Hyperbaric oxygenation (HBO) has been considered a controversial treatment in the mainstream medical community. The use of HBO has been tainted throughout its history by unsubstantiated claims that ranged from healing diabetes to being a cure for baldness. However, the last half of the 20th century saw an ever-increasing positive examination of the use of HBO in a variety of disease conditions that continues today. In addition, organizations such as the Undersea and Hyperbaric Medical Society routinely evaluate findings and make recommendations for the appropriate use of HBO.1

On August 30, 2002, the Centers for Medicare and Medicaid Services posted approval for reimbursement for the adjunctive use of HBO in the treatment of ulcers in patients with diabetes.2 This article will focus on HBO as an adjunct therapy in treating these problem wounds. The intent of this article is to provide a review of literature related to hyperbarics and wound healing with emphasis on wounds in patients with diabetes. The article will focus on wound healing failure related to hypoxia, the rationale for the use of HBO, patient selection, treatment protocols, the hyperbaric experience, potential complications related to hyperbaric treatment, and criteria for termination of hyperbaric treatment.

In brief, HBO therapy is the administration of 100% oxygen at greater than one atmosphere pressure absolute (ATA). This is only achieved in an environment of elevated atmospheric pressure. Topical application of oxygen to a wound site is not HBO. An assessment done for the Agency for Healthcare Research and Quality was unable to draw conclusions from reported research on topical application of oxygen, stating that this method of oxygen administration lacks basic and clinical research to support beneficial effects of topical oxygen in wound healing.3

HBO therapy is administered intermittently, usually once a day, to treat a variety of conditions. The Undersea and Hyperbaric Medical Society currently approves the treatment of 13 indications for HBO (Box 1). The benefits of HBO can be classified into 4 categories: mechanical effects, bacteriostatic effects, treatment of poisoning, and treatment of hypoxia. Mechanical effects are used to reduce air bubble size in situations of air or gas embolism or decompression sickness. Bacteriostatic effects are used to treat necrotizing infections and osteomyelitis. Bacteriostatic effects are used to treat necrotizing infections and osteomyelitis.
Treatment of poisoning is generally for carbon monoxide or cyanide poisoning by enhancing the displacement of carbon monoxide from hemoglobin and enhancing tissue oxygenation. Because of enhanced tissue oxygenation, hyperbaric treatment of hypoxia enhances healing in select problem wounds such as those resulting from delayed radiation injuries or compromised skin grafts and flaps.

**OXYGEN AND WOUND HEALING**

A review of the effects of oxygen and hypoxia will provide a framework to assist with the explanation of the use of HBO in the treatment of problem wounds. Oxygen tensions of less than 3 mmHg were reported in wounds more than 30 years ago. Oxygen tension in the periwound area is typically around 20 mmHg. Wound hypoxia is necessary for leukocyte adherence, neovascularization, collagen formation, and bone formation; however, chronic wound hypoxia blunts polymorphonuclear and antibacterial activity, cellular energy metabolism, collagen synthesis, and neovascularization.

The role of oxygen in wound healing is multifaceted. Disruption of microcirculation is the initial event leading to wound hypoxia. This hypoxia remains in chronic wound conditions. Cellular energy metabolism is dependent on oxygen, specifically the production of adenosine triphosphate (ATP). Whereas cellular energy metabolism can exist in an anaerobic state, hypoxia leads to acidosis. Anaerobic metabolism requires increased utilization of glucose to provide the same level of energy as ATP. The result is inadequate ATP to maintain cellular function in the wound.

Platelets exposed to fibrin release cytokines that serve as chemotactants, recruiting fibroblasts and macrophages to the wounded area. Oxygen consumption is increased as leukocytes migrate to the wounded area, adding to the already hypoxic state of the wound. An oxygen environment of 40 mmHg is needed to sustain fibroblast activity that leads to collagen deposition in a healing wound. Collagen synthesis is dependent on proline and lysine, which hydroxylate oxygen to produce collagen.

The ability of macrophages to phagocytize bacteria is greatly reduced in hypoxic tissue because hypoxic tissue decreases the oxidative killing of bacteria by the macrophages. Macrophages also produce cytokines that promote angiogenesis, specifically vascular endothelial growth factor. Epithelial growth factor is also oxygen dependent with decreased epithelialization in a hypoxic environment.

**HYPERBARIC OXYGEN EFFECTS ON WOUND HEALING**

HBO of local tissue has several beneficial effects on hypoxic wound healing. Edema in the periwound area is decreased through the vasoconstrictive action of oxygen, and the leukocyte-killing ability of bacteria and phagocytosis of bacteria is enhanced with the increased oxygen tensions. It is well documented that bacterial activity can cause significant oxygen consumption in a wound. HBO increases tissue oxygenation in infected wounds. It also acts synergistically with a variety of antibiotics, particularly the aminoglycosides, to increase their effectiveness. HBO improves collagen production in areas of hypoxia by increasing local diffusion of oxygen to the hypoxic wound, raising the partial pressure of oxygen in arterial blood of 40 mmHg or higher to allow normal collagen synthesis. Improving the oxygen gradient across the wound space promotes neangiogenesis. Epithelial migration is enhanced with adequate wound oxygenation, thus re-epithelialization is oxygen mediated. Finally, evidence from animal models suggests that HBO may improve platelet-derived growth factor uptake, thus enhancing granulation tissue formation. The evidence supporting the beneficial physiologic effects of HBO is encouraging (Box 2).

**HYPERBARICS AND DIABETIC WOUND HEALING RESEARCH**

Several studies and technical assessments have assessed the role of HBO in the treatment of ulcers in patients with diabetes. Abidia and colleagues reported results of wound healing from a double-blind randomized trial. Eighteen patients with ischemic, nonhealing lower extremity ulcers were randomly assigned to receive HBO or placebo. Thirteen of 19 ulcers in the group treated with HBO healed, compared with only 4 of 14 in the non-HBO treatment group (P = .024). A mean decrease in wound area was 83% for the treatment group versus 56% for the control (P = .021). No differences in major amputation rates were found. The authors concluded that HBO facilitated healing of the diabetic ulcer and that it was a valuable adjunctive therapy in persons when reconstructive surgery was not feasible.

The effect of HBO on chronic nonhealing wounds in patients with insulin-dependent diabetes also has been examined in a nonrandomized, blinded, and controlled prospective study with a sample size of 10. The control group consisted of 5 patients who were either claustrophobic or lived too far from the treatment facility. All patients received standard wound care consisting of debridement, application of topical silver sulfadiazine twice daily for 5 days, and application of moist saline solution dressings changed twice daily. Antibiotics were administered in patients with infection. Planimetry measures were obtained and wound surface area measurements were compared with the baseline measurement. Patients treated with HBO showed significantly greater reductions in wound size throughout the 7 days.
weeks of the study ($P < .05$). All patients were monitored for up to 6 months following the completion of the study. Four of 5 (80%) of the control group continued to have nonhealing wounds, whereas 4 of 5 (80%) of the treatment group had spontaneous healing of their wounds. No subject in either group underwent an amputation. Although the sample size was too small to allow generalization of the results, the study suggests that adjunctive HBO may reduce wound size and may be efficacious in the healing of chronic foot wounds in persons with diabetes.16

In an unblinded, randomized, and controlled trial, Faglia and co-workers17 compared HBO with a comprehensive protocol for decreasing major amputations in diabetic patients with severe foot ulcers. The experimental group consisted of 35 subjects and the control group consisted of 33 subjects. Both groups received a diagnostic and therapeutic protocol that included glycemic control, wound care, debridement, antibiotic therapy, angioplasty or bypass graft, and off-loading. In addition, the experimental group received a protocol of HBO. The authors found that 11 subjects (33.3%) in the non-HBO group versus 3 subjects (8.6%) in the HBO group underwent a major amputation ($P = .016$). The relative risk for the treatment group was 0.26 (CI 0.08 to 0.84). Thirty-two limbs were salvaged in the HBO group versus 22 in the non-HBO group ($P = .016$). HBO appeared to have a protective role against amputation (OR 0.084, $P = .033$, 95% CI 0.008 to 0.821) when compared with prognostic indicators for amputation of a low ankle brachial index (OR 1.715, $P = .013$, 95% CI 1.121 to 2.626) and a high Wagner classification grade (OR 11.199, $P = .022$, 95% CI 1.406 to 89.146). The authors concluded that hyperbaric oxygenation in addition to aggressive, multidisciplinary therapy was effective in decreasing major amputations.17

The efficacy of HBO in problem wounds was assessed in a retrospective review of 54 patients, including 17 with diabetic ulcers, 8 with arterial insufficiency ulcers, 13 with dehisced amputation stumps, 6 with gangrenous toes, and 10 with nonhealing operative wounds.18 HBO was administered according to an established protocol at 2.0 ATA for 90 minutes, twice daily. All wound types were grouped together for treatment outcome. Forty-three (80%) showed no improvement, 6 (11%) demonstrated some improvement, 5 (9%) had inconclusive results, and none had complete healing. This case series concluded that it is difficult to justify an ineffective, expensive, and complication-prone treatment for problem lower extremity wounds; however, other studies refute these findings.18

In another nonblinded, randomized controlled trial, 30 diabetic patients who had a foot lesion an average of 10 years were randomized to treatment group (n = 15) or control group (n = 15). The purpose of the study was to evaluate the effect of HBO in treating foot lesions in patients with diabetes and HBO’s use as an adjunctive treatment. Both groups received standard wound care that included surgical debridement, incision and drainage, topical dressing care, and administration of antibiotics and insulin. The treatment group also received 4 sessions of oxygen breathing at 3 ATA for 45 minutes during a 2-week period. The study found a relative risk reduction for major amputation of 72% (95% CI 6% to 100%), an absolute risk reduction of 0.334 (95% CI 0.029 to 0.639), and the number needed to treat to realize this reduction of 3 (2 to 35). The authors concluded that there was a significantly reduced rate of major amputation in subjects who received HBO.19

Baroni and colleagues20 studied strict metabolic control, daily debridement, and daily HBO in 28 hospitalized patients presenting with gangrenous lesions of the foot in a nonrandomized, nonblinded, controlled study. Patients were divided into 2 groups: group 1 (n = 18) was treated with HBO, metabolic control, and daily debridement; group 2 (n = 10) received the same standard treatment but no HBO. In group 1 (HBO), 16 of the 18 wounds healed, and 2 required an amputation; in group 2 (no HBO), only 1 patient healed, 4 required amputation, and 5 remained unchanged ($P = .001$). This study provides further support that the number of leg amputations may be decreased in patients who receive HBO treatment.20

TECHNICAL ASSESSMENTS

Technical assessments also have addressed the efficacy of HBO in the treatment of diabetic ulcers. Technical assessments are a methodology used to assess the clinical suitability of a medical intervention based on a systematic review of the literature. Qualitative and quantitative syntheses of data from multiple studies are used to reach a conclusion regarding an intervention’s clinical utility.21 The Blue Cross Blue Shield technical assessment reviewed a variety of treatment indications for HBO. This assessment concluded that adequate evidence exists to support the use of adjunctive HBO in the treatment of adequately perfused nonhealing wounds of the lower extremities with a program of standard wound care. In addition, this report concluded that patients with chronic, refractory wounds that are treated with HBO have fewer amputations and better rates of healing than do patients not treated with hyperbaric therapy.21

The Medical Services Advisory Committee technical assessment completed in Australia also found that diabetic persons with ulcers were less likely to undergo amputation if they were treated with HBO.22 It concluded that evidence exists to support the belief that HBO improves rates of healing in diabetic patients with ulcers and decreases hospital length of stay.

OTHER REPORTS RELATED TO HYPERBARICS AND WOUND HEALING

A Rapid Response Report done through the Agency for Healthcare Research and Quality Evidence-based Practice Center program summarized information from key studies.3 This report addressed the use of HBO as an adjunctive therapy to standard wound care. The report concluded that sufficient evidence exists on the benefits of HBO for compromised skin grafts, osteoradionecrosis, gas gangrene, progressive necrotizing infections, and chronic nonhealing wounds.

A consensus statement published by the American Diabetes Association in 1999 stated that there was insufficient evidence from randomized controlled trials to support the use of HBO as an adjunct for diabetic wounds.23 This report does not include the randomized, controlled trial done by Faglia and colleagues in 1996.17 nor does the consensus statement identify the articles that were reviewed.
PATIENT SELECTION FOR HBO TREATMENT OF DIABETIC WOUNDS

According to the Centers for Medicare and Medicaid Services guidelines, to qualify for HBO therapy, a patient must have diabetes mellitus and a wound of the lower extremity resulting from diabetes, Wagner grade III or higher, which has not responded to standard wound care treatment. Standard wound care is defined as assessment of vascular status with the correction of vascular problems; maximization of nutritional status and optimization of glycemic control; debridement of nonvital tissue and maintenance of moist wound healing with the use of topical dressings; appropriate off-loading of the wound; and, finally, resolving the infection. Failed standard treatment is defined as no measurable signs of wound healing for at least 30 days following standard wound care evidenced by no decrease in wound size as measured by surface area or volume, no decrease in the amount of exudates, and no decrease in the amount of necrotic tissue.2

In addition to criteria for reimbursement, other consideration in patient selection should include transcutaneous oximetry. Transcutaneous oxygen measures (TCOM) are quantitative measures of oxygen availability to tissue.24 A demonstration of periwound hypoxia with a baseline TCOM measurements of <40 mmHg that rise to >100 mmHg while breathing 100% oxygen at 1 ATA is an indication for adjunctive HBO.25 There also should be a demonstration of therapeutic transcutaneous oxygen values during HBO treatments. A therapeutic value of 200 mmHg or greater in nondiabetic patients and 400 mmHg in diabetic patients is the minimum value necessary to predict a successful outcome.26 A minimum of 200 mmHg has been found to be 74% reliable in predicting success with HBO.27 A TCOM of <15 mmHg with an in-chamber TCOM of <400 mmHg was found to be predictive of failure of HBO in lower extremity ulcers in diabetic patients.27

CONTRAINDICATIONS

Absolute contraindications to HBO include untreated pneumothorax and use of doxorubicin, bleomycin, disulfiram, cis-Platinum, and mafenide acetate. Untreated pneumothorax can lead to a tension pneumothorax during the decompression phase of the hyperbaric treatment. Concomitant use of chemotherapy with HBO has major associated morbidity: the mortality rate in rats is 87% with doxorubicin and HBO;28 pulmonary oxygen toxicity is increased with bleomycin;28 oxygen toxicity is increased with disulfiram;28 toxicity of cis-Platinum is increased;28 and CO2 buildup occurs with subsequent vasodilation with mafenide acetate and HBO.28 Other relative contraindications include known malignancies, pregnancy, implanted pacemakers, upper respiratory infections, chronic sinusitis, seizure disorders, emphysema, hyperthermia, history of thoracic surgery, pneumothorax, optic neuritis or otosclerosis, viral infections, and congenital spherocytosis.28

PROVIDERS OF HBO

Only trained professionals should perform hyperbaric procedures. Physicians should be in attendance during critical phases of the treatment, namely pressurization and depressurization of the chamber. Chamber operators should receive training not only in chamber operation but also in the theory and application of gas laws, chamber safety, and patient assessment particular to the hyperbaric environment. Physicians can receive board certification in hyperbaric medicine through the American Board of Preventive Medicine. Nurses can receive certification in hyperbaric nursing through the Baromedical Nurses Certification Board, and non-nurses can receive certification as hyperbaric technicians through the National Board of Hyperbaric and Medical Technology.

TREATMENT PROTOCOLS

HBO for the treatment of ulcers in diabetic patients is accomplished with daily treatments at 2 to 2.4 ATA for 90 to 120 minutes.29 This protocol can be changed with the addition of scheduled interruptions in oxygen breathing, known as air breaks. One air break for 5 minutes after 45 minutes of oxygen breathing or two 5-minute air breaks after each 30-minute oxygen breathing period will reduce the risk of oxygen toxicity.

THE PROCEDURE

HBO is only accomplished when the patient’s entire body is placed into an environment that increases barometric pressure while the patient is breathing 100% oxygen. Two chamber types allow this to happen: the multiplace chamber and the monoplace chamber. Multiplace chambers are typically compressed with air while the patient breathes 100% oxygen through a hood. Multiplace chambers allow multiple patients to be treated at a time and allow a nurse attendant to be in the increased barometric environment with the patient(s) to provide care. Multiplace chambers can treat from 1 to more than 12 patients during a single “dive” or compression of the chamber to the desired increase in atmospheric pressure for therapeutic benefit.29 While costly, these chambers are more readily equipped and appropriate for the treatment of critically ill patients; however, there is increased risk to the nurse attendant for decompression illness related to breathing compressed air. The physiologic effect of breathing compressed air at pressure presents the same risk as the person breathing compressed air during recreational SCUBA diving. Risk to the attendant is minimized by strict adherence to diving protocols that would allow for periods of decompression should the attendant exceed restrictions of nitrogen gas uptake due to the time spent breathing compressed air in an increased barometric environment. The major advantage of using a multiplace chamber is the ability to treat multiple patients during a single dive. Multiplace chambers also allow ease of administering an “air break” or an interruption of oxygen breathing during the treatment to prevent complications of oxygen toxicity.

More commonly, patients are treated in a monoplace, or single occupancy, chamber, which allows for appropriate treatment depths and use of 100% oxygen to compress the chamber. Interruptions of oxygen breathing are accomplished during a monoplace treatment by having the patient breath compressed air by mask during the treatment. This process can be problematic if the patient is unable to place the mask because of cognitive or physical disability. Alterations in treatment protocols may be made to lessen the risk for oxygen toxicity. Because of the 100% oxygen environment, rigorous preparation of the patient and
thorough screening for certain products is an absolute requirement for fire safety during the treatment. These preparations include wearing only 100% cotton fabrics or fabrics that have no spark potential and avoidance of all petroleum-based and alcohol-based products (eg, hair spray, cosmetics, and Vaseline) because vapor from these products can be spontaneously combustible in an increased atmospheric environment of 100% oxygen. Consideration also must be given to the selection of topical wound products. Topical wound and skin care products with a petrolatum base should not be used on a person undergoing HBO therapy.

Once the patient is prepared for the treatment, the chamber is compressed to the treatment depth. During this period of compression, the patient will experience pressure changes in closed air spaces in the body, most noticeably in the ears. The patient must be able to equalize these pressure changes to prevent middle ear barotraumas that may cause hemorrhage to the tympanic membrane or rupture of the eardrum. Yawning, swallowing, or a modified Valsalva maneuver can usually accomplish pressure equalization. Patients who are unable to equalize pressure may require myringotomy or placement of pressure equalization tubes.30

The other effect of compression is a sensation of warmth. As the pressure increases, temperature increases (Gay-Lussacs law). This sensation is minor and transient and can be overcome by decreasing the rate of compression of the hyperbaric chamber. The opposite occurs when pressure is reduced at the completion of the treatment, and some patients may complain of the chamber environment becoming cold.30

ADVERSE EFFECTS

The 2 most common adverse effects, which occur in less than 1% of all patients treated in a hyperbaric chamber, are middle ear barotrauma and confinement anxiety. Barotrauma can occur in any closed air space. Boyle’s Law states that as pressure increases, volume decreases. The inability to equalize pressures in sinus cavities because of allergies or sinusitis can lead to sinus barotrauma. Strict observation of the patient during compression minimizes the risk of barotrauma. During compression, patient complaints of ear pain or sinus pain signals the chamber operator of potential barotrauma, and the dive can be aborted to prevent injury. Although rare, pulmonary barotrauma as a result of air trapping also can occur. This is particularly important during the decompression phase of the dive. Pulmonary barotrauma can present as a life-threatening tension pneumothorax and must be treated as a medical emergency.30

Confinement anxiety is another complication of hyperbaric therapy. Claustrophobia can be minimized through adequate orientation to the process. In addition, attendance and reassurance by the nurse during the treatment will help to minimize anxiety. Select patients may require anxiolytic therapy with benzodiazepines. In some instances, treatment may be continued when interventions to relieve severe confinement anxiety fail.30

Hypoglycemia is another complication of HBO. Although the mechanism behind this phenomenon is not completely understood, it appears that persons with insulin dependency are at higher risk for episodes of hypoglycemia during periods of increased barometric pressure and 100% oxygen breathing. Hypoglycemia can be significant and can precipitate disorientation, loss of consciousness, and seizures. This complication is preventable and can easily be managed by appropriate pretreatment monitoring of blood sugars and appropriate administration of nutrients during treatment to maintain blood glucose levels. Consideration also must be given to the timing of insulin doses in relation to the hyperbaric treatment so that peak insulin activity does not occur while the patient is receiving hyperbaric therapy.30

Oxygen toxicity, a rare complication of hyperbaric therapy, is most dramatic when it presents as a generalized seizure. Signs and symptoms to observe for the development of central nervous system oxygen toxicity include twitching, auditory hallucinations, disorientation, and grand mal seizure activity. Central nervous system oxygen toxicity is self-limiting and is treated by stopping 100% oxygen breathing. Risk of future occurrences of oxygen toxicity are minimized by providing scheduled interruptions in oxygen breathing during the treatment. Pulmonary oxygen toxicity is a cumulative oxygen dose-dependent phenomenon and can be limited by monitoring the total oxygen consumption during both hyperbaric treatment and oxygen consumption in nonhyperbaric environments.30

Overall, complications of HBO are rare, and most can be avoided or treated without any ill effect to the patient. HBO is a safe procedure, and attempts should be made to avoid or lessen complications so that the beneficial effects can be achieved.

TERMINATION OF HBO AS AN ADJUNCTIVE TREATMENT

HBO therapy should be stopped if there is no measurable improvement in the wound following 30 days of standard wound care and adjunctive HBO.2 HBO should continue until a transcutaneous oxygen pressure measure of 40 mmHg is reached, indicating neoangiogenesis.27 The patient should be reevaluated for other reasons of wound healing failure if healing is not demonstrated following 20 to 40 treatments.

KEY POINTS

- Research suggests that hyperbaric oxygenation is beneficial as an adjunct treatment for wounds in diabetic patients.
- Research suggests that hyperbaric oxygenation may play a role in decreasing amputations in diabetic persons with wounds.
- The Centers for Medicare and Medicaid Services have recently approved reimbursement for hyperbaric oxygenation as an adjunctive treatment in select wounds in patients with diabetes.
- Hyperbaric oxygenation is a relatively safe procedure with rare serious complications.
- Hyperbaric oxygenation should not preclude traditional wound care strategies but rather should be used to enhance those strategies.
CONCLUSION

HBO is an adjunct to standard wound care. It is not a panacea, and rigorous patient selection should be followed to optimize wound healing. In the studies reviewed for this manuscript, the evidence suggests that HBO is of benefit to diabetic persons with ulcers. These studies represent small heterogeneous samples and range from retrospective to nonrandomized designs to randomized, controlled clinical trials. Despite the design concerns, HBO appears to have benefit in the treatment of ulcers in diabetic patients, and may help to avoid the trauma of amputation. Amputation as an end point of wound nonhealing is particularly debilitating and can end careers and restrict social life and independence that mobility affords. It is of note that the 3-year survival rate following a major amputation is 50%, with the 5-year survival rate being only 40%. Thus, the use of HBO could definitely be considered in those persons who meet the criteria for treatment to not only heal wounds and prevent amputation but to maintain and improve the quality of life.

The use of HBO should not preclude other treatment methodologies, including vascular interventions, metabolic control, off-loading techniques, and scrupulous ulcer care. The challenge remains with the health care professionals who are using hyperbaric therapy to report outcomes based on this adjunct therapy in diabetic persons with ulcers. The systematic reporting of HBO outcomes will not only further support the efficacy of this treatment but will provide evidence that its use in conjunction with other treatment modalities improves outcomes.

REFERENCES


