent effect of MIRE.

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