Does Hyperbaric Oxygen Therapy Work in Facilitating Acute Wound Healing: A Systematic Review

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Background: Adjunctive hyperbaric oxygen therapy is a safe and effective modality with which to increase tissue oxygenation and aid in healing of difficult wounds. The majority of the literature surrounding hyperbaric oxygen therapy supports its use in chronic wounds, but its use in acute wounds, flaps, and grafts is less well supported.
Methods: The authors reviewed the Ovid, PubMed, and Cochrane Library databases, and selected studies, level III and above, using hyperbaric oxygen therapy in the treatment of complicated acute wounds, flaps, and grafts.
Results: A total of eight studies were found to meet criteria for evaluation of adjunctive hyperbaric oxygen therapy in the treatment of complicated acute wounds, flaps, and grafts.
Conclusions: When combined with standard wound management principles, hyperbaric oxygen therapy can augment healing in complicated acute wounds. However, it is not indicated in normal wound management. Further investigation is required before it can be recommended as a mainstay in adjuvant wound therapy. (*Plast. Reconstr. Surg.* 133: 208e, 2014.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

The first description of altering atmospheric pressure to treat medical illness was in 1662, when Henshaw, a British clergyman, constructed a sealed chamber called the "Domicilium," in which changes in ambient pressure were driven by valved organ bellows. Despite lack of scientific support, he believed that hyperbaric conditions accelerated healing in acute conditions and that hypobaric conditions accelerated healing in chronic conditions. Henshaw did not use isolated oxygen therapy in his early experiments, as it had yet to be discovered.[1]

In 1772, elemental oxygen was isolated by a Swedish chemist, Carl Scheele, and an English cleric, Joseph Priestley. Over a century later, with an understanding of the physical properties of ideal gases provided by the work of Robert Boyle in the 1660s, elemental oxygen was combined with the barometric chamber to provide hyperbaric oxygen therapy to deep sea divers suffering from decompression illness.

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Modern clinical use of hyperbaric oxygen therapy began in 1955 when Churchill Davis treated cancer patients with hyperbaric oxygen therapy to potentiate the effects of radiation therapy. The introduction of hyperbaric oxygen therapy to the surgical patient occurred in 1956, when Ite Boerema, a cardiovascular surgeon and professor of surgery in Amsterdam, found that operating in a pressurized chamber allowed longer cross-clamping of vessels and more advanced cardiac repairs.[2]

Over the past 50 years, hyperbaric oxygen therapy has been applied broadly to a myriad of illnesses and medical conditions, with little scientific evidence supporting treatment. In 1976, the Undersea and Hyperbaric Medical Society developed a list of conditions for which hyperbaric oxygen therapy is indicated. This list is updated every 2 years to include new indications (Table 1).[3]

Hyperbaric oxygen therapy was first described for use in plastic surgery in 1966, when McFarlane and Wermuth described it for composite graft

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Table 1. 2012 Undersea and Hyperbaric Medical Society Indications for Hyperbaric Oxygen Therapy

Air or gas embolism
Carbon monoxide with and without cyanide poisoning
Central retinal artery occlusion
Clostridial myonecrosis
Crush injury
Decompression sickness
Enhancement of healing in selected problem wounds
Severe anemia
Intracranial abscess
Necrotizing soft-tissue infections
Osteomyelitis (refractory)
Delayed radiation injury
Compromised grafts and flaps
Acute thermal burn injury
Idiopathic sudden sensorineural hearing loss

salvage in a rat model.[4] Since then, use of hyperbaric oxygen therapy has been explored for a multitude of surgical indications that are relevant to the modern plastic surgeon. Its use in chronic and acute wounds of various causes has been shown to be beneficial by multiple level I studies, and in 2006 Friedman et al. provided a thorough evidence-based appraisal of the use of hyperbaric oxygen therapy with flaps and grafts.[5] Its use in cosmetic surgery has been evaluated using photometric analysis to reduce postoperative ecchymosis in face-lift patients requiring quicker return-to-work times.[6] It has also been described for use to accelerate wound healing and improve cosmetic outcome in reduction mammaplasty in the previously irradiated breast.[7]

Multiple animal trials have proven the wound healing benefits of hyperbaric oxygen at the cellular level; a methodical review of these mechanisms was provided by Thom in 2011.[8] Through multiple cellular mechanisms triggered by reactive oxygen species and reactive nitrogen species, the wound treated with hyperbaric oxygen therapy exhibits increased collagen synthesis, growth factor production, improved cell migration, and tube-formation functions. Another free radical–mediated mechanism by which hyperbaric oxygen treatment augments wound healing is through stimulation of stem/progenitor cells.

Treatment protocols have been established for decompression sickness and air embolism, but there has been no consensus on ideal treatment parameters for complicated wounds. Most wounds, regardless of cause, treated with hyperbaric oxygen therapy receive a degree of clinical benefit regardless of treatment frequency or duration.

The benefit of hyperbaric oxygen in the treatment of chronic wounds has been well established by multiple prospective, blinded studies.[9–12] However, the contribution of this therapy to the healing of the complicated acute wound, flap, or graft is less well supported, with the majority of studies being animal models. This article reviews the literature to establish the current role of adjunctive hyperbaric oxygen therapy in the healing of the acute wound, flap, or graft in human subjects.

PATIENTS AND METHODS

Study Inclusion Criteria

Types of Studies

Any controlled study, prospective or retrospective, that evaluated the use of hyperbaric oxygen in the therapy of an acute surgical or traumatic wound in human subjects was included in this study. This review is limited to studies published in the English language.

Types of Participants

Subjects of any race, sex, age, or comorbidities with an acute wound of any cause were included.

Types of Clinical Outcomes

Resolution or improvement of acute wounds, flaps, or grafts treated with adjunctive hyperbaric oxygen therapy was evaluated. Secondary outcomes evaluated included length of hospital stay, number of operations, transcutaneous oxygen pressure, and perfusion indices.

Search Strategy for Identification of Studies

A systematic review of the literature was performed using the Ovid, PubMed, and Cochrane Library databases from 1946 to October 1, 2012. Our search was composed of keywords pertaining to hyperbaric oxygen therapy and wound healing (Fig. 1).

Standard Methods of Review

Selection of Trials

Using the keywords stated in Figure 1, two researchers independently conducted thorough reviews of the literature. A high-sensitivity, low-specificity search strategy was used (keywords "hyperbaric oxygen" AND "wound"). A combined search by the two reviewers (P.D. and B.P.) revealed 789 studies in the Ovid database, 777 studies in the PubMed database, and 39 studies in the Cochrane Library database. Of the selected studies, 125 titles from Ovid, 131 from PubMed, and nine from the Cochrane Library were found to meet our selection criteria. Of the selected titles, seven abstracts from Ovid, nine from PubMed, and six from the Cochrane Library were

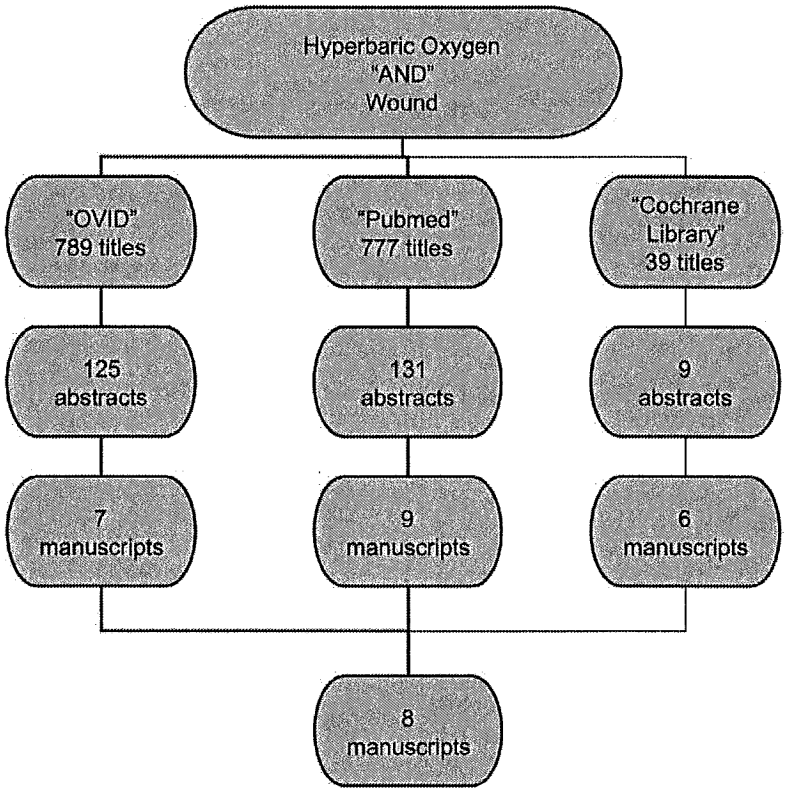

Fig. 1. Search flowchart.

found to meet our selection criteria. After complete article analysis, the final number of studies found to meet selection criteria from both databases was eight, with a Cohen kappa correlation coefficient of 1.0 between the two reviewers.

Data Extraction

Data from each of the studies were entered into standardized forms (Tables 2 and 3).[6,7,13–18]

RESULTS

Description of Studies

Articles meeting inclusion criteria included eight studies from the Ovid, PubMed, and Cochrane Library databases. Four of the selected studies are prospective, randomized, controlled trials. Three studies are prospective, nonrandomized, controlled, and one study is retrospective, controlled.

Risk of Bias in Included Studies

This review offers no more statistical significance than the significance of its included studies. In addition, publication bias (selective publishing of positive results) is a significant risk of bias in this review, as failed attempts of wound healing with adjunctive hyperbaric oxygen therapy are not realized.

Two included studies were performed in 1967 and 1974. However, pressurized oxygenation

Table 2. Treatment Parameters

Reference	No. of Sessions	Oxygen (%)	ATA	Time per Session (min)
Perrins, 1967[15]	5	100	2	120
Hart et al., 1974[13]	Three times on day 1, then twice daily until healed	100	2	90
Hammarlund et al., 1991[18]	3	NR	2.79	60
Bouachour et al., 1996[16]	12	100	2.5	90
Snyder et al., 2010[7]	20 preoperatively, 10 postoperatively	100	2.4	90
Brannen et al., 1997[14]	Minimum of 10	NR	2	90
Stong and Jacono, 2010[6]	2 preoperatively, 3 postoperatively	100	2	60
Gehmert et al., 2011[17]	1	100	2.36	90

ATA, atmosphere; NR, not reported.

Table 3. Study Parameters

Reference	Level of Evidence	No.	Age (yr)	Wound Cause	Endpoint	*p*
Perrins, 1967[15]	I	48	NR	STSG	STSG survival (>95 percent)	<0.001
Hart et al., 1974[13]	I	16	21 (mean)	Burn 10–50%	Healing time	<0.005
Hammarlund et al., 1991[18]	II	7	24–29	UV radiation	Wound "length," peripheral hyperemia	<0.005
Bouachour et al., 1996[16]	II	36	29–71	Crush injury	Complete wound healing	<0.01
Snyder et al., 2010[7]	III	5	38–57	Breast reduction	Complete wound healing	NA
Brannen et al., 1997[14]	I	125	NR	Burn	Mortality, no. of operations, length of stay	NR
Stong and Jacono, 2010[6]	II	13	47–71	Face lift	Degree of ecchymosis	0.005
Gehmert et al., 2011[17]	II	6	19–65	Free flap	$Ptco_2$ level	<0.001

STSG, split-thickness skin graft; NR, not reported; NA, not available; UV, ultraviolet; $Ptco_2$, transcutaneous oxygen pressure.

technology has not changed significantly since it was discovered more than 60 years ago, so the study date is likely insignificant.

Analysis of Interventions

Perrins randomized 48 burn patients to undergo standard excision and grafting versus adjuvant hyperbaric oxygen therapy in addition to standard burn care.[15] They treated half the patients with 100% oxygen at 2.0 ATA for 2 hours the evening of the operation and twice daily for 3 days postoperatively. Measured outcome included percentage of graft take. Using the *t* test and Wilcoxon two-sample test, a significant ($p < 0.001$) benefit was noted in the treatment group, with 91.7 percent graft survival versus 62.7 percent graft survival in controls. These are compelling data from a well-designed study; however, the control group skin graft take was much lower than typical skin graft success rates. This calls into question the relative benefit of hyperbaric oxygen therapy. Strengths of this study include its randomized, prospective design; statistical analysis; and single-surgeon experience. The power of this study would be called into question given the likely lower effect size than what is reported. If the control group had closer to standard expected graft take, the study would be underpowered with 48 patients.

Hart et al. prospectively evaluated hyperbaric oxygen therapy in 16 burn patients sustaining between 10 and 50 percent total body surface area burns.[13] Patients were randomized to receive hyperbaric oxygen therapy at 2.0 ATA three times in the first 24 hours of treatment and twice daily until the wounds were healed. Using two-way factorial analysis, the mean time to healing was significantly decreased in the treatment group (mean, 19.7 days versus 43.8 days; $p < 0.005$). Strengths of this study include its randomized, prospective design; standardization of the treatment arms; objectivity of outcome measures (healing time); and statistical analysis. Weaknesses are limited only to its small sample size.

Hammarlund et al. prospectively evaluated the use of hyperbaric oxygen treatment in seven patients with ultraviolet radiation–induced dermal burn injuries.[18] Wounds were induced on the forearm and occluded so that normal wound healing could be observed. Ten days later, similar wounds were induced on the contralateral forearm, occluded, and treated with three sessions of hyperbaric oxygen therapy at 2.8 ATA for 60 minutes each session at 1.5, 10.5, and 21.5 hours after injury. Wound "length" (including surrounding edema), evaporation rate, and degree of hyperemia were measured daily for 6 days after injury. Using the Wilcoxon signed rank test, the hyperbaric oxygen therapy group had significantly lower values in all parameters except epithelialization ($p < 0.005$). The authors conclude that hyperbaric oxygen therapy has beneficial effects on wound healing at the superficial dermal level. It decreases edema and wound exudates, but does not improve rate of epithelialization. Strengths of this study include its prospective, controlled design and statistical analysis. Weaknesses include its small sample size, subjective treatment response measures subject to observer bias, and nonrandomization of patients.

Bouachour et al. randomized 36 patients with extremity crush injury, Gustilo grade II or greater, to hyperbaric oxygen therapy or sham hyperbaric oxygen therapy study groups within 24 hours of the initial débridement.[16] The treatment group received 100% oxygen at 2.5 ATA for 90 minutes twice daily for 6 days. Endpoints included complete wound healing, transcutaneous oxygen pressure, bilateral perfusion index, and need for revision procedures. Using two-way factorial analysis, the hyperbaric oxygen treatment group had significantly higher complete healing rates (94 percent versus 59 percent) and required fewer new procedures ($p < 0.01$). In age- and injury severity–matched patients, the only significant finding was a higher rate of complete healing in patients older than 40 years

with grade III injuries. Increased transcutaneous oxygen pressure values and perfusion indices correlated with higher healing rates. Strengths of this study include its prospective, randomized, double-blinded, placebo-controlled design; standardization of the treatment arms; adequate sample size; objective outcome measures (complete wound healing, transcutaneous oxygen pressure); and statistical analysis. No weaknesses were identified.

Brannen et al. prospectively studied the effect of hyperbaric oxygen treatment in 125 randomized burn patients.[14] In the treatment arm, patients received 100% oxygen at 2.0 ATA within 24 hours of admission for 90 minutes twice daily for a minimum of 10 treatments and a maximum of one treatment per total body surface area percentage burn. Using two-stage stepwise regression analysis, a statistically significant benefit was noted in neither primary (i.e., length of stay) nor secondary (i.e., mortality and number of operations) outcome measures. The strengths of this study include its prospective, controlled, randomized design; statistical analysis; and sample size. No weaknesses were found with this study.

Stong and Jacono prospectively evaluated the effect of perioperative hyperbaric oxygen treatment on postoperative ecchymosis in patients undergoing face lift surgery.[6] Thirteen patients were enrolled, six of whom were nonrandomly enrolled in the treatment group and the remaining seven of whom acted as controls. The treatment group underwent two preoperative hyperbaric oxygen sessions and three postoperative sessions at 2 ATA for 60 minutes per session. The degree of cheek ecchymosis was evaluated with digital photometric analysis on postoperative days 1, 5, 7, and 10. The internal control for degree of ecchymosis was provided by analysis of each patient's earlobe, temple, nasal, and cervical skin. Using a paired t test, the authors found that on postoperative days 7 and 10, patients had 35 percent ($p = 0.005$) and 30 percent ($p = 0.03$) reduction in skin color change, respectively. They concluded that adjunctive hyperbaric oxygen therapy hastens recovery in patients with limited available recovery time. Strengths of this study include the study's prospective, controlled design; statistical analysis; single-surgeon experience; and objective measure of facial ecchymosis. Weaknesses include the nonrandomization of patients and the small sample size.

Snyder et al. retrospectively evaluated the use of hyperbaric oxygenation in five patients with previously irradiated breasts undergoing elective reduction mammaplasty.[7] All patients had undergone unilateral partial mastectomy and radiation therapy within the past 2 to 6 years. All patients acted as their own controls, as the contralateral breast received no radiation. Each patient received 100% oxygen at 2.36 ATA for 90 minutes for 20 treatments preoperatively and 10 treatments postoperatively. The authors report complete wound healing in all breasts, with delayed wound healing in two irradiated breasts at 4 and 11 weeks and in two normal breasts at 5 and 6 weeks. The cosmetic result and patient satisfaction scores were good. The authors conclude that with adjunctive hyperbaric oxygen therapy, elective breast surgery in women who have undergone prior breast irradiation is a safe option with acceptable cosmetic results. Although this study found benefit of hyperbaric oxygen therapy in their patients, no objective measure was used, and only a small number of patients were included. Strengths of the study include standardization of treatment arms and relative uniformity of radiation dosage. Weaknesses of this study include the study's retrospective design, absence of controls (all breasts received hyperbaric oxygen therapy), nonrandomization, and small sample size. The authors do not state whether patients included were operated on by a single surgeon or multiple surgeons. No statistical analysis was performed in this study.

Gehmert et al. evaluated the effect of hyperbaric oxygen treatment on six patients with free parascapular flaps for lower extremity reconstruction.[17] The patients were treated with 100% oxygen at 2.36 ATA for one 90-minute session. The transcutaneous oxygen pressure was then measured over the flaps at times −120, 0, 30, 60, and 120 minutes. With each flap acting as its own matched control, the authors found a significant increase in the partial oxygen pressures in all flaps up to 30 minutes after the hyperbaric oxygen session was discontinued (42.59 mmHg at −120 minutes versus 87.2 mmHg at 60 minutes and 83.5 mmHg at 120 minutes). Although peripheral hyperoxygenation is ideal in free-tissue transfer, no control was used and no clinical outcome data were gained such as time to healing, time to discharge, or performance in postoperative dangling protocols. Strengths of this study include the study's prospective design, standardization of treatment with hyperbaric oxygen therapy, and objectivity of measured outcomes (transcutaneous oxygen pressure). Weaknesses include its lack of controls, insufficient power, and lack of data showing clinical impact on flap survival.

DISCUSSION

Hyperbaric oxygen therapy has been studied for use in wounds of varying causes, such as necrotizing infection, radiation, crush injury, osteomyelitis, burn, and chronic ulcer, each for varying treatment lengths and frequencies. The studies included in this review largely support the use of hyperbaric oxygen therapy as an adjunct in the treatment of compromised acute wounds; however, the heterogeneity of outcome data, small sample sizes, and confounding variables make it difficult to make a concerted recommendation based on this review.

The mechanism by which hyperbaric oxygen affects wound healing is controversial when studied at the cellular level. It is known that hyperbaric oxygen therapy elevates arterial oxygen tension to greater than 2000 mmHg and up to 400 mmHg in tissues.[8] This hyperoxemia results in increased production of reactive oxygen species, which can have therapeutic and detrimental effects on the wound healing environment, depending on concentration. Reactive oxygen species cause damage to DNA and oxidation of lipids, amino acids, and enzymatic cofactors, resulting in defective cellular function.[19]

The body's cellular defense mechanisms to oxidative insults are adequate with brief hyperbaric oxygen treatments. Thus, treatment protocols are kept brief and interrupted periodically with "oxygen breaks" during which the patient breathes room air for 5 minutes between 100% oxygen treatments. With brief interruptions in treatment sessions, the body's antioxidant defense mechanisms are not overwhelmed, and any biochemical stress created by the hyperoxemia is completely reversible.[20]

The antimicrobial effects of oxygen have been well studied in the prevention of surgical-site infections[21–23] and the treatment of acute necrotizing soft-tissue infections.[24] The ability of leukocytes to generate reactive oxygen species is substantially impaired in a hypoxic environment and, as demonstrated by Mader et al., leukocyte performance significantly improves with higher oxygen pressures.[25] In addition to enhanced leukocyte function, increased tissue oxygenation decreases peripheral edema and improves skin viability, which improves skin flap adherence, neovascularization, and penetration of concomitant antibiotic therapy.

Hyperbaric chambers are safe and routinely used for treating even critically ill patients; however, complications and contraindications have been described. Absolute contraindications include pneumothorax, restrictive lung disease (air-trapping), pregnancy, concomitant Sulfamylon (UDL Laboratories, Inc., Rockford, Ill.) use,[26] viremia,[13] and concomitant chemotherapy.[27] Other complications include barotrauma to otic, sinus, or pulmonary structures; claustrophobia; reversible myopia; and seizure. Irreversible nuclear cataracts have been described with hyperbaric oxygen treatments exceeding 150 to 200 hours.[28]

Among the 15 Undersea and Hyperbaric Medical Society–approved indications for hyperbaric oxygen therapy, six are relevant to the general scope of plastic surgery (Table 4).[13,29–34] First, when prescribing adjunctive hyperbaric oxygen treatment for one of these indications, one must consider the cost and time implications for the patient, which are perhaps more important when related to uninsured procedures. Second, one must consider availability, as not all tertiary centers have access to a hyperbaric chamber. Third, complications of hyperbaric oxygen therapy are rare and usually self-limiting, but they can be serious. One must weigh the risks and benefits, before prescribing this therapy.

This article includes four level I trials, three level II trials, and one level III case series; seven of these eight trials support the use of hyperbaric oxygen therapy in compromised acute wounds. The heterogeneity in treatment regimens, outcome variables, and study design makes it impossible to uniformly analyze the data.

Two of the randomized controlled trials evaluate adjunctive hyperbaric oxygen treatment in burn injuries, and of these trials, only one found

Table 4. Plastic Surgery Indications for Hyperbaric Oxygen Therapy

Indication	Reference	Level of Evidence	Benefit
Late radiation tissue injury	Bennett et al., 2012[29]	I	Yes
Chronic ulcers (diabetic, venous, arterial, decubitus)	Kranke et al., 2012[30]	I	Yes
Acute wounds	Eskes et al., 2011[31]	I	Yes
Migraine headache	Bennett et al., 2009[32]	I	Yes
Thermal burn	Hart et al., 1974[13]	I	Yes
Necrotizing infection	Willy et al., 2012[33]	III	No
Osteomyelitis	Yu et al., 2011[34]	III	Yes

a statistically significant benefit.[13] Furthermore, the evaluation of burn wound treatment is confounded by the effect of hyperoxygenation on the systemic inflammatory response of the patient[13,35]; thus, its local effect on wound healing cannot be reliably extracted from these studies.

Statistical Analysis

Seven of eight studies included in this review achieved statistical significance in their primary endpoints but with a relatively low patient enrollment (n = 16 to 125 patients). Although statistical power can be determined only if the effect size is known, the only inference we can make from these studies is that statistical significance was achieved, with the acceptance that a type I error may have been made.

CONCLUSIONS

This review provides the current state of knowledge of adjunctive treatment with hyperbaric oxygenation for acute wounds of various causes. As stated by Baynosa and Zamboni in their review, hyperbaric oxygen therapy is neither necessary nor recommended for the support of normal, uncompromised wounds.[36] Despite the support that each study lends to including hyperbaric oxygen therapy in the treatment of complicated acute wounds, this review cannot reliably recommend its routine use in plastic surgery.

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