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The effects of hyperbaric oxygen therapy on chronic diabetic ulcer healing

By

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ABSTRACT

Current wound management for chronic diabetic ulcers is unreliable and frequently fails. Due to this unsatisfactory outcome, many diabetic patients are at risk for further complications such as amputations or death. Hyperbaric oxygen therapy (HBOT) has the potential to promote chronic diabetic ulcer healing as an adjunct treatment tool by reducing tissue hypoxia and ischemia. The purpose of this medical literature review is to examine the effect of HBOT, compared to standard wound care alone, on chronic diabetic lower extremity ulcer healing. Unfortunately, limitations of existing medical evidence hinder the use of HBOT as a conventional treatment modality for non-healing diabetic wounds. Further discussion involves diabetic lower extremity ulcer etiology, normal wound healing physiology, chronic wound physiology in diabetic patients, and present HBOT research.

INTRODUCTION

Chronic lower extremity ulcers are a common complication seen in diabetic patients. Currently there is no defined treatment regimen used to heal chronic diabetic wounds effectively and to ultimately decrease the associated costs and risks involved. In the United States, it is estimated that 15% of diabetic patients develop foot ulcers, and 14-24% of those patients will require an amputation. The average cost of healing a single non-infected ulcer is $8,000, and the average cost for a major amputation is $45,000. In addition, about 50% of people with amputations will develop ulcers in the opposite limb within 18 months, and the three-year mortality after one amputation is estimated to be 20-50%. Due to these facts, there is debate whether hyperbaric oxygen therapy (HBOT) can play an effective role as an adjunct tool in the chronic wound repair process.
Wound management has evolved substantially over the years to promote healing in different types of cutaneous injuries through various treatment regimens. However, there are several situations that make the wound healing process a grueling challenge. These conditions include extensive burns, ischemia, venous or arterial insufficiency, immune compromise, and pressure areas. One of the most common diseases that yields complication in the wound healing process, eventually leading to chronic wound status, is diabetes. Non-healing lower extremity ulcers are a prevalent complication among the diabetic population, potentially leading to a decline in quality of life, and even amputation and death. The chronic ulcers frequently arise from complications of diabetic neuropathy, peripheral vascular disease, edema, calluses, or trauma. The wounds require extensive treatment practices such as tissue debridement, infection control, and pressure relief. However, many of the treatments leave these patients with poor results.

A chronic diabetic ulcer is described to be any lower extremity wound that has been present for over one month and where attempts to heal by standard wound care methods have failed. Standard wound care is considered to be any localized treatment, such as topical ointments or solutions, dressings, or tissue debridement. One possible solution to treating non-healing diabetic ulcers is the addition of HBOT to current treatment regimens. HBOT is the administration of 100% oxygen exposure at a high pressure, generally around 2-3 atmosphere absolute (ata) pressure, for several minutes once or twice daily. It is performed by placing the patient’s body in a pressurized chamber and allowing them to breathe the concentrated oxygen in order to increase the availability for body tissues. The role of HBOT as a modality for chronic wound treatment is to maintain tissue oxygen saturation for several hours after therapy.
sessions; therefore, stimulating and continuing the healing process. Although chronic diabetic ulcers involve hyperglycemia in addition to ischemia, HBOT may demonstrate benefit as supplementary care by acting on the ischemic portion of the chronic wounds. The purpose of this literature review is to examine the effect of HBOT, compared to standard wound care alone, on wound healing in chronic diabetic lower extremity ulcers, up to one year after treatment. It is important to identify new treatment regimens for chronic diabetic ulcers in order to improve quality of life and prevent further complications such as amputation.

**DISCUSSION**

Normal wound healing consists of three confluent phases: inflammatory, proliferative, and tissue remodeling (Fig. 1). The inflammatory phase consists of vessel constriction and platelet aggregation. It begins immediately after the wound injury occurs and continues for four to six days. Next, the proliferative phase involves granulation, blood vessel formation, and re-epithelization. This process can take a few weeks to complete. Finally, the tissue remodeling phase concludes the entire process via wound contraction and fibroblast activation, which ultimately leads to wound closure. This phase can take up to a couple years. The first two stages utilize acute hypoxia and reactive oxygen species (ROS) activity to begin and promote the healing process, while oxygen recovery in the third phase enables completion of the process. Throughout the healing series, vascular endothelin growth factor (VEGF) plays an important role for the development and maintenance of blood vessels, endothelin-1 is necessary for vasoconstriction to essentially maintain vascular tone, and interleukin 6 (IL-6) has both pro-inflammatory and anti-inflammatory action that promote wound closure.

**Fig 1.** Normal physiologic phases of the wound healing process and corresponding activity response over time. Chronic wound physiology is also represented by continuation of the inflammatory phase.¹⁰

In chronic wounds, such as lower extremity diabetic ulcers, the normal events of wound healing are not accomplished. Many factors not only contribute to the etiology, they play a role in the prevention of wound closure as well. Some of these causes include tissue hypoxia, bacterial overgrowth, and ischemia. Due to these issues, chronic wounds remain in the inflammatory phase and cannot progress to full tissue healing (Fig. 1).¹⁰ This is also true for chronic diabetic ulcers. With the persistence of tissue hypoxia, vascular insufficiency, immune incompetence and hyperglycemia, many diabetic ulcers remain in the first phase of the healing process and thus become chronic. The continuation of the ulcers can then lead to further complications that greatly affect quality of life (e.g. disability or amputation), or even threaten patient lives.
HBOT is considered to be an adjunct treatment modality to promote diabetic ulcer healing by ending the ongoing hypoxic and ischemic state of the chronic wounds. This idea is demonstrated in a study conducted on rats, which investigates the role of HBOT in ischemic and/or hyperglycemic wound states. It was found that the ischemic and hyperglycemic wounds that underwent HBOT (experimental groups) had decreased wound size and less closure time when compared to the control groups. However, there was no significant difference found in wound contraction and re-epithelialization between the groups. In addition, ischemic wounds in hyperglycemic conditions benefited the most from HBOT. Based on these results, HBOT may possess the potential to promote ulcer healing in diabetic patients.

In data collected from 971 diabetic patients that underwent HBOT, it was found that wounds with a modified Wagner grading of 3 or higher showed the most benefit from HBOT. It was also found that the greatest wound healing appeared within the first fifteen treatments. Amputation rates were seen to be doubled in patients with interrupted treatments as opposed to those with uninterrupted therapy sessions. This suggests that patients with more extensive ulcers may benefit most from HBOT, as opposed to less severe wounds. Nevertheless, the study was retrospective and did not incorporate a control group.

Additionally, HBOT was found to significantly impact VEGF, enothelin-1 and IL-6 plasma levels. In a study that examined chronic wounds and their responses to HBOT, it was found that VEGF and IL-6 levels significantly increased after each treatment session, whereas endothelin-1 progressively decreased over the sessions. These level changes promoted angiogenesis, regulation of vascular tone, and decreased inflammation in the wounds, ultimately leading to faster and complete wound closures. By utilizing HBOT, chronic wounds have a greater
potential to break out of a prolonged inflammatory phase, and progress through the remaining stages of the healing process. Unfortunately, the study included a small sample size and various chronic wound etiologies, as opposed to focusing primarily on diabetic ulcers.

Although HBOT is considered safe at common treatment pressures, there are still risks involved. Complications are categorized as either pressure- or oxygen-related. These include middle ear barotrauma, sinus squeeze, pulmonary barotrauma, seizures, myopia, claustrophobia, and pulmonary-related oxygen toxicity. The most frequent adverse event experienced during treatment is middle ear barotrauma, which is also the most common reason for termination of HOBT. Nevertheless, the majority of complications are benign and treatable. To decrease the risk, it is recommended that patients be evaluated before, during, and after each session. It is also important that operational protocols are set and followed for each session. When these precautions are followed, HBOT is considered a safe treatment modality.\(^7,13\)

CONCLUSION

The effect of HBOT on chronic diabetic lower extremity ulcer healing appears to be more beneficial than standard wound care alone. Based on current studies, adding HBOT to treatment regimens may promote complete chronic wound healing, and at a quicker rate. This response is due to the influence of HBOT on tissue oxygenation and stimulation of the proper wound healing cycle. Ultimately, HBOT may end the persistence of chronic diabetic ulcers, and thus decrease the necessity for amputations and the risk of developing other complications.

Although HBOT has the potential to positively impact chronic diabetic wounds, more research must be conducted in order to make it a common treatment modality. Current
research has demonstrated the beneficial effect of HBOT; however, many of the supporting studies include small sample sizes, numerous chronic wound etiologies, experimentation on animals, various treatment protocols, etc. In order to make a strong recommendation for the use of HBOT in diabetic patients with chronic lower extremity ulcers, more research must be performed on larger numbers of patients with diabetic wounds, and specific treatment protocols need to be established. It is also important to determine the cost effectiveness of HBOT and establish which types of chronic diabetic ulcers will benefit most from the therapy. In conclusion, current therapies for chronic diabetic wounds regularly have poor outcomes; therefore, it is essential to find new treatment regimens. HBOT may prove to be a promising adjunct modality to standard wound care, and if this is the case, it can positively impact the quality of life and mortality rates in diabetic patients.

REFERENCES


