Topical Hyperbaric Oxygen and Electrical Stimulation: Exploring Potential Synergy

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Treatment of chronic wounds involves interventions ranging from dressings to surgery. Modalities gaining popularity in clinical settings include topical hyperbaric oxygen and electrical stimulation. A prospective, uncontrolled study was conducted to obtain preliminary observations and data about the effects of topical hyperbaric oxygen therapy and topical hyperbaric oxygen used with electrical stimulation on the healing of chronic wounds. All subjects were geriatric residents of long-term care facilities with Stage III or Stage IV pressure ulcers. Topical hyperbaric oxygen was applied daily to the wounds of eight subjects; three also received electrical stimulation. Initial wound size ranged from 87.75 cm² to 7.04 cm² with an average size of 30.1 ± 28.5 (mean ± sd) cm². Healing times ranged from 8 to 49 weeks. After 4 weeks of treatment with topical hyperbaric oxygen, wound size decreased an average of 34.4% ± 22.9%. Incidentally, the wounds of five of the eight subjects decreased more than 20%, for an average of 51.8% ± 17.9%. No significant differences in healing were observed between patients receiving topical hyperbaric oxygen alone and those receiving topical hyperbaric oxygen/electrical stimulation. Preliminary data indicate that topical hyperbaric oxygen facilitates wound healing and full closure for pressure ulcers in patients with and without diabetes mellitus. A multicenter, prospective, randomized, double-blind controlled study is currently under way.

Ostomy/Wound Management 2002;48(11):42–50

The incidence of chronic wounds, including pressure ulcers, diabetic ulcers, venous ulcers, and arterial ulcers, is increasing as our population ages. The prevalence of pressure ulcers has been reported to be as high as 11% in the hospitalized population and 20% in the nursing home population.[1] The cost associated with the treatment of these wounds is staggering and estimated to exceed $7 billion per year.[2] Chronic wounds are painful and may lead to a number of complications, including: disability, need for assisted living or home care, depression, loss of digit or limb, infection, or death. The presence of pressure ulcers increases the risk of death for geriatric patients and nursing home residents and increases the rate of mortality for hospitalized patients.[3]

Wound healing is a complex process, which follows a sequence of biochemical and cellular events. These events can be divided into four phases: coagulation, inflammation, tissue formation, and remodeling.[4-7] In a normally healing wound, specific cell types are present at each phase as particular biochemical reactions occur. When events leading to normal wound healing are disrupted by pathophysiologic or metabolic factors anywhere along the highly complex process, chronic, nonhealing wounds occur.

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Oxygen and Wound Healing

Although the process of wound healing is well documented, the chronic wound presents a difficult problem. Any interruption of normal healing will result in a chronic wound; the disruption can occur anywhere along the highly complex process. Differences between types of wounds may result in differences in the delay of the wound healing process. The most common chronic wounds are vascular (venous and arterial), pressure, and foot ulcers in people with diabetes, with a notable variability between wounds.[8,9] Each type of chronic wound is associated with a particular wound environment. Mulder[8] suggests that delay in wound closure may result not from a lack of growth factors or other necessary components, but rather from the presence of secondary negative signals and factors which, when removed, would allow closure. Each of the chronic wound types has complications associated with microvascularity of the tissue at the wound.[8] People with diabetic wounds often have micovascular disease, people with venous ulcers have systemic problems (eg, venous hypertension), and people with pressure ulcers have compromised vascularity.

Lack of perfusion and oxygenation contribute to impaired healing.[10] Tissue perfusion is critical to wound healing; insufficient tissue perfusion results in disturbances of nutrients and metabolic function.[5] Falcone[4] found that the metabolism of the cellular infiltrate directs biochemical events of wound healing. The function of macrophages, fibroblasts, and endothelial cells is impaired if local perfusion and oxygenation are limited.[6] Collagen deposition is directly related to oxygen tension; at oxygen levels less than 20 mm Hg, collagen synthesis halts.[10-12] Also, perfusion is critical for granulocytes to ingest bacteria and foreign bodies, and insufficient oxygen may lead to an increased bacterial load.[10-12]

Hypoxia (decreased tissue oxygen) in the wound space is a stimulus to angiogenesis, but collagen production in mature fibroblasts requires oxygen.[6,13,14] Thus, hypoxia results in a delay in healing. Alternatively, hyperoxia results in faster healing.[6] Angiogenesis is accelerated when oxygen in the circulation is increased.[6] Hunt et al[15] showed that the rate of synthesis of collagen in closed wounds is accelerated in hyperoxia. Pai et al[15] also found that hyperoxia accelerated healing and epithelialization in open wounds in rats. Other researchers have found hyperbaric oxygen accelerated healing in devascularized wounds.[16]

The premise for hyperbaric oxygen use is that increased tissue oxygen tension in the wound improves and accelerates resistance to bacteria, collagen synthesis, angiogenesis, and epithelialization.[17,18] Several investigators have shown that hyperbaric oxygen improved healing in chronic wounds.[17,19-24]

In 1943, the United States Navy began to use hyperbaric oxygen therapy for treatment of decompression sickness and air embolism. However, the chambers used for systemic hyperbaric oxygen are expensive and have potentially toxic side effects.[19,25] Topical hyperbaric oxygen therapy is an inexpensive alternative to chambers. Researchers using topical hyperbaric oxygen (THBO) have reported decreased infection and increased healing rates.[19,24,26,27]

Electrical Stimulation and Wound Healing

Several studies have demonstrated that electrical currents exist in living organisms. Cells follow the path of the flow of current, referred to as the galvanotaxic effect. Use of electrical stimulation (E-Stim) for the treatment of chronic wounds has increased in popularity during the last several years.[28] It is theorized that electrical stimulation augments the endogenous bioelectric system in the body.[29,30] The increase in the rate of wound healing with electrical stimulation is also theorized to be a result of attraction of different cell types. Studies have shown that the migration of macrophages,

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KEY POINTS

- Despite the use of appropriate treatment regimens, some chronic wounds fail to heal in a timely fashion.
- To obtain closure of these refractory wounds, some clinicians employ modalities such as electrical stimulation (E-Stim) or topical hyperbaric oxygen therapy (THBO).
- In this eight-patient, prospective evaluation, the authors explored the effects of THBO, with and without E-Stim, on pressure ulcer healing.
- Results of the controlled clinical study that was initiated following the completion of this evaluation will help determine if the findings reported can be applied to other populations.

Figure 1
Topical hyperbaric oxygen therapy sacral unit

fibroblasts, mast cells, neutrophils, and epidermal cells is influenced by electrical stimulation.[31-37] Electrical stimulation also has been shown to increase the proliferation of fibroblasts and protein synthesis, as well as the growth of neurites.[38] Each of these factors plays a significant role in wound healing. Furthermore, the tensile strength of the collagen has been shown to increase with E-Stim use; thus, increasing the strength of scar tissue.[39]

High-voltage monophasic pulsed current (HVPC) has been reported to improve blood flow, decrease edema, and inhibit bacterial growth.[40-42] Several studies have reported that HVPC augments wound healing.[43,44] Electrical stimulation is a standard treatment modality in the authors' facility, where previous related work has shown HVPC to be a safe and effective treatment for ulcers.[45,46]

The effects of electrical stimulation on cell migration and proliferation are important factors in its successful use in healing wounds. Topical hyperbaric oxygen has also been reported to stimulate angiogenesis.[24] The effect of using these modalities together, particularly the effect on rate of healing, are of great interest. The purpose of this prospective, uncontrolled study was to obtain preliminary data about the effects of THBO therapy and THBO used with E-Stim on the healing rates of chronic wounds.

Materials and Methods

Subjects. Participants in this study were residents of two facilities: Manor Oak Life Center, a 150-bed skilled nursing facility located in Buffalo, NY, and Oakwood Health Care Center, Inc., Williamsville, NY. People with a Stage III or Stage IV pressure ulcer that had not responded after two or more weeks of treatment were eligible to participate. Each lesion was evaluated using the Pressure Sore Status Tool (PSST) by the licensed physical therapist before participation and every 30 days thereafter, until healed. Studies by Bates-Jensen et al[47,48] demonstrated that the mean interrater reliability coefficient of the PSST is 0.91 and intrarater reliability of practitioners averaged 0.89 with this tool. Exclusion criteria included patients with cardiac pacemakers and wounds exhibiting neoplasm. Patients or wounds with any diagnostic history of a neoplasm were excluded, as were wounds of suspicious or indeterminate etiology. Subjects selected for the study gave informed consent and were assigned an ID code to ensure confidentiality.

The eight participants in the study included four men and four women, with an average age of 75.4 years (± 13.9, range 48 to 95). Three participants had diabetes mellitus. All participants were Caucasian and had nonhealing Stage III or Stage IV pressure ulcers that showed no improvement or response to conventional treatments for at least 2 weeks. Seven ulcers were located on the sacral and one in the ischial area (one ulcer per patient).

Ulcer site, stage, support surface type, gender, race, height, weight, age, history of smoking, diabetes, cardiovascular disease, cancer, and other wound and patient variables were noted in a database. The study and consent forms were reviewed and approved by the Institutional Review Board.

Treatment. All wounds received THBO twice daily, 7 days a week. Three wounds also received E-Stim. The wounds that also received E-Stim were treated once daily, 5 days per week. Both treatments were administered by a licensed physical therapist. The THBO was applied morning and evening using a chamber with disposable self-adhering polyurethane units (Advanced Hyperbaric Technologies, Inc., Farmingdale, N.J.) (see Figure 1). Patients received two 90-minute treatments daily with 2L to 3L of humidified oxygen delivered per minute at 22 mm Hg. The wounds receiving E-Stim were treated midday with E-Stim high voltage pulsed current (HVPC) at 150 volts, 120 pulses/second, and 255µ pulse-pair intervals for 30 minutes using a monopolar, nondispersive technique. The subjects chosen to receive E-Stim were selected based on wound eti-

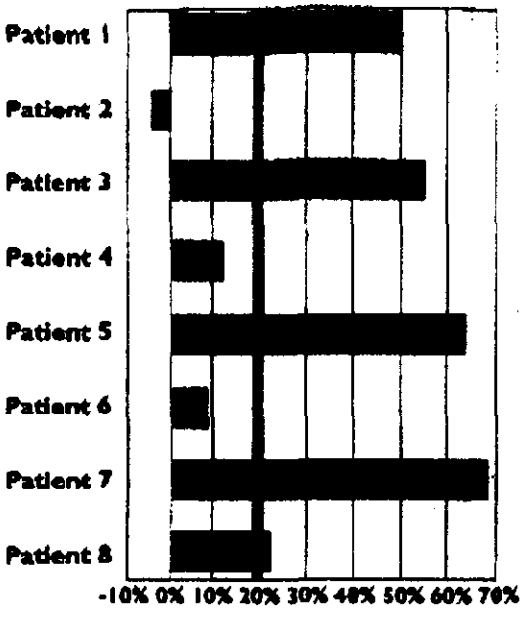

Figure 2
Percent reduction in wound size at 4 weeks.

ology, wound status, and assessed potential in association with documented evidence-based use of E-Stim.

Dressings. Dressings varied and included an adhesive dressing (Allevyn, Smith and Nephew, Largo, Fla.) and saline-soaked gauze. Dressings were chosen based on the immediate wound status. Saline-soaked gauze, when used as the wound dressing, was changed every shift to minimize desiccation and to minimize or prevent patient discomfort associated with dressing removal.

Assessment. Each wound was photographed weekly with a digital camera. The images were analyzed and measured using VEV MD Wound Measurement Software (Vista Medical Ltd., Winnipeg, Manitoba, Canada). This software, which employs a stereophotogrammetry technique, has been shown to be more accurate and less biased than linear measurement or planimetry.[46] The accuracy of the software provides an objective technique for wound evaluation, measurement, and tracking.[46-48]

Data analysis. A Wilcoxan Matched-Pairs Sign Rank Test was conducted to compare wound area initially and after 4 weeks of treatment. A Friedman's nonparametric ANOVA was used to compare wound areas at the initial, 4-week, 8-week, and final evaluation point. A Mann Whitney U-Test was conducted to test for differences post-treatment in 4-week wound areas between patients with and without diabetes. A Mann Whitney U-Test also was used to compare healing responses between patients receiving THBO treatment alone and patients receiving THBO and E-Stim.

Results

Four weeks of THBO treatment significantly reduced wound area relative to initial wound area ($T = 1.0$, $n = 8$, $P = 0.017$). After 4 weeks of treatment with THBO, average wound size had decreased 34.4% ± 22.9%. After 4 weeks of treatment, five of the eight wounds decreased in area by more than 20%, with an average decrease in area of 51.8% ± 17.9% (see Figure 2). Initial wound size ranged from 87.75 cm^2 to 7.04 cm^2 with an average size of 30.1 cm^2 ± 28.5 cm^2. Due to small sample size, no significant differences were observed in wound areas between patients with and without diabetes after 4 weeks of treatment ($U = 4$, $P > 0.1$). Although this was a small sample size, these results suggest that people with diabetes may heal as effectively as people without diabetes when treated with THBO. No significant differences in healing were observed between THBO and THBO/E-Stim subjects, due to small sample size ($U=4$, $P > 0.1$). It is important to note that average baseline was 15.97 cm^2 ± 13.3 cm^2. Six of the eight wounds healed completely. The remaining two wounds did not heal during the course of the study because both subjects expired due to unrelated medical conditions. Wounds exhibited significant closure over the duration (8 to 44 weeks) of individual treatments ($x2r = 18.82$, $n=7$, $P = 0.0003$) (see Figure 3). The two largest wounds, 52.64 cm^2 and 87.75 cm^2, were 100% healed at 22 and 16 weeks, respectively. Healing times ranged from 8 to 49 weeks.

The healing trajectories were similar for five of the wounds in this study; of these wounds, four healed completely (see Figure 4). These four wounds also healed in the shortest period of time. The patients with the remaining three wounds had different healing trajectories; two healed completely. One of the two wounds that did not heal during the course of the study due to the expiration of the patient had a trajectory similar to the four fastest healing wounds. Assessing the other nonhealing wound trajectory is difficult.

Discussion

Electric current or charge has been used to treat injured tissue for centuries[25] and the efficacy of high

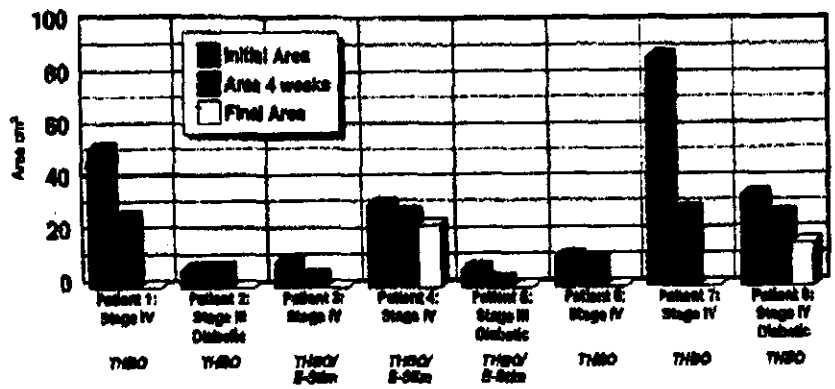

Figure 3
Wound area comparisons throughout the study.

voltage pulsed current for the treatment of pressure ulcers has been reported by a number of researchers.[48-52]

In the past 30 years, other researchers have evaluated the use of topical hyperbaric oxygen for treatment of pressure ulcers, but very few have evaluated modern THBO advances.[19,20,34,48,52] Heng et al[34] reported significantly greater percentages of healing, rates of healing, and capillary density for necrotic ulcers treated with THBO. The authors of the current study did not focus on necrotic ulcers, but significant decreases in wound area were noted. No studies evaluating the use of E-Stim with THBO for the treatment of pressure ulcers have been reported.

In this study, THBO treatment significantly reduced wound area after 4 weeks of treatment. Specifically, average wound size decreased 34.4% after 4 weeks. A limitation of this study is the lack of controls for comparison. Also, the use of a variety of dressings may add variability, but for the scope of this project, standardizing the dressings utilized was not possible. As a pilot study, the data collected served as indicators that a larger, controlled study to further evaluate the efficacy of THBO and THBO with E-Stim for the treatment of chronic wounds is needed.

Several researchers have evaluated the rates of healing and healing trajectories.[53-56] Clinical studies have shown that ulcers that decreased 20% to 40% in area after 2 to 4 weeks of treatment are more likely to heal and will heal significantly faster than ulcers that do not demonstrate this percentage of healing.[53-55] Robson et al[56] compared wound healing trajectories between centers and found the trajectories of healing or lack of healing to be similar. The trajectory or rate of healing may be more significant than the endpoints alone when evaluating the efficacy of a treatment used in healing. Monitoring the rate of wound healing may allow clinicians to more effectively treat wounds by recognizing the progress or lack of progress present with a particular treatment and patient.

Although no significant differences in healing were noted between patients treated with THBO and THBO/E-Stim, an interesting finding was the complete resolution of epiboles (rolled over edges) in two patients. Often in cases of epibole, clinical reduction of the edges of the wound is necessary so the normal process of epithelialization can continue once the proliferation phase (granulation) has caught up. Typically, reduction can be done surgically (debridement) or with pharmaceuticals (silver nitrate). The reduction of the epibole in the study wounds was complete with the use of THBO/E-Stim and no further intervention. Thus, an unexpected but beneficial effect of the THBO/E-Stim treatment was the reduction of epiboles. Further studies will be necessary to evaluate this apparent side effect of treatment with combined THBO and E-Stim.

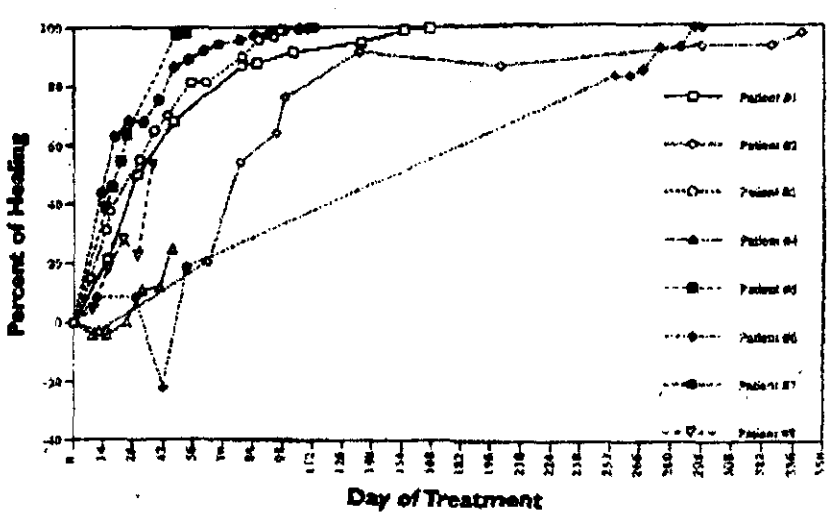

Figure 4
Wound healing trajectory plot. Percentage of wound healing versus time of treatment. Note patients 4 and 8 did not achieve 100% healing.

Conclusion

Based on these preliminary findings, THBO is a promising modality, but further research is needed. The initial results for THBO and THBO with E-Stim indicate significant changes in wound area, but the differences between both treatments should be evaluated. Also, the efficacy of both treatments when used in people with and without diabetes needs further study.

Comparing findings across studies is often extremely difficult due to differences in outcome measurement, methodology, and analyses.[36,37,41] Clinical studies for evaluating chronic nonhealing wounds represent a major challenge because of the extreme heterogeneity of the patient population.[36] Chronic, nonhealing wounds can be a result of a variety of conditions, and the healing rate can be affected by a number of variables, including nutritional status, medication, compliance, support surface, dressings, and modality.[36] In the ideal study, all patients would have the same type of wound, same location, same medical history, and all the patients would be in a strictly controlled environment for the duration of the study. Realizing the impossibility of such a study, multicenter, prospective, randomized, double-blind controlled studies with larger numbers of subjects are necessary to definitively evaluate the effect of THBO on the healing of chronic wounds. As a result of the initial findings of this study, a multicenter prospective, randomized, double-blind controlled study will be undertaken. - OWM

Acknowledgment

The research was performed at the Natural and Health Sciences Research Center, Daemen College, Amherst, NY. It was sponsored by the New York Chapter American Physical Therapy Association Research Foundation and Advanced Hyperbaric Technologies, Inc., Farmingdale, NJ.

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