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Research Article

HYPERBARIC OXYGENATION THERAPY AND WOUND HEALING

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ABSTRACT

This report analyzes articles on hyperbaric oxygenation (HBO) therapy to find correlations in its usage towards the treatment of acute and chronic wounds. Conducting a review of the literature will assist in the identification of concepts to address in future HBO investigations as it relates to wound care and recovery. By finding background information relating to the history of HBO use in medical and clinical practice, its effectiveness, treatment standards, and protocols are further evaluated to determine standard oxygen pressures and treatment duration times when utilized in wound healing. Articles that emphasize HBO as a compliment to standard wet and/or dry applications are prioritized in this review. Assessment of HBO administration allows for proper utilization of HBO treatments and findings may indicate HBO's limitations and expose inconsistencies in treatment methodologies necessary to refine and improve its clinical application. By expanding knowledge of HBO effectiveness, its availability will decrease costs because of improved demand. If research continues in this area, HBO therapy is projected to show significant gains in improving the lives of patients suffering from severe burns, cuts, ulcers, etc., and non-healing wounds such as Alzheimer's disease and cancer.

INTRODUCTION

Hyperbaric oxygenation (HBO) therapy is becoming an increasingly popular medical technique that involves applying a high percentage of pure oxygen to patients in an oxygenated chamber or via mask. HBO therapy is believed to provide a more prompt wound healing process as a supplement to current wound care methods, though findings to this effect have been debated due to experimental bias. HBO treatments utilize 100% oxygen at pressures that exceed normal atmospheric pressure (Bhutani S, Vishwanath, 2012), and shows great promise in healing acute and chronic wounds. HBO therapy exhibits significant benefits when used as a therapeutic regimen for healing wounds (such as burns and ulcers) and non-healing wounds (such as diabetes and hypertension). An acute wound is categorized by the degree of soft tissue decomposition present surrounding any part of the body successive to surgery or trauma. Most acute wounds heal without difficulty and occur more frequently than chronic wounds (Eskes *et al*., 2011). A chronic wound, on the other hand, is characterized as an area where the skin remains absent, failing to heal within eight weeks. Chronic wounds usually develop on lower limbs of the body due to complications such as diabetes, venous insufficiency, or inadequate arterial perfusion (Ruttermann *et al*., 2013). Roughly 7 million patients are affected by chronic wounds in the United States, costing an estimated $25 billion annually to treat such wounds (Castilla *et al*., 2012). With more patients experiencing complications due to diabetes and other chronic wounds annually, chronic wound care costs are on a continual rise. Patients with foot ulcers have substantially higher healthcare costs than the average patient, attributing to a cost of approximately $27,987 two years after diagnosis (O'Reilly *et al*., 2011). Additionally, loss of mobility to patients with chronic wounds bear a great burden to the individual and the health care system (Londahl *et al*., 2010). The incidence of foot ulcers is estimated between 1.2-3.0% annually, with a rate of lower extremity amputation (LEA) between 6-23.5% (O'Reilly *et al*., 2011). Additionally, foot ulcers can lead to amputations of the toes, foot, or entire lower limb (Ruttermann *et al*., 2013), leading to even higher healthcare costs to the individual and the healthcare system. HBO treatments are proving successful because oxygen is a vital element in wound care and is involved in various biological processes, including cellular proliferation, angiogenesis, and protein synthesis. These processes are responsible for restoring tissue function and integrity, triggering healing responses that rapidly promote the healing process (Castilla *et al*., 2012). Oxygen is vital for the hydroxylation of lysine and proline residues during collagen synthesis and maturation, which is essential in the wound healing process (Bhutani S, Vishwanath, 2012). HBO pressure

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increases the amount of oxygen being dissolved in blood plasma, having a positive effect on wound healing (O'Reilly *et al*., 2011). Acute and chronic wounds experience hypoxia on a molecular level and the greatest area of tissue hypoxia is at the center of the wound (Castilla *et al*., 2012). HBO has been shown to have antimicrobial effects in wound care, in addition to increasing oxygenation of hypoxic wound tissues (Londahl *et al*.). This makes HBO treatments beneficial in treating infected wounds from diseases like clostridial myonecrosis, Fournier's gangrene, and necrotizing soft tissue infections as well as traumatic wounds, compartment syndrome, crush injury, compromised skin grafts and flaps, and thermal burns (Bhutani S, Vishwanath, 2012). HBO also increases the production of oxygen free radicals that oxidize proteins and membrane lipids, damage DNA and inhibit bacterial metabolic functions and is particularly effective against anaerobes that lack superoxide dismutase, facilitating the oxygen dependent peroxidase system that promotes bacteria killing by leukocytes (Bhutani S, Vishwanath, 2012). For this reason, HBO therapies can improve healing in diabetic patients with ischemic and chronic foot ulcers, as well as other acute and chronic wounds.

HBO in Wound Care

HBO therapy has shown significant improvements in the healing time of non-healing wounds, such as diabetes and ulcers. Non-healing wounds such as these are caused by vascular insufficiency can be improved by through angiogenesis and/orother mechanisms that promote fibroblast proliferation, collagen synthesis, and stimulating vascular endothelial growth factors (Bhutani S, Vishwanath, 2012).

The Food and Drug Administration (FDA) currently approves clinical use of hyperbaric oxygen chambers toward the treatment of the following

- Air or gas embolism
- Carbon monoxide poisoning
- Enhancement of healing in diabetic derived illnesses such as diabetic foot, diabetic retinopathy, and diabetic nephropathy
- Exceptional blood loss (anemia)
- Intracranial abscess
- Clostridal myositis and myonecrosis (gas gangrene)
- Crush injury, compartment syndrome, and other acute traumatic ischemia
- Decompression sickness
- Necrotizing soft tissue infections (NSTIs; necrotizing fasciitis)
- Osteomyelitis (refractory)
- Delayed radiation injury (soft tissue and bony necrosis)
- Skin grafts and flaps (compromised)
- Thermal burns
- Actinomycosis
- Cyanide poisoning

Delayed radiation injury (soft tissue and bony necrosis) (Hyperbaric Centers of Texas, Inc., 2012)

Types of Wound Care Therapies

Various wet and dry treatment options exist for acute and chronic wounds and include wound rinsing solutions, hydrogels, foams, film overlays, microfiber dressings, hydrocolloids, polyacrylates and vacuum therapy. The appropriate treatment selection for a particular wound depends on cost and is determined by the type of application best suited to avoid pain and maceration, provide adequate absorption and retention of the exudate, adheres adequately to the wound site, and is considered practical for the patient (Ruttermann *et al*., 2013). Wound rinsing solutions, hydrogels, and vacuum therapy are standard wound care practices that exhibit remarkable results when used appropriately. Wound rinsing solutions that contain chemical additives, such as polyhexanide, hydrogen peroxide, octenidine, hypochlorite, ethacridine lactate and dye solutions, promote wound healing better than saline solutions. However, if the wound is not infected it is recommended to avoid using aggressive antiseptic substances such as these, for there is no evidence that these substances promote wound healing (RR = 1.06, 95% CI = 0.819-1.375) nor prevents infection (RR = 1.06, 95% CI = 0.87-1.3) (Ruttermann *et al*., 2013). Hydrogels are moderately beneficial in treating diabetic foot ulcers (RR = 1.83, 95% CI = 1.19-2.82), and general wound cleansing techniques that incorporate the use of hydrogel and fly larvae actually promotes a quicker healing time (RR = 1.14, 95% CI = 0.86-1.53); however, it is more painful (Ruttermann *et al*., 2013). Vacuum therapy techniques have demonstrated the ability to reduce wound size (standard mean difference = 0.45, 95% CI = 0.87-0.04), but have shown no significant benefit in accelerating wound healing time (Ruttermann *et al*., 2013).

In an experimental analysis of five trials where 360 patients were administered HBO, oxygen therapy effectively managed acute wounds, including those that had difficulty healing (Eskes *et al*., 2011). HBO operates through four known mechanisms of action to improve acute traumatic ischemia in crush injuries: vasoconstriction, hyperoxygenation, and by influencing reperfusion and host factors (Bhutani S, Vishwanath, 2012). HBO also lessens free radical production by neutrophils, preventing injury due to reperfusion (Bhutani S, Vishwanath, 2012). HBO has the propensity to promote wound recovery in various types of wound injuries. A French study reported more crush wound healing (RR = 1.70, 95% CI = 1.11-2.61) in patients that used HBO in contrast to those who used a sham (Eskes *et al*., 2011). Even skin grafts, which heal successfully for normal patients but are more challenging for patients with compromised circulation, are more successful with HBO. Because hypoxia is the leading cause of failed skin grafts and flaps, HBO treatments improve thesuccess rate two-fold due to the hyperoxic, angiogenic, and antimicrobial actions of HBO (Bhutani S, Vishwanath, 2012). A British study compared HBO therapy to standard wound care practices

of 48 patients, revealing that patients who received HBO therapy had a higher percentage of healthy skin graft area in split skin grafts (RR = 3.50, 95% CI = 1.35-9.11) (Eskes *et al*., 2011). Additionally, fewer surgical procedures were performed amongst patients in this study (RR = 1.60, 95% CI = 1.03-2.50); also, a significantly lower amount of tissue necrosis was observed (RR = 1.70, CI = 95% CI = 1.11-2.61) among patients in these studies (Eskes *et al*., 2011). An American trial where 141 patients with burn wounds were administered HBOshowed that burn wounds healed significantly with routine HBO wound care (P < 0.005) (Eskes *et al*., 2011). HBO therapy has also shown promising results in chronic, non-healing ulcers of the foot in diabetes mellitus patients. In a randomized, double- blind study where 118 patients received HBO treatments or a placebo, HBO promoted more wound healing than the control (O'Reilly *et al*., 2011). HBO treatments prove effective in treating patients with diabetic ulcers in a whole-body pressure chamber (RR = 2.14, 95% CI = 1.18-3.88), where other wound care practices did not bring about total healing (Ruttermann *et al*., 2013). HBO treatments also cause a reduction in major amputation rates (RR = 0.31, 95% CI = 0.13-0.31) ((Ruttermann *et al*., 2013)), proving to be an effective supplemental treatment option in patients with diabetic foot syndromes.

Studies have also revealed that HBO treatments are more effective than standard wound care therapies alone, and should be utilized in addition to standard therapies to improve wound recovery outcomes of patients. A prospective, double-blind, randomized, controlled clinical trial is currently being conducted by the Programs for Assessment of Technology in Health (PATH) Research to determine the effectiveness of HBO therapy in treating chronic ulcers of the lower limb in patients with diabetes mellitus. In this study, 118 patients with Wagner grade lesions 2, 3, or 4 of the lower limb that neglected to heal after at least 4 weeks are being subjected to HBO therapy to determine if the patients will meet the criteria for a major (below knee amputation, or metatarsal level amputation) amputation 12 weeks after treatment initiation (O'Reilly *et al*., 2011). Qualifying patients were randomized into experimental and placebo groups using a computerized block randomization schedule. Researchers and patients are also blinded in this study, where the technician is the only unblinded individual in the study (O'Reilly *et al*., 2011). All patients received standard wound care dressings (e.g. silver, simple gauze, alginate, collagen/ oxidized cellulose) at least twice per week as applicable, depending on whether or not the patients had wet or dry wounds (O'Reilly *et al*., 2011). Patients randomized into the experimental group received 90 minutes of HBO at 2.4 ATA, while patients randomized into the placebo group received 90 minutes of compressed air at an atmospheric pressure equivalent to 10 feet, or 0.3 ATA (O'Reilly *et al*., 2011). The treatments are scheduled five days a week for six weeks, allowing patients to receive a total of approximately thirty treatments before entering the "follow-up" stage, where amputation eligibility is determined (O'Reilly *et al*., 2011). The results of this study have the capacity to make physicians reconsider their treatment diagnosis for patients over 18 years of age with Type 1 or 2 diabetes. Clinical evidence suggests that HBO therapy initiates repair mechanisms which promote wound healing. A study of six chronic wound patients who showed improvements after 20 treatments of 2.0 ATAs of HBO for 90 minutes demonstrated that nitrogen oxide concentrations within the fluid of wounds increases after 4 weeks of therapy (Boykin and Baylis, 2007). This suggests that HBO stimulates tissue formation by an unknown mechanism that involves high nitric oxide levels. More research in this area will provide insight into thespecifics HBO effectiveness.

MATERIALS AND METHODS

Manuscripts included in this publication were selected from PubMed database, using combinations of keywords HBO, hyperbaric oxygen therapy, and wound care. Primary articles selected in this review were published within the last ten years and provide information relating to HBO treatments, specifically as they relate to wound care and recovery. Secondary selections were made from online medical dictionaries and health insurance reports, but also include interviews with an HBO technician and facility director from the Mississippi Gulf Coast. Because studies show varying experimental designs and statistically testing, this review simply presents that data from relevant publications so as to easily make comparisons in treatment options. Priority was given to publications that performed data analysis of HBO effectiveness and/or explored experimental applications and outcomes of patients who received HBO treatment(s) for healing and non-healing wounds.

RESULTS AND DISCUSSION

HBO methods are understood to be completely non-invasive; however, this misconception may prove untrue if the degree of wound trauma is extreme. Wounds that have experienced trauma may be subject to cleaning, probing and/or surgical procedures that allow for the alleviation of debris prior to HBO application. Following non-invasive and invasive wound evaluations that may require additional surgical procedures to restore all or some functionality, the wound is assessed for oxygen concentration (Zamboni *et al*., 2003). Transcutaneous oxygen measurement (TCOM level) is a diagnostic technique that records the partial pressure of oxygen at the skin's surface, providing information regarding the supply and delivery of oxygen to the wound site (Rich, 2001). This allows physicians to perform wound evaluations to determine whether to administer hyperbaric oxygen treatments or to seek plastic surgery, amputation, or to perform other peripheral vascular disease assessments (AvMed, 2014). Following pre-observational testing, most HBO treatments are administered to patients at 2 or 3 atmospheres absolute (ATA) for an average period of 60-90 minutes of therapy. Depending on the type of wound, the number of therapy treatments vary from 3 to 5 treatments for acute conditions and 50 to 60 treatments for radiation illnesses (Bhutani S, Vishwanath, 2012). Treatment sessions for patients with chronic foot ulcers are typically conducted in multi-place hyperbaric chambers five days per week for eight weeks, for up to forty treatment sessions. Each session includes a 5 minute period of air compression, followed by an 85 minute treatment period of pure oxygen at 2.5 ATA, ending with a 5 minute decompression period (Londahl *et al*., ?). Standardized wound care for foot ulcers in diabetes patients requires maintaining optimal blood glucose levels; antibacterial, debridement and dressing usage; antibiotic management to control infections; proper nutrition; pressure relief in areas subjected to excessive weight; and, sometimes, amputation (O'Reilly *et al*., 2011). This rigorous process

produces unfavorable outcomes for many patients whom do not have access to the financial resources nor personnel necessary to monitor and achieve adequate wound healing results. In a randomized, double-blind study of patients with foot ulcers due to diabetes mellitus, HBO therapy exhibited significant improvements after daily treatments for 90 minutes at 2.4 ATA for a period of 6 weeks, totaling 30 treatments. Patients randomized to the placebo group received 0.3 ATA of compressed air (O'Reilly *et al*., 2011). In another study to determine if long-term HBO therapy improved experimental traumatic brain injury in rats, HBO was administered between 2.2-2.5 ATA of oxygen for treatment periods of 1 hour (Kraitsy Klaus *et al*., 2014). HBO treated rats showed significantly better improvements than the sham group $\{F(1,24) = 7.00, p < 0.05\}$, where brain trauma regressed after three weeks of consistent HBO treatments (O'Reilly *et al*., 2011). Overall, HBO treatments appear to be administered more effectively at range between 2.2 – 2.5 ATAs.

HBO Treatments and Cancer

HBO treatments also show possible applications in treating different forms of cancer. Solid tumors have areas that are subjected to acute and chronic hypoxia, and hypoxia is a critical trademark of tumors that involves improved cell survival, angiogenesis, metastasis, and glycolytic metabolism (Moen and Stuhr, 2012). Hypoxia was once thought to reduce the ability of cancerous cells to survive, but it has been proven to cause further cancer progression (Moen and Stuhr, 2012). Now, hypoxia is known to induce cellular processes that enhance oxygenation and survival through angiogenesis, increasing genetic instability, preserving an undifferentiated state of cells, and initiating invasive growth (Moen and Stuhr, 2012). Research shows that HBO treatments block and reduce cancer cell growth in some cancer types, like breast cancer, but are unresponsive in cervical and bladder cancer (Moen and Stuhr, 2012). HBO treatments can be used to overcome hypoxia in treating some forms of cancer, though further research is necessary to discern significant improvements in treating all cancer types and subtypes, including breast, cervical, and bladder cancer. A study conducted by the Department of Otolaryngology at Sunnybrook Health Sciences Centre in Toronto, Canada on fourteen patients who developed an irradiated bone disease due to chemotherapy for head and neck cancer, called osteoradionecrosis (ORN), was performed to determine the effectiveness of HBO treatments as an adjunct to surgical debridement. However, HBO did not improve patient outcome; in fact, most stage 2 and stage 3 patients had to receive mandible surgery (Gevorgyan *et al*., 2013). Remarkably, twenty-six (26) month follow-ups revealed that all patients were cancer free and 84% of patients no longer had ORN (Gevorgyan *et al*., 2013).

Complications and Limitations

The most common side effect of HBO is barotrauma, which is an injury of the middle ear caused by an inability to equalize pressure during treatment (Bhutani S, Vishwanath, 2012). Other complications could also arise, such as acute central nervous system toxicity (known as Paul Bert effect) due to continued exposure to high oxygen pressures and leading to seizures, and continued exposure to low oxygen pressures could cause pulmonary oxygen toxicity (known as Loraine Smith effect) in patients being treated for wound care (Bhutani S, Vishwanath, 2012). Pulmonary barotrauma could also occur, due to cavity or fibrotic lesions in the lung parenchyma (Bhutani S, Vishwanath, 2012). To decrease the chance of developing these side-effects, patients are given breaks lasting about a week in between HBO treatments (Bhutani S, Vishwanath, 2012). A cohort study that analyzed the effects of HBO on 6,259 individuals with diabetes, adequate lower limb arterial perfusion, and foot ulcer reveals that HBO is ineffective in treating diabetic foot ulcers and preventing amputation in patients who are less likely to have a healing foot ulcer (hazard ratio, 0.68; 95% CI: 0.63-0.73) and whom are more likely to have an amputation (2.37; 1.84-3.04) (Margolis *et al*., 2013). This suggests that HBO treatments may be an ineffective therapy choice for diabetes patients suffering from foot ulcers who are at a high risk of amputation.

Conclusion

In conclusion, there are many positive outcomes when utilizing hyperbaric oxygen therapy to treat acute and chronic wounds in patients. HBO has proved useful in treating wounds varying from foot ulcers in diabetic patients to infected lesions that require skin grafts and/or amputation. Transcutaneous oximetry ($TcPO_2$) measures the wound oxygenation, allowing physicians to achieve a high oxygen gradient in order to initiate wound healing (Zamboni *et al*., 2003; Kaur *et al*., 2012). Currently, a standard method of treatment is being used that has fewer side effects that medicinal treatments alone; additionally, HBO treatments are successful as a complimentary treatment to other forms of wound care that are proving unsuccessful alone. Yet, more experimental and clinical studies are required to find a standard administration method that takes the patients' size into account to reduce side effects. More studies are also necessary to provide consistent evidence of HBO efficacy in treating all wound types and other possible applications such as its use to treat cancer and autism (Ghanizadeh, 2012). As future considerations of HBO are considered in all field of medicine, hyperbaric oxygen is projected to become the standard of wound and complimentary care therapy, used by every field of medicine world-wide.

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