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HYPER BARIC OXYGEN THERAPY VERSUS MONOCHROMATIC INFRARED THERAPY IN THE MANAGEMENT OF DIABETIC FOOT ULCER

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ABSTRACT

Objective :
The purpose of this study was to compare the effectiveness of Monochromatic infrared therapy (MIRE) or hyperbaric oxygen therapy(HPOT) in the management of diabetic foot ulcer.

Materials and methods:
Forty patients who had diabetic foot ulcer for more than 6 months and not respondent well to medical treatment. Patients were classified into 4 equal groups 10 of each, Group (1): control group which received conventional therapy of the ulcer. Group (2) received 40 minute of monochromatic infrared energy(MIRE) , Group (3): received 40 minutes of HPOT. , And group (4): received 20 minutes of MIRE in addition to 20 minutes of HPOT (MIRE/HPOT). All groups received treatment 5 days per week for 60 days. Measurements of ulcer surface area were conducted before treatment, and after 60 days of treatment.

Results:
The one way analysis of variance was used to compare ulcer surface area which revealed that both treatment groups (MIRE and HPOT) had significant ($P < 0.05$) decrease in ulcer surface area after 60 days post application of treatment. On the other hand, the combination of MIRE and HPOT showed a highly significant decrease in ulcer surface area when compared with control or with individual treatment.

Conclusion:
The results of this study suggest that combination of MIRE to HPOT is more effective than individual treatment to enhance the healing rate of diabetic foot ulcer.

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INTRODUCTION

Diabetes mellitus is a disease known for its multifaceted complications, and foot ulceration, which often results in lower extremity amputations, is one of the most common complications associated with the disease [1, 2]. The prevalence of foot ulcers ranges from 4% to 10% among persons diagnosed with diabetes [3]. This translates to an annual population-based incidence of 1.0% to 4.1% and a lifetime incidence as high as 25% [3]. At least 15% of people with diabetes will eventually develop a lower-extremity ulcer of some sort [4].

Although the precise pathophysiological mechanism underlying the development of diabetic foot ulcerations is complex [5], it is generally associated with the presence of peripheral neuropathy and repetitive trauma due to normal walking activities which expose the foot to moderate or high pressure and shear forces [6, 7]

Neuropathic foot ulcers generally do not respond well to treatment, and several novel treatment modalities have been proposed over the past few years[8–10], including the development of new dressings, growth factors, bioengineered skin and tissue substitutes, hyperbaric oxygen, negative pressure wound therapy and other novel approaches to stimulate wound healing [11–13].

The Anodyne Therapy System emits monochromatic infrared photo energy (MIRE) at a wavelength of 890 nanometers through therapy arrays, each containing 60 superluminous Gallium Aluminum Arsenide (GaAIAs) diodes that pulse at 292 times per second[14]. 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 (NO) from hemoglobin, has been documented in the clinical literature[15].

As tissue hypoxia is one of the pathophysiological characteristics of diabetic ulcers, hyperbaric oxygen therapy (HBOT) has been considered as a therapeutic strategy to reduce tissue hypoxia and enhance wound healing. However, there are no uniform and evidence-based guidelines for treatment of the diabetic foot with hyperbaric oxygen[16].

The main objective of the current study is to compare the effectiveness of MIRE versus HBOT on the management of diabetic foot ulcer.

MATERIAL AND METHODS:

This study is a randomized, prospected, controlled, clinical trial. A total of 40 patients were recruited from the Diabetic Unit of Om El- Maserin hospital (Cairo - Egypt). Study subjects were evaluated for a total of 8 weeks. Inclusion criteria were neuropathic foot plantar ulceration below the malleoli for a period of at least 6 months with an area wider than 1 cm^2, age 30-50 years, a diameter of the lesion between 0.5 and 5 cm and type 1 diabetes mellitus with insulin treatment for at least 5 years prior. Patients also should have had peripheral neuropathy, as defined by insensitivity to a 10-g monofilament and by a vibration perception threshold measured at the malleolus of at least 25 volts [17]. The vascular assessment consisted of an ankle-brachial index > 0.7 and palpation of the dorsalis pedis and posterior tibial arteries. If one or both arterial pulses were not palpable, the subject was excluded Exclusion criteria included patients with any of the following around the time of applications: peripheral vascular disease, coronary bypass, pregnancy, coagulation diseases or history of neoplasia or other conditions, based on the principal investigator's clinical judgment.

The population was randomized into four groups that received standard care consisting of therapeutic footwear, debridement and dressing.

Control group : Patients in the control group were treated with the essentials of foot ulcer care, namely debridement, adequate pressure relief and treatment of infection, as required by current international guidelines [18]. Patients were permitted to ambulate as tolerated, and each patient was provided with an orthopedic device to remove mechanical stress and pressure at the site of the ulcer during walking.

HPOT group : Patients in the HPOT group were treated with the essentials of foot ulcer care, in addition to HPOT treatment which performed with patients in a sealed multi-place chamber at a pressure of 2.5 atmospheres absolute (ATA). The air pressure was gradually increased from 1 to 2.5 ATA in 15 min. Oxygen of 100% medical grade was inhaled through a plastic facemask for 25 min with a 5-min break in between for a total of 90 min per treatment. The air pressure was then decompressed from 2.5 ATA down to 1.0 ATA within 15 min to complete the treatment. HBO was performed once a day, 5 times a wk for a total of 40 treatments.

MIRE group : Patients in the MIRE group were treated with the essentials of foot ulcer care, in addition to MIRE treatment Which was done by Anodyne Therapy Model 120 for Professionals, 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. MIRE was performed 40 minutes, once a day, 5 times a wk for a total of 40 treatments.

MIRE/HPOT group: Patients in MIRE/HPOT group received both treatment modalities in addition to essentials of foot ulcer care. MIRE followed by HPOT was performed once a day, 5 times a wk for a total of 40 treatments.

For Evaluation:

The overall period of study period was 2 months and the evaluation was done before treatment intervention i.e at day one and after treatment intervention i.e after 2 months.

1- Measurement of ulcer surface area:

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[19] : 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 was 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).

2- Overall clinical result :

The overall clinical result was judged based on the total number of cases which achieved complete healing or at least equal or more than 50 % of healing at specific time which is 20 days.

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 , ulcer size and the duration of ulcer prior to treatments intervention as showed in table (1).

Table(1):Patients demographic data

Parameters	Control group	MIRE group	HPOT group	MIRE/HPOT group
Average age (y)	37.2±1.5	38.4±1.7	38.4±1.6	39.3±2.1
Average size cm^2	10.9± 0.2	10.9±0.2	11.1± 0.2	10.6±0.3
Average duration (mo)	17.1± 0.5	16.2±0.2	17.3± 0.5	17.5±0.5
Location of ulcer (dorsal /planter)	3/7	4/6	2/8	1/9

Data were expressed as Means ± SE

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 20 in comparison with base line measurement at day 1, on the other hand , there was no significant difference between MIRE group and HPOT group at day 20, but there was a highly significant difference between MIRE/HPOT group and Mire group, HPOT group, and control group at day 20.

Table (2): Comparison of ulcer surface area of HPOT ,MIRE, MIRE/HPOT with Control groups.

Treatment groups / Days	Control group	MIRE group	HPOT group	MIRE/HPOT group
Day 1	10.9± 0.6	10.9±0.8	11.1± 0.6	10.6±0.9
Day 20	$9.7\pm0.7^{B,C,D,\dagger}$	$4.8\pm0.9^{A,C,D,\dagger}$	$4.9\pm0.5^{A,B,D,\dagger}$	$0.1\pm0.2^{A,B,C,\dagger}$

Data were expressed as Means ± SD of 10 Diabetic ulcer patients /group. C; Control group, MIRE; monochromatic infrared energy treated group, HPOT group; hyper baric oxygen therapy group, MIRE/ HPOT; monochromatic infrared plus hyperbaric oxygen therapy. ^{A} significantly different versus control group; ^{B} significantly different versus MIRE group; ^{C} significantly different versus HPOT group; ^{D} significantly different versus MIRE/HPOT group at $P \leq 0.05$. †significantly different versus Day 1; at $P \leq 0.05$. Significance was carried out by One-way ANOVA and Tukey- Krammer test.

The overall improvement of the treatment groups in comparison with control group regarding the percentage of healing wither it is completely healed or healed by more than 50 % of the baseline measurement or remain relatively unchanged was shown in table (3) which demonstrated that either MIRE or HPOT treatment have succeeded in getting more than 50% improvement in all the cases but the combination of both treatment have succeeded in getting 5 cases complete healing and 5 cases more than 50% improvement in relation to baseline measurement.

Table (3) The Overall Clinical Results After Treatment

Parameters	Control group	MIRE group	HPOT group	MIRE/HPOT group
No. patients/ulcers	10/10	10/10	10/10	10/10
Completely healed	0	0	0	5
≥50% improved	0	10	10	5
Unchanged	10	0	0	0

DISCUSSION

The causes of diabetic foot ulcers are multifactorial, including ischemia, hypoxia, neuropathy, and infection, and they often coexist[20]. The management of chronic diabetic foot ulcers require multidisciplinary approaches including control of blood sugar, antibiotics, shoe wear, wound care, and surgery in selected cases with the primary goal to control the diabetic mellitus and to avoid complications[21].

Many patients present with recurrent refractory chronic foot ulcers that respond inconsistently to various surgical or nonsurgical treatments. Therefore, chronic diabetic foot ulcer remains as an unresolved medical entity.

Many studies used different adjunctive therapies with the intention to cure the diabetic skin ulcers including HBOT[22] and MIRE[23]. HBOT is a controversial treatment in chronic diabetic foot ulcers. Many studies reported positive effects of HBOT in chronic diabetic foot ulcers[24, 25], whereas other studies reported HBOT to have little to no credible evidence for its effectiveness in chronic diabetic foot ulcers[26].

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 ulcer size changed 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. 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%.[27] Increased circulation possibly accounts for the reported increased healing rates after 12 weeks of MIRE application.

The ability of photo energy to increase microcirculation, possibly through the release of nitric oxide (NO) from hemoglobin, has been documented in the clinical literature[15]. NO initiates and maintains vasodilation through a cascade of biological events that culminate in the relaxation of smooth muscle cells that line arteries, veins, and lymphatic's. NO gas released from nitrosothiols in hemoglobin or from endothelial cells diffuses into smooth muscle cells that line small blood vessels. Once inside the smooth muscle cell, NO binds to guanylate cyclase (GC) and this binding results in GC activation. Activated GC is able to cleave two phosphate groups from guanosine triphosphate (GTP), which results in the formation of cyclic guanosine monophosphate (cGMP) that is used to phosphorylate myosin. Once phosphorylated, smooth muscle cell myosin relaxes, resulting in dilation of the vessel[28]. MIRE appears to break the bond between nitric oxide and hemoglobin making it bioavailable to cause vasodilation, analgesia, angiogenesis, and other physiologic effects known to be produced by NO.

On the other hand, The result of the current study showed that there was a significant improvement in healing in the HPOT group compared to the control group, as measured by a reduction in ulcer area. Possible reasons for improved healing rates in the HPOT group may be due to Hyperbaric oxygen exposure increases tissue oxygen levels and thereby results in increased cellular proliferation, improved collagen synthesis and increased angiogenesis. Furthermore, anaerobic organisms are found in low oxygen-tension tissues, which are present in one-third of cases of diabetic foot infections[29]. HBOT increases the killing ability of leukocytes and is lethal to certain anaerobic bacteria [30]. Edema in the periwound area is decreased through the vasoconstrictive action of oxygen and the leukocyte-bacterial-killing ability. HBOT enhances phagocytosis of bacteria and inhibits toxin formation [31].

Finally the result of the current study have shown that the combination of MIRE and HPOT is very effective in the reduction of diabetic foot ulcer size because MIRE have gained more vasodilation and HPOT have gained more oxygen necessary for the repair process as discussed earlier.

CONCLUSION

It was concluded that the combination of MIRE and HPOT was highly effective in the enhancement of Diabetic foot ulcer healing.

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CONFLICT OF INTEREST

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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ETHICAL CLEARANCE

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

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