ORIGINAL ARTICLE

Hyperbaric Oxygen for Treating Wounds

A Systematic Review of the Literature

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Objective: To determine whether hyperbaric oxygen (HBO) therapy is an effective adjunct treatment for hypoxic wounds.

Methods: We identified studies from technology assessment reports on HBO and a MEDLINE search from mid-1998 to August 2001. We accepted randomized controlled trials (RCTs), cohorts, and case series that reported original data, included at least 5 patients, evaluated the use of HBO for wound care, and reported clinical outcomes. Demographics, wound conditions, HBO regimen, adverse events, and major clinical outcomes were extracted from each study.

Results: Fifty-seven studies, 7 RCTs, 16 nonrandomized studies, and 34 case series involving more than 2000 patients are included in this review. None of the studies used wound tissue hypoxia as a patient inclusion criterion. The study results suggest that HBO may be beneficial as an adjunctive therapy for chronic nonhealing diabetic wounds, compromised skin grafts, osteoradionecrosis, soft tissue radionecrosis, and gas gangrene compared with standard wound care alone. Serious adverse events associated with HBO include seizures and pressure-related traumas, such as pneumothorax. A few deaths in the studies were associated with these adverse events.

Conclusions: The overall study quality is poor, with inadequate or no controls in most studies. The studies suggest that HBO may be helpful for some wounds, but there is insufficient evidence to ascertain the appropriate time to initiate therapy and to establish criteria that determine whether patients will benefit. Serious adverse events may occur. High-quality RCTs that evaluate the short- and long-term risks and benefits of HBO are necessary to better inform clinical decisions.

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THE CENTERS for Medicare and Medicaid Services (Baltimore, Md) requested assistance from the Agency for Healthcare Research and Quality (AHRQ) (Rockville, Md) to perform an assessment of the use of hyperbaric oxygen (HBO) to treat hypoxic wounds. This article is derived from the assessment,[1] summarizing information from relevant studies that have addressed several key questions.

Wounds often have a reduced oxygen supply (hypoxia), which impairs leukocyte bacteriocidal activities and wound healing.[2] Researchers have hypothesized that improving oxygenation of the area surrounding the wound would improve wound healing.[2-5] Hyperbaric oxygen therapy involves the intermittent inhalation of 100% oxygen in chambers pressurized above 1 atmosphere absolute (ATA). An ATA is defined as the atmospheric pressure at sea level and is equivalent to 101.3 kiloPascals or about 14.7 pounds per square inch. The benefit of HBO is based on the premise that raising tissue oxygen levels will enhance wound healing ability.[2,6-9] Use of adjunctive HBO therapy has been reported in the management of a variety of disorders, such as refractory wounds,[10,11] gas gangrene,[12-28] necrotizing infections,[29-37] radiation injuries, and chronic osteomyelitis.[10,11]

See Invited Critique at end of article

Hyperbaric oxygen is administered either in a monoplace or a multiplace chamber. A monoplace chamber accommodates only a single patient, and the chamber is pressurized to about 2 to 2.5 ATA with 100% oxygen. A multiplace chamber can accommodate several patients and/or health care personnel. The chamber is compressed with air up to 2 to 2.5 ATA while the patient breathes 100% oxygen via head tent, face mask, or endotracheal tube. In either case, the arterial P_{O_2} will approach 1500 mm Hg.[8] No studies address the issues of efficacy or safety differences between monoplace vs multiplace chambers.

Potential risks for patients undergoing therapy with HBO include pressure-

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related traumas (eg, barotraumatic otitis, pneumothorax) and adverse effects due to oxygen toxicity (eg, myopia, seizures). Some patients may experience claustrophobia due to the confined space of the treatment chambers. Most adverse events are self-limiting and resolve after termination of therapy. Patients with barotraumatic otitis may require the placement of tympanostomy tubes. Some centers routinely insert tympanostomy tubes prophylactically. Serious, life-threatening events are probably rare but not well quantified.

Ten specific categories of wounds are considered in this review: acute traumatic peripheral ischemia; crush injuries and suturing of severed limbs; acute peripheral arterial insufficiency; compromised skin grafts; osteoradionecrosis; soft tissue radionecrosis; gas gangrene; progressive necrotizing infections; chronic refractory osteomyelitis; and chronic nonhealing wounds.

The following questions are addressed:

- Is there sufficient objective evidence that the use of HBO as adjunctive therapy to standard wound care aids in wound healing? Also, what other treatment modalities must be employed along with HBO therapy to maximize therapeutic benefits?
- At what point in treatment should HBO therapy be introduced?
- Wounds are generally classified based on diagnosis. Could wounds be classified based on a level of "hypoxia" rather than on diagnosis?
- Are there useful criteria to determine when an individual is likely to benefit from HBO therapy or when an individual will be nonresponsive to HBO therapy?
- Are there absolute contraindications when considering HBO therapy in monoplace or multiplace chambers?
- Which method of measuring tissue oxygen is most reliable and lends itself to standardization?
- What are the adverse effects of HBO therapy?

METHODS

LITERATURE SEARCH

There have been several systematic reviews on the role of HBO in the treatment of certain conditions examined in this review.[1,38-44] We updated the literature used in the existing systematic reviews by conducting a MEDLINE search for articles published between mid 1998 to August 2001. We searched for human subject studies published in English on HBO for wound care using the search terms "hyperbaric oxygen" and "wound*" or "injur*." This search yielded 159 citations. We also searched for articles that measured tissue oxygen levels in conjunction with HBO therapy using search terms of "hypox*" and "anoxia"; this search yielded 149 citations. We also included articles suggested by expert reviewers.

SELECTION OF PRIMARY STUDIES

We considered only published articles that reported original data, included at least 5 human subjects, evaluated the use of HBO for wound care, and reported clinical outcomes. Acceptable clinical outcomes included, but were not restricted to, mortality, amputation, wound healing, duration of hospitalization, and infection control. We included randomized controlled trials (RCTs), nonrandomized comparison studies, and case series. Conference reports that did not provide primary data, animal studies, and review articles were excluded.

REPORTING OF RESULTS

We assessed the characteristics of the original research articles and their results. We extracted the following data from each original study and summarized this information: patient demographics, description of the conditions, diagnostic criteria, wound duration, measurements of tissue oxygen levels around the wound, study design, adverse effects of treatment, and major clinical outcomes.

There were several nonrandomized prospective controlled trials. In some of these nonrandomized trials, patients who refused HBO because of claustrophobia or patients with contraindications served as controls. Most studies were retrospective reviews of patient series and compared the results of patients treated with HBO with those not treated with HBO. This group of studies was labeled "retrospective comparison." We labeled the specific diagnostic criteria as "clinical" for studies that did not report them.

RESULTS

Table 1 presents the characteristics of the studies that we evaluated. There were a total of 57 studies, 7 RCTs, 16 nonrandomized comparison studies, and 34 case series that studied a total of 2070 patients (1 study did not report the number of subjects). Only 8 studies used measurements of tissue oxygen to define hypoxia. The number of HBO therapy sessions varied from 4 to 44 sessions. No studies included patients with acute peripheral arterial insufficiency. We describe the findings of the studies for the 9 remaining conditions. **Table 2** presents a summary of the overall effects of HBO on each of the conditions.

ACUTE TRAUMATIC PERIPHERAL ISCHEMIA

One case series of 23 patients addressed this condition.[45] In this study, all of the patients who received adjunctive HBO therapy had improved wound recovery and complete healing. Tissue oxygen levels ($PtcO_2$) were measured under 3 successive conditions: the patient breathing normal air, the patient breathing normobaric pure oxygen by facial mask, and the patient breathing pure oxygen at 2.5 ATA. The overall sensitivity and specificity for predicting the limb's final outcome, when the ratio of $PtcO_2$ in traumatized and nontraumatized limbs is less than 0.40 at 2.5 ATA of pure oxygen, are 100% and 94%, respectively. The study concluded that the comparison between transcutaneous oxygen measurements at a normal level and at 2.5 ATA of hyperbaric pure oxygen is a reliable test to predict the final outcome in posttraumatic limb ischemia.

CRUSH INJURIES AND SUTURING OF SEVERED LIMBS

One RCT of crush injuries and suturing of severed limbs was found.[46] Hyperbaric oxygen treatments were typically given at 2.5 ATA for 90 minutes, twice daily for 6 days, in a multiplace chamber. The study concluded that

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Table 1. Outcomes Reported and Main Results Evaluating Hyperbaric Oxygen (HBO) for Various Wound Conditions

Source	No. of Subjects	Study Design	Results
			Chronic Nonhealing Wounds (Diabetic Ulcers)
Faglia et al[65]	70	RCT	Major amputations: HBO, 3 (8.6%) of 35; control, 11 (33.3%) of 33; RR (95% CI), 0.26 (0.08-0.84)
Doctor et al[66]	30	RCT	Above ankle amputations: HBO, 2 (13%) of 15; control, 7 (47%) of 15; RR, 0.27; $P<.05$ Minor (other) amputations: HBO, 4 (27%) of 15; control, 2 (13%) of 15; RR, 2.1; P = NS Number of positive cultures decreased from baseline of 19 to 3 in HBO; 16 to 12 in control; $P<.05$
Faglia et al[67]	115	NRS	Major amputations: HBO, 7 (14%) of 51; control, 20 (31%) of 64; $P = .01$
Zamboni et al[68]	10	NRS	Complete healing: HBO, 4 (80%) of 5; control, 1 (20%) of 5; $P<.05$ No amputation in either group
Baroni et al[69]	28	NRS	Healing: HBO, 16 (89%) of 18; control, 1 (10%) of 10; $P = .001$ Amputation: HBO, 2 (11%) of 18; control, 4 (40%) of 10; $P = .01$
Oriani et al[70]	80	NRS	"Recovery": HBO, 59 (95%) of 62; control, 12 (67%) of 18 Amputation: HBO, 3 (5%) of 62; control, 6 (33%) of 18; $P<.001$
Wattel et al[71]	20	CS	Complete healing: 15 (75%) of 20
Wattel et al[72]	59	CS	Complete healing: 52 (88%) of 59 Treatment failure in 7 led to amputation
			Chronic Nonhealing Wounds (Nondiabetic Ulcers)
Hammarlund et al[73]	17	NRS	Mean wound surface area decreased at 6-week end point; HBO, mean ± SD, 35.7% ± 17%; control, mean ± SD, 2.7% ± 11%; $P<.001$
			Acute Traumatic Peripheral Ischemic
Mathieu et al[45]	23	CS	Recovery and complete healing (no detailed data, only reported that $PtcO_2$ measurements in HBO predicts patients who will undergo amputation
			Crush Injuries and Suturing of Severed Limbs
Bouachou et al[46]	36	RCT	Complete healing: HBO, 17 (94%) of 18; control, 10 (55%) of 18; RR, 1.7; $P<.01$ Amputation: HBO, 0 (0%) of 18; control, 2 (11%) of 18 Wound dressings, mean ± SD: HBO, 15.8 (±9.4); control, 16.3 (±12.1); $P = .45$ Time of Healing, mean ± SD: HBO, 50.2 (±21.1); control, 55.8 (±19.9); $P = .21$
			Compromised Skin Grafts
Marx et al[47]	160	RCT	Wound infection: HBO, 5 (6%) of 80; control, 19 (24%) of 80; RR, 0.25 Wound dehiscence: HBO, 9 (11%) of 80; control, 38 (48%) of 80; RR, 0.23; $P = .001$ Delayed wound healing: HBO, 9 (11%) of 80; control, 44 (55%) of 80; RR, 0.20; $P = .001$
Perrins et al[48]	48	RCT	Improved survival of skin grafts: HBO, 64%; control, 17%: RR, 3.8; $P<.01$
			Osteoradionecrosis
Marx et al[49]	74	RCT	Rate of osteoradionecrosis: HBO, 5.4%; control, 30%; RR, 0.18; $P = .01$
Tobey et al[50]	12	RCT	"Significant improvement for healing progress in HBO group according to x-ray interpretation, clinical signs and symptoms." This is a preliminary report, full analysis of the study apparently was never published
McKenzie et al[51]	26	CS	Improvement: 21 (81%) of 26 (13 [50%] of 26 met strict criteria for resolution of disease)
			Gas Gangrene
Gibson et al[12]	46	NRS	Mortality: HBO, 9 (31%) of 29; control, 7 (58%) of 12; $P<.05$
Hitchcock et al[13]	33	NRS	Mortality: HBO, 7 (37%) of 19; control, 7 (50%) of 14
Schweigel et al[14]	43	NRS	Mortality: (No quantitative results reported.) "Fewer deaths reported among patients treated with HBO compared to those with HBO compared to those not treated with HBO"
Jackson et al[15]	24	NRS	Mortality: HBO, 4 (27%) of 15; control, 5 (56%) of 9 Amputation (among survivors): HBO, 2 (18%) of 11; control, 3 (75%) of 4
Rudge et al[16]	77	CS	Survival correlated well with site of infection ($P = .004$) and time to HBO ($P = .08$); a total of 23% of cases with limb involvement required an amputation after the start of HBO (16% had a primary amputation after starting HBO, and 7% had an amputation prior to HBO but required a revision one or more joints higher after starting HBO)
Trivedi et al[17]	15	CS	Infection controlled (100%) within 18 hours as judged by smear and culture methods
Hirn et al[18]	32	CS	Mortality: 9 (28%) of 32
Unsworth et al[19]	73	CS	Mortality: 15 (22%) of 73
Hart et al[20]	139	CS	Mortality: 27 (19%) of 139; amputations: 24 (17%) of 139
Guidi et al[21]	21	CS	Mortality: 4 (19%) of 21; amputations: 7 (33%) of 21
Tonjum et al[22]	30	CS	Mortality: 9 (30%) of 30; amputations: 6 (20%) of 30
Skiles et al[23]	33	CS	Mortality: 17 (52%) of 33
Fowler et al[24]	9	CS	Mortality: 1 (11%) of 9; amputations: 3 (60%) of 5, lower extremities cases
Darke et al[25]	88	CS	Mortality: 28 (32%) of 88
Holland et al[26]	49	CS	Mortality 13 (27%) of 49
Hart et al[27]	44	CS	Mortality: 10 (23%) of 44
Roding et al[28]	130	CS	Mortality: 29 (22%) of 130

(continued)

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Table 1. Outcomes Reported and Main Results Evaluating Hyperbaric Oxygen (HBO) for Various Wound Conditions (cont)

Source	No. of Subjects	Study Design	Results
			Soft Tissue Radionecrosis
Matthews et al[52]	17	NRS	Hematuria resolved completely: 11 (65%) of 17, 2 had only residual microscopic hematuria, 2 had improvement before death from complications of cancer, and 2 had recurrence of gross hematuria. Early application of HBO was associated with earlier resolution of hemorrhagic cystitis
Woo et al[53]	ND	NRS	Symptoms partially or completely resolved in more than half of the patients
Warren et al[54]	14	CS	5 (36%) of 14 classified as nonresponders: 3 of these had significant improvement during treatment but relapsed, and 2 had no symptomatic improvement
Neovius et al[55]	15	CS	12 (80%) of 15 patients healed completely, 2 healed partially, and only 1 did not heal at all
Feldmeier et al[56]	8	CS	6 (75%) of 8 patients healed without requiring surgical debridement but 4 required flaps or grafts
Bevers et al[57]	40	CS	Haematuria disappeared completely or improved in 37 patients. Recurrence rate 0.12/year in mean follow-up of 23.1 mo (range, 1-74 mo)
Weiss et al[58]	13	CS	12 (92%) of 13 patients experienced cessation of hematuria
Norkool et al[59]	14	CS	8 (57%) of 14 patients had complete resolution of symptoms, 2 (14%) of 14 had marked improvement in a follow up ranging from 10 to 42 mo
Feldmeier et al[60]	9	CS	7 (77%) of 9 patients maintained good voice quality; 2 exhibited some hoarseness
Williams et al[61]	14	CS	All patients with radiation necrosis of the vagina alone or in association with rectovaginal fistula had complete resolution of necrosis 1 (7%) of 15 treatment failure
Nakada et al[62]	6	CS	Improvement in symptoms and cystoscopic findings: 5 (83%) of 6. No recurrence during follow-up period (mean ± SD, 1.0-0.1 y)
Rijkmans et al[63]	10	CS	6 (60%) of 10 patients macroscopic hematuria stopped completed; decreased in other patients who had recurrent or residual bladder malignancies
Ferguson et al[64]	8	CS	Signs and symptoms of radionecrosis dramatically ameliorated in 7 (86%) of 8
			Progressive Necrotizing Infections
Risenman et al[29]	29	NRS	Mortality: HBO, 4 (23%) of 17; control, 8 (67%) of 12; $P<.025$ Mean debridements/patients: HBO, 1.2 per case; control, 3.3 per case; $P<.03$
Brazilai et al[30]	11	NRS	Mortality: HBO, 2 (66%) of 3; control, 5 (62%) of 8
Hollabaugh et al[31]	26	NRS	Mortality: HBO, 1 (7%) of 14; control, 5 (42%) of 12
Shupak et al[32]	37	NRS	Mortality: HBO, 9 (36%) of 25; control, 3 (25%) of 12; P = NS Length of hospital stay: HBO, 16d ± 6.4; control, 20d ± 13.8; P = NS
Sawin et al[33]	7	NRS	Mortality: HBO, 2 (50%) of 4; control, 0 (0%) of 3
Brown et al[34]	54	NRS	Mortality: HBO, 9 (30%) of 30; control, 10 (42%) of 24; P = NS; no significant differences in duration of hospital or ICU stay, or duration of antibiotic therapy
Korhonen et al[35]	33	CS	Mortality: 3 (9%) of 33
Eltorai et al[36]	9	CS	All patients recovered
Gozal et al[37]	16	CS	Mortality: 12.5%
			Chronic Refractory Osteomyelitis
Esterhal et al[10]	28	NRS	Treatment failures: HBO, 3 (21%) of 14; control, 1 (7%) of 14
David et al[11]	38	CS	Free of clinical signs of osteomyelitis for an average of 34 months in HBO: 34 (89%) of 38

Abbreviations: CI, confidence interval; CS, case series; ICU, intensive care unit; ND, not determinable; NRS, nonrandomized studies; NS, not significant; RCT, randomized controlled trial; RR, risk ratio.

HBO improved complete healing rates and reduced wound infection and wound dehiscence in crush injury.

COMPROMISED SKIN GRAFTS

Two RCTs were found on compromised skin grafts.[47,48] Hyperbaric oxygen treatments were typically given either for a total of 20 sessions or twice daily for 3 days. The authors concluded that HBO improved the survival of skin grafts, wound infection, and compete wound healing.

OSTEORADIONECROSIS

Two RCTs and 1 case series on osteoradionecrosis were found.[49-51] Hyperbaric oxygen treatments were typically given at 2 to 2.5 ATA for a total of 20 sessions. Clinical signs and symptoms and radiographic examinations were performed to evaluate each patient's progress in the 2 trials. Persistent mucosal and cutaneous coverage of the

Table 2. Summary of Evidence and Effect of HBO for Various Wound Conditions

	Study Design and No. of Studies		
Indications	RCT	NRS	CS
Chronic nonhealing wound (diabetes and nondiabetes)	2+	5+	2+
Acute traumatic peripheral ischemia	. . .	. . .	1+
Crush injuries	1+	. . .	. . .
Acute peripheral arterial insufficiency			
Skin grafts	2+	. . .	. . .
Osteoradionecrosis	2+	1+	. . .
Soft tissue radionecrosis	. . .	. . .	13+
Gas gangrene	. . .	4+	13+
Necrotizing infections	. . .	6±	3+
Chronic osteomyelitis	. . .	1–	1+

Abbreviations: CS, case series; NRS, nonrandomized comparison study; RCT, randomized controlled trial; +, overall beneficial effect; ±, conflicting results; –, no effect.

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wound was used as the outcome in the case series. The authors concluded that HBO treatment reduced the rate of osteoradionecrosis. Detailed information about the patients' characteristics, such as age, sex, and wound duration, or clearly defined diagnostic criteria of the underlying conditions, were not given in reports of studies of compromised skin grafts and osteoradionecrosis.

SOFT TISSUE RADIONECROSIS

We found 13 case series on soft tissue radionecrosis.[52-64] All of these studies reported a beneficial effect of the HBO treatment regimen for this condition. One study compared the patients with historical controls[55]; in this study, a greater number of patients in the HBO group healed without surgical intervention, but the authors did not calculate whether this difference was statistically significant. In several of the studies, patients had failed to heal from standard treatments received before the trial of HBO.[52,53,59,61]

GAS GANGRENE

Four retrospective comparison studies[12-15] and 13 case series were found.[16-28] The number of patients in these series varied from 9 to 139 and included both children and adults. Mortality was used as an outcome measure in most of the studies along with the rates of clinical improvement, infections, and amputation. The HBO regimen used was 2 to 3 ATA for 4 to 44 sessions. Each session usually lasted 90 minutes.

Most authors commented that adjunctive HBO was beneficial. However, because of the noncomparative nature of case series, it is difficult to assess the therapeutic effects of HBO reliably. The reported mortality rates in these studies ranged from 11% to 52%.

PROGRESSIVE NECROTIZING INFECTIONS

Six nonrandomized studies and 3 case series that evaluated the use of HBO in necrotizing fasciitis were identified.[29-37] Hyperbaric oxygen was generally given at 2 to 3 ATA for 5 to 7 sessions (a typical session lasted for 90 minutes), but 2 studies did not report how the HBO was given.[30,33]

There were inconsistent findings regarding the survival rates in patients with necrotizing fasciitis. Three studies found that there was no significant difference between HBO and control groups, casting doubt on HBO's effectiveness in reducing patient mortality and morbidity rates.[30,32,34] Three other studies found significantly reduced mortality rates in the HBO group.[29,31,33] However, 3 case series found increased recovery rates and reduced mortality.[35-37]

CHRONIC REFRACTORY OSTEOMYELITIS

One nonrandomized controlled trial[10] and one case series[11] were identified for this condition. Hyperbaric oxygen was generally given at 2 and 2.4 ATA for 2 hours and 6 days per week in one study. Outcomes assessed in the studies included recurrence of infection, length of hospitalization, wound healing, and clinical signs of osteomyelitis.

The nonrandomized controlled trial revealed that HBO had no significant effect on the healing outcomes for patients with chronic refractory osteomyelitis.[10] However, the case series reported that 34 of 38 patients remained free of clinical signs of osteomyelitis for an average of 34 months.[11]

CHRONIC NONHEALING WOUNDS (DIABETIC AND NONDIABETIC ULCERS)

Two RCTs,[65,66] 4 nonrandomized studies,[67-70] and 2 case series[71,72] that evaluated the use of HBO on diabetic wounds were identified. Hyperbaric oxygen was generally given at 2 to 2.8 ATA, 5 days per week (a typical session last for 45-90 minutes). The authors of the studies concluded that HBO is beneficial in the management of diabetic wounds. They found that the use of HBO significantly reduced wound size when compared with standard wound care alone and that the use of HBO was associated with a higher rate of complete healing as well as a decrease in major amputation rates in diabetic wounds.[67-70]

Only one study included patients with nondiabetic wounds.[73] Hyperbaric oxygen was generally given at 2.5 ATA, 5 days per week, for total of 30 treatments in a multiplace chamber (a typical session lasted for 90 minutes). The study found that the use of HBO significantly reduced the wound surface area. The wound size decreased at the 6-week end point when compared with the control group; the investigators concluded that the use of HBO is beneficial in the management of nondiabetic wounds.

Because the direct evidence base on nondiabetic wounds is limited to a single study of only 16 patients, more research is needed to assess the efficacy of HBO in these patients. The information on the clinical studies of diabetic and nondiabetic wounds is not sufficient to determine whether results in studies on diabetic wounds are generalizable to nondiabetic wounds.

COMMENT

Fifty-seven studies covered 9 acute and chronic wound conditions. There were only 7 RCTs among these studies. Nonrandomized comparative studies and case series were also identified through searches of the literature and described in this systemic review.

HBO AS AN ADJUNCTIVE THERAPY TO STANDARD WOUND CARE

In all studies, HBO was used as adjunctive therapy in addition to the main treatment modalities of wound debridement and antibiotics. The studies that we reviewed on progressive necrotizing infections and chronic refractory osteomyelitis reported inconsistent results on whether HBO is a beneficial adjunctive therapy to standard wound care. We found only 1 case series on acute traumatic peripheral ischemia and 1 RCT on crush injuries and suturing of severed limbs. These studies found that HBO

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was beneficial, but no confirmation from a separate study was available.

From the studies that we evaluated, the evidence suggests that HBO aids in wound healing for compromised skin grafts, osteoradionecrosis, gas gangrene, soft tissue radionecrosis, and chronic nonhealing diabetic wounds. There is evidence from case series suggesting the beneficial effect of HBO for soft tissue radionecrosis. However, the overall study quality is poor, with inadequate or no controls in most studies. Therefore, the benefits found in the studies may be due to factors other than HBO treatment. Still, the wounds studied were severe. Some of the wounds were chronic and had not responded to other treatments. There may have been no alternative treatments, or the alternative might have been a drastic step, such as amputation. For these wound conditions, the studies consistently showed a benefit for HBO. The uncertainties in the results, possibly due to poor study design, must be weighed against the harms of alternative treatments.

AT WHAT POINT IN TREATMENT SHOULD HBO THERAPY BE INTRODUCED?

The literature provides no guidance on when HBO therapy should be initiated for chronic nonhealing wounds. Only 2 studies that evaluated the effect of HBO on chronic diabetic wounds reported the duration of the wounds prior to treatment, which ranged from at least 6 to 12 months. For acute wounds such as necrotizing faciitis, HBO treatments generally were reported to begin immediately on hospitalization or after the initial wound debridement. In the case series reports on soft tissue radionecrosis, many studies began HBO treatment after failure of a course of standard therapy; however, 1 study[52] reported that earlier treatment with HBO led to earlier resolution of cystitis.

CLASSIFICATION OF WOUNDS BASED ON LEVEL OF HYPOXIA RATHER THAN DIAGNOSIS

There is insufficient evidence based on the studies we examined to use measured tissue hypoxia as a criterion to determine whether adjunctive HBO treatments might be efficacious in reducing mortality and morbidity. None of the studies evaluated in this report used tissue hypoxia measurement as a patient inclusion criterion. Only 2 RCTs,[46,65] 2 nonrandomized comparison studies,[67,68] and 4 case series[45,73,74,75] reported levels of transcutaneous tissue oxygen. Mean (SD) transcutaneous tissue oxygen levels on admission in these studies were: 12 mm Hg in the HBO group and 35 mm Hg in the control group,[68] 28 (13.4) mm Hg ,[67] 22 (10.6) mm Hg,[65] and about 15 to 19 mm Hg.[44] The distal transcutaneous oxygen tension at 2.5 ATA pure oxygen was considered a reliable test to predict the final outcome of wound healing. However, these measurements represent averages of the study populations and were not correlated with outcomes of individual patients. Therefore, this information is not useful to guide treatments for individual patients. The large difference in tissue oxygen levels between the HBO group and the control group in the study by Zamboni et al[68] also suggests that the patient selection bias in this nonrandomized study has made interpretation of the outcomes difficult.

CRITERIA DETERMINING WHO WILL BENEFIT FROM HBO THERAPY

Several studies measured whether patients' tissue oxygen level during HBO was predictive of response. One study[71] of 20 patients with chronic arterial insufficiency ulcers (n=11) and diabetic ulcers (n=9) reported that wound healing was achieved in all patients who were able to achieve a distal transcutaneous tissue oxygen level of at least 100 mm Hg during HBO therapy. Complete healing occurred in 15 of the 20 patients. Similar findings were reported in a study of 15 patients[75] undergoing musculocutaneous flap transplantation and a case series[45] of 23 patients with posttraumatic limb ischemia. Both found that Pt_cO_2 measurements in HBO predict patients who will undergo amputation. None of the studies stratified results by any other potential predictors of response.

CONTRAINDICATIONS TO MONOPLACE VS MULTIPLACE CHAMBERS

We found no studies that addressed the issues of efficacy or safety differences between monoplace and multiplace chambers. Examination of the adverse events reported by all of the studies revealed that oxygen toxicity in the form of seizures was observed in up to about 10% of the patients in several studies. One seizure-related death occurred in a "severely toxemic" patient who died 2 hours after an uncontrolled seizure. A patient with pneumothorax was one among several deaths reported in a case series of 30 patients. The pneumothorax was not reported to be the immediate cause of death in this patient. The need to provide emergency care during HBO treatment suggests that multiplace chambers may provide a safer treatment modality although this has not been demonstrated.

MOST RELIABLE AND STANDARDIZABLE METHOD OF MEASURING TISSUE OXYGEN

This issue cannot be resolved based on the studies reviewed in this report. Only 2 RCTs[46,65] and 2 nonrandomized comparison studies[67,68] reported transcutaneous measurements of tissue oxygen levels. Three studies evaluated 195 patients with diabetic leg ulcers. The fourth study,[46] involving 36 patients with acute limb injuries, reported that it used the miniature Clarke electrode as the method of transcutaneous measurement. Zamboni et al[68] used an instrument (TCM3/TINA) from Radiometer America Inc (Westlake, Ohio) and took measurements in noninflamed skin 1 cm medially, away from the wound edge at the midpoint of the ulcer. The other 2 reports did not provide specific information about the method of tissue oxygen measurement.

ADVERSE EVENTS

Nine studies* of the conditions listed in the "Results" section reported adverse events with the use of HBO therapy.

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One case of transient minor blurring of vision occurred with the treatment of osteoradionecrosis.[51] Two patients reported transient vision changes, and 3 patients required tympanostomy tubes in chronic refractory osteomyelitis.[11] The only adverse event reported was a case of barotraumatic otitis due to HBO therapy in diabetic ulcers, and there was no reporting of adverse effects in nondiabetic ulcers.[65] Most of the adverse events were reported in articles on gas gangrene. Six case series[17,18,20,22,23,25] reported adverse events attributed to HBO, and in 5 studies, a total of 23 of 322 patients with seizures attributed to oxygen toxicity were reported.[18,20,22,23,25] One death occurred in a study of 88 patients.[23] This patient had an uncontrolled seizure and died 2 hours after decompression. This patient was also reported to be severely toxemic; the infection was due to an anaerobic streptococcus. One pneumothorax was reported in one study of 30 patients.[22] Another case of "oxygen toxicity" was reported in the same study[22] but the details were not reported. This patient died with pulmonary embolism, pneumonia, and peritonitis. Other adverse effects included earaches and barotraumatic otitis. In addition to these 9 studies, 1 article[72] reported 3 cases of pulmonary edema (1 death) in patients who underwent HBO therapy for chronic wounds.

LIMITATIONS

The purpose of this report was to evaluate the evidence of the benefits and risks of HBO as adjunctive therapy to standard wound care. There are studies of the use of HBO for other indications; some of these studies probably reported adverse events. A full search and analysis of studies reporting adverse events associated with the use of HBO for indications other than wound care was outside the scope of this assessment. Adverse events in these studies may or may not be applicable to the wound care patient population, depending on factors such as comorbid conditions.

CONCLUSIONS

The overall methodologic quality of the studies that we found in this systemic review is poor, consisting mostly of small case series or nonrandomized comparisons. However, the consistency of the results of these studies suggests that HBO may aid in wound healing for compromised skin grafts, osteoradionecosis, soft tissue radionecrosis, gas gangrene, progressive necrotizing infection, and chronic nonhealing diabetic wounds. The studies found conflicting results regarding the survival rates in patients with necrotizing fasciitis. Serious adverse events, such as seizures and barotraumatic otitis, were reported in 9 studies. High-quality RCTs that evaluate the short- and long-term risks and benefits of HBO therapy are necessary to better inform clinical decisions about the use of HBO to improve recovery.

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*References 11, 17, 18, 20, 22, 23, 25, 51, 65.

REFERENCES

1. Wang C, Lau J. *Hyperbaric Oxygen Therapy in Treatment of Hypoxic Wounds.* Available at: http://www.cms.gov/coverage/8b3-mm2.asp. Accessed December 30, 2002.
2. Jefferson CD, Hunt TK. *Problem Wounds: The Role of Oxygen.* New York, NY: Elsevier Science Publishing Co Inc; 1988.
3. Fischer BH. Hyperbaric oxygen treatment. *Dev Med Child Neurol.* 1969;47:12-17.
4. Fischer BH. Topical hyperbaric oxygen treatment of pressure sores and skin ulcers. *Lancet.* 1969;2:405-409.
5. Fischer BH. Treatment of ulcers on the legs with hyperbaric oxygen. *J Dermatol Surg.* 1975;1:56-59.
6. Jonsson K, Jensen JA, Goodson WH, et al. Tissue oxygenation, anemia and perfusion in relation to wound healing in surgical patients. *Ann Surg.* 1991;214:605-613.
7. Kurz A, Sessler D, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical wound infection and shorten hospitalization. *N Engl J Med.* 1996;334:1209-1215.
8. Grim PS, Gottlieb LJ, Boddie A, Batson E. Hyperbaric oxygen therapy. *JAMA.* 1990;263:2216-2220.
9. Hopf HW, Hunt TK, West JM, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. *Arch Surg.* 1997;132:997-1004.
10. Esterhai JL Jr, Pisarello J, Brighton CT, Heppenstall RB, Gellman H, Goldstein G. Adjunctive hyperbaric oxygen therapy in the treatment of chronic refractory osteomyelitis. *J Trauma.* 1987;27:763-768.
11. Davis JC, Hechman JD, DcLee JC, Buckwold FJ. Chronic nonhematogenous osteomyelitis treated with adjunct hyperbaric oxygen. *J Bone Joint Surg.* 1986;68:1210-1217.
12. Gibson A, Davis FM. Hyperbaric oxygen therapy in the management of clostridium perfringens infections. *N Z Med J.* 1986;99:617-620.
13. Hitchcock CR, Burbick MP. Gas gangrene infections of the small intestine, colon and rectum. *Dis Colon Rectum.* 1976;19:112-119.
14. Schweigel JF, Shim SS. A comparison of the treatment of gas gangrene with and without hyperbaric oxygen. *Surg Gynecol Obstet.* 1973;136:969-970.
15. Jackson RW, Waddell JP. Hyperbaric oxygen in the management of clostridial myonecrosis. *Clin Orthop Rel Res.* 1973;96:271-276.
16. Rudge FW. The role of hyperbaric oxygenation in the treatment of clostridial myonecrosis. *Military Med.* 1993;158:80-83.
17. Trivedi DR, Raut VV. Role of hyperbaric oxygen therapy in the rapid control of gas gangrene infection and its toxaemia. *J Postgrad Med.* 1990;36:13-15.
18. Hirn M, Niinikoski J. Hyperbaric oxygen in the treatment of clostridial gas gangrene. *Ann Chirurgiae et Gynaccologiae.* 1988;77:37-40.
19. Unsworth LP, Sharp PA. Gas gangrene: an 11-year review of 75 cases managed with hyperbaric oxygen. *Med J Aust.* 1984;140:256-258.
20. Hart GB, Lamb RC, Strauss MB. Gas gangrene, I: a collective review. *J Trauma.* 1983;23:991-1000.
21. Guidi ML, Proietti R, Carducci P, Magalini SI, Pelosi G. The combined use of hyperbaric oxygen, antibiotics and surgery in the treatment of gas gangrene. *Resuscitation.* 1981;9:267-273.
22. Tonjum S, Digranes A, Gjengsto H, Eidsvik S. Hyperbaric oxygen treatment in gas-producing infections. *Acta Chir Scand.* 1980;146:235-241.
23. Skiles MS, Covert GK, Fletcher HS. Gas-producing clostridial and nonclostridial infections. *Surg Gynecol Obstet.* 1978;147:65-67.
24. Fowler DL, Evans LL, Mallow JE. Monoplace hyperbaric oxygen therapy for gas gangrene. *JAMA.* 1977;238:882-883.
25. Darke SG, King AM, Slack WK. Gas gangrene and related infection: classification, clinical features and aetiology, management and mortality: a report of 88

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cases. *Br J Surg*. 1977;64:104-112.
26. Holland JA, Hill GB, Wolfe WG, Osterhout S, Saltzman HA, Brown IW Jr. Experimental and clinical experience with hyperbaric oxygen in the treatment of clostridial myonecrosis. *Surgery*. 1975;77:77-85.
27. Hart GB, Lamb RC, Strauss MB. Gas gangrene, II: a 15-years experience with hyperbaric oxygen. *J Trauma*. 1983;23:991-1000.
28. Roding B, Groeneveld PHA, Boerema I. Ten years of experience in the treatment of gas gangrene with hyperbaric oxygen. *Surg Gynecol Obstet*. 1972;134:579-585.
29. Riseman JA, Zamboni WA, Curtis A, Graham DR, Konrad HR, Ross DS. Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. *Surgery*. 1990;108:847-850.
30. Barzilai A, Zaaroor M, Tolebano C. Necrotizing fasciitis: early awareness and principles of treatment. *Israel J Med Sci*. 1985;21:127-132.
31. Hollabaugh RS Jr, Dmochowski RR, Hickerson WL, Cox CE. Fournier's gangrene: therapeutic impact of hyperbaric oxygen. *Plast Reconstr Surg*. 1998;101:94-100.
32. Shupak A, Shoshani O, Goldenberg I, Barzilai A, Moskuna R, Bursztein S. Necrotizing fasciitis: an indication for hyperbaric oxygenation therapy? *Surgery*. 1995;118:873-878.
33. Sawin RS, Schaller RT, Tapper D, Morgan A. Early recognition of neonatal abdominal wall necrotizing fasciitis. *Am J Surg*. 1994;67:481-484.
34. Brown DR, Davis NL, Lepawsky M, Cunningham J, Kortbeek J. A multi-center review of the treatment of major truncal necrotizing infections with and without hyperbaric oxygen therapy. *Am J Surg*. 1994;167:485-489.
35. Korhnen K, Hirn M, Niinikoski J. Hyperbaric oxygen in the treatment of Fournier's gangrene. *Eur J Surg*. 1998;164:251-255.
36. Eltorai IM, Hart GB, StraussMB, Montroy R, Juler GL. The role of hyperbaric oxygen in the management of Fournier's gangrene. *Int Surg*. 1986;71:53-58.
37. Gozal D, Ziser A, Shupark A, Ariel A, Melamed Y. Necrotizing fasciitis. *Arch Surg*. 1986;121:233-235.
38. *Hyperbaric Oxygen Therapy for Wound Healing, Part I*. Vol 13, No.15. Chicago, Ill: Assessment Program, Technology Evaluation Center, Blue Cross and Blue Shield Association; 1999.
39. *Hyperbaric Oxygen Therapy for Wound Healing, Part II*. Vol 14, No.15. Chicago, Ill: Assessment Program, Technology Evaluation Center, Blue Cross and Blue Shield Association; 1999.
40. *Hyperbaric Oxygen Therapy for Wound Healing-Part III*. Vol 14, No.16. Chicago, Ill: Assessment Program, Technology Evaluation Center, Blue Cross and Blue Shield Association; 1999.
41. *Hyperbaric Oxygen Therapy: Medicare Services Advisory Committee applications 1018-1020, Assessment Report*. Canberra, Australia: Medicare Services Advisory Committee; 2000.
42. Mason J, O'Keeffe C, Hutchinson A, McIntosh A, Young, Booth A. A systematic review of foot ulcer in patients with type 2 diabetes mellitus.II: treatment. *Diabet Med*. 1999;16:889-909.
43. Mitton C, Hailey D. Hyperbaric oxygen treatment in Alberta: technology assessment report, Alberta, Canada, April 1998. Available at: www.Ahfmr.ab.ca/hta/hta-publications/reports/hbot.shtml. Accessed December 30, 2002.
44. Saunders P. *Hyperbaric Oxygen Therapy in the Management of Carbon Monoxide Poisoning, Osteoradionecrosis, Burns, Skin Grafts And Crush Injury: A West Midlands Development and Evaluation Service Report*. Birmingham, England: University of Birmingham; 2000.
45. Mathieu D, Wattel F, Bouachour G, Billard V, Defoin JF. Post-traumatic limb ischemia: Prediction of final outcome by transcutaneous oxygen measurements in hyperbaric oxygen. *J Trauma*. 1990;30:307-314.
46. Bouachour G, Cronier P, Gouello J, Toulemonde J, Talha A, Alquier P. Hyberbaric oxygen therapy in the management of crush injuries: a randomized double-blind placebo-controlled clinical trial. *J Trauma*. 1996;41:333-339.
47. Marx RE. Clinical applications of hyperbaric oxygen. In: Kindwall E, ed. *Hyperbaric Medicine Practice*. Flagstaff, Ariz: Best Publishing Co; 1994:460-462.
48. Perrins DJD. Influence of hyperbaric oxygen on the survival of split skin grafts. *Lancet*. 1967;1:868-871.
49. Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *J Am Dental Assoc*. 1985;111:49-54.
50. Tobey RE, Kelly JF. Osteroadionecrosis of the jaws. *Otolaryngol Clin North Am*. 1979;12:183-186.
51. McKenzie MR, Wong FL, Epstein JB, Lepawsky M. Hyperbaric oxygen and postradiation osteonecrosis of the mandible. *Eur J Cancer*. 1993;29B:201-207.
52. Mathews R, Rajan N, Josefson L, Camporesi E, Makhuli Z. Hyperbaric oxygen therapy for radiation induced hemorrhagic cystitis. *J Urol*. 1999;161:435-437.
53. Woo TC, Joseph D, Oxer H. Hyberbaric oxygen treatment for radiation proctitis. *Int J Radiat Oncol Biol Phys*. 1997;38:619-622.
54. Warren DC, Feehan P, Slade JB, Cianci PE. Chronic radiation proctitis treated with hyperbaric oxygen. *Undersea Hyperbaric Med*. 1997;24:181-184.
55. Neovius EB, Lind MG, Lind FG. Hyperbaric oxygen therapy for wound complications after surgery in the irradiated head and neck: a review of the literature and a report of 15 consecutive patients. *Head Neck*. 1997;19:315-322.
56. Feldmeier JJ, Heimbach RD, Davolt DA, Court WS, Stegmann BJ, Sheffield PJ. Hyperbaric oxygen as an adjunctive treatment for delayed radiation injury of the chest wall: a retrospective review of twenty-three cases. *Undersea Hyperbaric Med*. 1995;22:383-393.
57. Bevers RF, Bakker DJ, Kurth KH. Hyperbaric oxygen treatment for haemorrhagic radiation cystitis. *Lancet*. 1995;346:803-805.
58. Weiss JP, Mattei DM, Neville EC, Hanno PM. Primary treatment of radiation-induced hemorrhagic cystitis with hyperbaric oxygen: 10-year experience. *J Urol*. 1994;151:1514-1517.
59. Norkool DM, Hampson NB, Gibbons RP, Weissman RM. Hyperbaric oxygen therapy for radiation-induced hemorrhagic cystitis. *J Urol*. 1993;150(suppl 2, pt 1):332-334.
60. Feldmeier JJ, Heimbach RD, Davolt DA, Brakora MJ. Hyperbaric oxygen as an adjunctive treatment for severe laryngeal necrosis: a report of nine consecutive cases. *Undersea Hyperbaric Med*. 1993;20:329-335.
61. Williams JA Jr, Clarke D, Dennis WA, Dennis EJ III, Smith ST. The treatment of pelvic soft tissue radiation necrosis with hyperbaric oxygen. *Am J Obstet Gynecol*. 1992;167:412-415.
62. Nakada T, Yamaguchi T, Sasagawa I, Kubota Y, Suzuki H, Izumiya K. Successful hyperbaric oxygenation for radiation cystitis due to excessive irradiation to uterus cancer. *Eur Urol*. 1992;22:294-297.
63. Rijkmans BG, Bakker DJ, Dabhoiwala NF, Kurth KH. Successful treatment of radiation cystitis with hyperbaric oxygen. *Eur Urol*. 1989;16:354-356.
64. Ferguson BJ, Hudson WR, Farmer JC Jr. Hyperbaric oxygen therapy for laryngeal radionecrosis. *Ann Otol Rhinol Laryngol*. 1987;96(suppl 1, pt 1):1-6.
65. Faglia E, Favale F, Aldeghi A, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. *Diabetes Care*. 1996;19:1338-1343.
66. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. *J Postgrad Med*. 1992;38:112-114.
67. Faglia E, Favales F, Aldeghi A, et al. Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognosis determinants for major amputation. *J Diabetes Comp*. 1998;12:96-102.
68. Zamboni WA, Wong HP, Stephenson LL, Pfeifer MA. Evaluation of hyperbaric oxygen in the treatment for diabetic wounds: a prospective study. *Undersea Hyperbaric Med*. 1997;24:175-179.
69. Baroni G, Porro T, Faglia E, et al. Hyperbaric oxygen in diabetic gangrene treatment. *Diabetes Care*. 1987;10:81-86.
70. Oriani G, Meazza D, Favales F, Pizzi GL, Aldeghi A, Faglia E. Hyperbaric oxygen therapy in diabetic gangrene. *J Hyperbaric Med*. 1990;5:171-173.
71. Wattel F, Mathieu D, Coget JM, Billard V. Hyperbaric oxygen therapy in chronic vascular wound management. *Angiology*. 1990;41:59-65.
72. Wattel F, Mathieu D, Fossatti P, Neviere RR, Cogel JM. Hyperbaric oxygen in the treatment of diabetic foot lesions: search for healing predictive factors. *J Hyperbaric Med*. 1991;6:263-268.
73. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. *Plast Reconstr Surg*. 1994;93:829-833.
74. Weaver LK, Churchill S. Pulmonary edema associated with hyperbaric oxygen therapy. *Chest*. 2001;120:1407-1409.
75. Mathieu D, Neviere R, Pellerin P, Patenotre P, Wattel F. Pedicle musculocutaneous flap transplantation: prediction of final outcome by transcutaneous oxygen measurements in hyperbaric oxygen. *Plast Reconstr Surg*. 1993;91:329-334.

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