Hyperbaric Oxygen Therapy: Solution for Difficult to Heal Acute Wounds? Systematic Review

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Abstract

Background Hyperbaric oxygen therapy (HBOT) is used to treat various wound types. However, the possible beneficial and harmful effects of HBOT for acute wounds are unclear.
Methods We undertook a systematic review to evaluate the effectiveness of HBOT compared to other interventions on wound healing and adverse effects in patients with acute wounds. To detect all available randomized controlled trials (RCTs) we searched five relevant databases up to March 2010. Trial selection, quality assessment, data extraction, and data synthesis were conducted by two of the authors independently.
Results We included five trials, totaling 360 patients. These trials, with some methodologic flaws, included different kinds of wound and focused on different outcome parameters, which prohibited meta-analysis. A French trial ($n = 36$ patients) reported that significantly more crush wounds healed with HBOT than with sham HBOT [relative risk (RR) 1.70, 95% confidence interval (CI) 1.11–2.61]. Moreover, there were significantly fewer additional surgical procedures required with HBOT (RR 1.60, 95% CI 1.03–2.50), and there was significantly less tissue necrosis (RR 1.70, 95% CI 1.11–2.61). In one of two American trials ($n = 141$) burn wounds healed significantly quicker with HBOT ($P < 0.005$) than with routine burn care. A British trial ($n = 48$) compared HBOT with usual care. HBOT resulted in a significantly higher percentage of healthy graft area in split skin grafts (RR 3.50, 95% CI 1.35–9.11). In a Chinese trial ($n = 145$) HBOT did not significantly improve flap survival in patients with limb skin defects.
Conclusions HBOT, if readily available, appears effective for the management of acute, difficult to heal wounds.

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Introduction

Acute wounds are characterized by breakdown of the integrity of the soft tissue envelope surrounding any portion of the body [1] and are mostly subsequent to a surgical intervention or trauma. Such wounds occur more frequently than chronic wounds [2]. Most acute wounds heal without difficulty. However, some are subject to factors that impede healing, such as poor local blood and oxygen supply, infection, or damage to the vasculature. If one of these complicating factors occurs, these wounds can be considered potential problem wounds with an extended healing time. In these cases, more specific care is needed.

Hyperbaric oxygen therapy (HBOT)—delivering 100% oxygen at pressures above one atmosphere—is thought to assist wound healing, as it delivers a significantly increased amount of oxygen to the skin and surrounding tissues [3, 4]. For this reason, HBOT has been used as a treatment for various chronic and acute wounds [5–7]. HBOT was shown to be effective for patients with diabetic foot ulcers, and it significantly reduced the risk of major amputation and improved the chance of healing at 1 year [6, 8]. Two other Cochrane systematic reviews showed that the potential value of HBOT for open fractures and burns was unclear [7, 9]. Another literature review by Goldman showed some evidence that HBOT promotes healing of arterial ulcers, calciphylactic ulcers, refractory vasculitic ulcers, and osteomyelitis, as well as the successful "take" of compromised flaps and grafts [10]. However, that review included randomized clinical trials (RCTs), nonrandomized trials (CCTs), cohort studies, retrospective analyses, and case series. Inclusion of the latter study designs and the fact it was a single-author review may produce results that are at a considerable risk of bias.

Evidence regarding the effectiveness of HBOT for acute wounds has never been appreciated systematically. We therefore carried out a Cochrane systematic review to answer the following question: Is HBOT more effective than other types of treatment (e.g., usual care, sham HBOT, different intensities of HBOT, or different numbers of treatment applications) for acute wounds in terms of wound healing, adverse effects, pain, and cost?

Methods

Protocol and registration

Methods of the analysis and inclusion criteria were specified in advance and documented in a protocol described elsewhere [11]. Here, our methods and results are summarized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12, 13].

Eligibility criteria

In this review, we included all RCTs that evaluated the effects of HBOT as treatment for acute wounds in adult patients. These RCTs compared HBOT with any other intervention or sham HBOT, or they make comparisons between different intensities of HBOT or the use different numbers of treatment applications. We included such RCTs if they assessed at least one of the following primary outcome parameters: wound healing and adverse effects. As secondary outcome parameters, we recorded mortality, pain scores, quality of life, patient satisfaction, activities of daily living, increase in transcutaneous oxygen pressure ($tcPO_2$), amputation rate, length of hospital stay, and cost.

Information sources

The RCTs were identified by searching the following databases: Cochrane Wounds Group Specialised Register, Ovid Medline, Ovid Embase, and EBSCO Cinahl up to March 2010, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to issue 1, 2010. The search strategy is detailed elsewhere [11]. Furthermore, we used our wound expert network to check for ongoing or unpublished trials. We also screened the reference lists of all included articles to identify additional relevant trials. We used no restriction on language, publication data, or publication status.

Study selection

Two review authors independently selected potentially relevant trials based on the titles and abstracts of the articles retrieved by the search. These authors were not masked for any information about the article, such as the publishing journal, the authors, the institution, or the magnitude or direction of the results.

Full-text versions of the articles were obtained if they matched the inclusion criteria or if further scrutiny was needed about eligibility. The final selection of trials to be included was made independently by the same review authors. A third review author was involved in case of any discrepancies.

Data collection process

Two authors independently extracted and summarized characteristics and data from the included trials. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, a third author would decide. We contacted one author to obtain missing information but received no response. Data from trials published in duplicate were included only once.

Risk of bias in individual studies

The methodologic quality of each trial was determined by two of the authors independently. We used the Cochrane Collaboration appraisal tool to assess risk of bias [14]. This involves consideration of six quality items: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and "other" potential sources of bias [14]. Again, a third review author arbitrated any discrepancies.

Data items

From each included study, information was extracted about (1) characteristics of trial participants and inclusion and exclusion criteria; (2) type of intervention (including type, dose, duration, and frequency of the treatment) versus control intervention; (3) type of outcome.

Summary measures and methods of analysis

Quantitative data were entered and analyzed in RevMan 5.0.24 (Cochrane Collaboration, Oxford, UK) by one author and checked by another. We calculated summary estimates of the treatment effects with 95% confidence intervals (95% CI) for every comparison. For continuous outcome parameters, we calculated the mean differences (MD) when appropriate. For dichotomous outcome parameters we calculated the risk ratio (RR). To present the number needed to treat (NNT), the risk difference (RD) was calculated.

Results

Study selection

The search provided a total of 137 publications. The study inclusion process is shown in Fig. 1. Five RCTs fulfilled our inclusion criteria. No new RCTs were found by reference checking. Also, no unpublished relevant RCTs were obtained.

Characteristics of included studies

Participants and intervention

Four of the five included trials were in English. One trial was translated from Chinese into Dutch by a national translation institute. Trials ranged in size from 16 to 135 patients, totaling 360 patients. HBOT was applied for various indications: crush injuries [15], burns [16, 17], split-skin grafts (SSG) [18], and flap grafting for limb skin defects [19]. The type of HBOT chamber and the duration and dose of the treatment were different among the trials. In addition, HBOT was compared to other treatments (Table 1).

Primary and secondary outcomes

In four trials the primary outcome assessed was wound healing, although measured differently. In one trial length of hospital stay was described as the primary outcome [16]. Adverse effects (including new surgical procedures and amputation rates) and length of hospital stay were described in only two trials [15, 16]. Mortality was described twice [16, 17]. Other outcomes were not reported (Table 1).

Risk of bias within studies

The methodologic quality of the trials was moderate. Hence, their internal validity was reasonable (Table 2). Only one of the trials reported their method of randomization [17]. As a consequence, we could not appreciate allocation concealment in the other trials. Bouachour et al. [15] and Hart et al. [17] blinded care provider, patients, and outcome assessor to treatment allocation. Patients and care providers were not blinded in the trial of Brannen et al., and blinding of the outcome assessor was unclear [16]. Perrins blinded the surgeon to treatment allocation [18] and Xie and Li reported that no one was blinded [19]. All randomized participants were analyzed in the group to which they had been allocated in the trials of Bouachour et al. [15] and Xie and Li [19]. However, in Perrins' trial two patients were excluded from the analysis [18]. Nevertheless, we were able to perform an intention-to-treat analysis post hoc. Furthermore, in the trials of Brannen et al. [16] and Hart et al. [17], it was unclear if they used an intention to treat-analysis for all the endpoints.

Hart et al. [17], Perrins [18], and Xie and Li [19] did not report the characteristics of the participants at baseline. Hence, we were unable to judge baseline comparability. Bouachour et al. [15] and Hart et al. [17] were supported by a research grant received from their hospital but had no financial conflict of interest with respect to the trial outcome.

Quantitative data

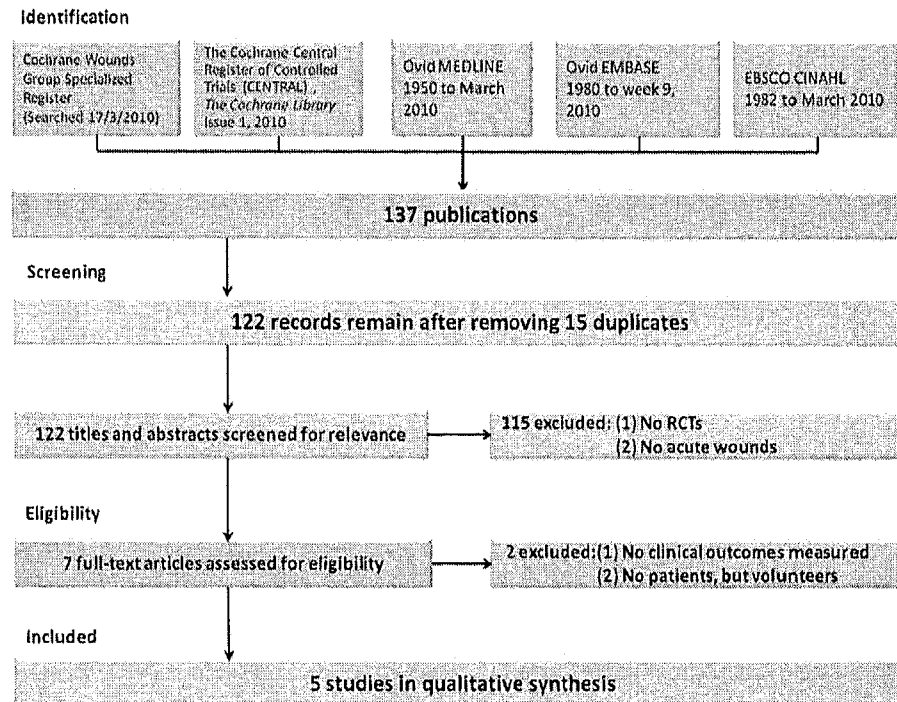The trials varied markedly in terms of wound types, comparator treatments, and outcome parameters. Therefore, the clinical heterogeneity was substantial, so we focused on describing individual trial results, applicability, and limitations rather than using a meta-analysis.

Crush injuries

Bouachour et al. [15] studied HBOT in patients with crush injuries [15]. In this French trial, complete wound healing

Fig. 1 Flow of information through the various phases of a systematic review

Identification

Cochrane Wounds Group Specialised Register (Searched 17/3/2010)

The Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* Issue 1, 2010

Ovid MEDLINE 1950 to March 2010

Ovid EMBASE 1980 to week 9, 2010

EBSCO CINAHL 1982 to March 2010

137 publications

Screening

122 records remain after removing 15 duplicates

122 titles and abstracts screened for relevance → 115 excluded: (1) No RCTs (2) No acute wounds

Eligibility

7 full-text articles assessed for eligibility → 2 excluded:(1) No clinical outcomes measured (2) No patients, but volunteers

Included

5 studies in qualitative synthesis

(without tissue necrosis requiring surgical excision) was achieved in 17 patients (94%) treated with HBOT versus 10 patients (56%) in the sham-HBOT group, showing a statistically significant difference in favor of HBOT therapy (RR 1.70; 95% CI 1.11–2.61; NNT 3). However, they found no statistical difference between the two groups in time to complete healing (mean ± SD) 50.2 ± 21.1 days in the HBOT group versus 55.8 ± 19.9 days in the sham-HBOT group (MD 5.60; 95% CI 19.00–7.80).

Bouachour et al. [15] also compared HBOT with sham-HBOT in terms of adverse effects. Two additional surgical procedures (in one patient) were needed in the HBOT group versus eight (in six patients) in the sham-HBOT group (RR 1.60, 95% CI 1.03–2.50; NNT 3), as the first operation did not have the desired effect. In addition, one patient in the HBOT group versus eight patients in the sham-HBOT group developed necrotic tissue (RR 1.70, 95% CI 1.11–2.61; NNT 3). No amputations occurred in the HBOT group versus two amputations in the sham-HBOT group (RR 1.12, 95% CI 0.93–1.36) and no significant differences were observed between the two groups for length of hospital stay (MD 0.50; 95% CI 9.96–8.96). Other (secondary) endpoints were not reported.

Burns

Brannen et al. [16] and Hart et al. [17] studied HBOT in burn patients in the United States. Brannen et al. did not study wound healing but found no significant differences in mortality rates between HBOT and routine burn

management (RR 0.98, 95% CI 0.37–2.64). Also, no significant differences in length of hospital stay or number of surgeries were found. However, we did not have access to the original data and therefore could not reanalyze it. Hart et al. reported a significantly lower mean healing time in the HBOT-treated group (mean 19.7 days) than in the sham-HBOT group (mean 43.8 days) (P < 0.005). No SDs were given to check this result. No deaths were observed. Three patients in the HBOT group experienced sinus barotrauma, and one patient in the control group had transient viremia during the treatment.

Split-skin grafts

Perrins studied HBOT applied to patients who had undergone a split-skin graft (SSG) [18]. In this British trial, complete survival was defined as 95% take of the graft. Patients treated with HBOT had a significantly higher percentage complete survival (>95% healthy graft area: RR 3.50; 95% CI 1.35–9.11; NNT 2). Consistently, he found better results in the HBOT group, but two grafts (8%) in the HBOT group failed completely versus no failures in the control group (RR 5.00; 95% CI 0.25–98.96). However, this was not significantly different. Other secondary outcomes were not reported for these SSGs.

Flap grafting

Xie and Li studied HBOT in patients with skin defects in the limbs, for which they underwent flap grafting [19]. In

Table 1 Characteristics of included studies

Study	Year	Country	No. of patients	Wound type	Type of HBOT chamber	Atmosphere absolute (ATA)	Duration of the treatment	Control treatment	Outcomes	Follow-up (days)
Bouachour [15]	1996	France	36 (18 vs. 18)	Crush injuries	Multiplace	100% oxygen at 2.5 ATA	For 90 min Twice during 6 days Routine burn management with the addition of HBOT	Sham HBOT	Wound healing Time of healing Adverse effects Amputation rates Length of hospital stay	Until complete wound healing
Brannen [16]	1997	USA	125 (63 vs. 62)	Burns	Not reported	% oxygen not reported, 2.0 ATA	For 90 minutes (first HBO treatment within 24 hours of burn injury) Twice daily Minimum of 10 treatments and maximum of one treatment for each percent TBSA burn	Routine burn management	Length of stay Mortality No. of surgeries	?
Hart [17]	1974	USA	16	Burns	Monoplace	100% oxygen at 2.0 ATA	Routine burn management and HBOT For 90 minutes every 8 hours during 1 day Next days: 90 minutes every 12 hours until healed	Routine burn management and sham-HBOT	Mean healing time Mortality Adverse effects Patient safety	?
Perrins [18]	1967	UK	48 (24 vs. 24)	Split skin grafts	Vicker's clinical transparent pressure chamber	100% oxygen at 2.0 ATA	For180 minutes Twice during 1 day Next 3 days once	Usual care	- Complete survival	7
Xie [19]	2007	China	135 (45 in each group)	Flap grafts	Not reported	Not reported	Minutes: unclear Twice daily during 3 days Next days: once a day Total of 6–12 treatments	Dexamethasone or local heparin treatment	- Flap survival	7

HBOT hyperbaric oxygen therapy, *ATA* temperature absolute, *TBSA* total body surface area

Table 2 Quality assessment of included studies

Study	Sequence generation	Allocation concealment	Blinding care provider	Blinding outcome assessor	Blinding participant	Dropout rate acceptable?	Intention-to-treat analysis	Free of selective reporting	Free of other bias	Financial interest?
Bouachour [15]	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes
Brannen [16]	Unclear	Unclear	No	Unclear	No	Unclear	Unclear	Unclear	No	Unclear
Hart [17]	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	No	Yes
Perrins [18]	Unclear	Unclear	Yes	Unclear	No	Yes	No	Unclear	Unclear	Unclear
Xie [19]	Unclear	Unclear	No	No	No	Yes	Yes	Unclear	Unclear	Unclear
Total	20%	20%	60%	0%	40%	60%	40%	20%	20%	40%

this Chinese trial, no significant differences in complete flap survival were found between HBOT and dexamethasone (RR 0.50, 95% CI 0.19–1.35) and between HBOT and heparin (RR 0.42, 95% CI 0.16–1.09).

Discussion

This review shows that some evidence is available based on robust study designs regarding the effectiveness of HBOT for the management of acute wounds, although the trials found were few and showed several methodologic flaws. Only five RCTs were found, the results of which could not be pooled. However, based on individual trial data, HBOT appears beneficial in patients with crush injuries, which show improved wound healing and less adverse outcomes such as necrosis or the need for additional surgical procedures. Also, burns appear to heal quicker with HBOT. Furthermore, HBOT appears to improve the take of split-skin grafts. On the other hand, complete wound healing is the most patient-relevant outcome. Hence, incomplete graft take, leading to a mere reduction in wound size, is not very meaningful.

Our findings are supported by those of previous reviews by Goldman [10] and Wang et al. [5]. Their reviews included studies with designs other than RCTs. Additionally, burns were not included. They concluded that HBOT may be beneficial as an adjunctive therapy for compromised skin grafts. In contrast, our review is based on randomized evidence alone, using Cochrane Collaboration methodology. It includes only studies with high internal validity, which offers more robust evidence.

In the present review, two of the included studies were published more than 35 years ago. However, the HBOT technique is merely meant to compress air, and this technology has not changed since then. Hence, we do not think that this time interval affects our conclusions.

One of the included trials reported some major adverse effects in both treatment arms [15]. However, these cannot be explained by a biological rationale and are therefore unlikely to be due to HBOT. From larger descriptive studies, we know that about 20% of patients experience only mild adverse effects, such as some degree of middle ear barotrauma, and 60 to 70% of them suffer from measurable, but reversible, worsening myopia [20].

The body of evidence on the usefulness of HBOT is larger for chronic wounds than for acute wounds [6, 8, 21]. Chronic wounds generally have poor local perfusion, which hampers wound healing. This may be counteracted by HBOT. Similarly, with ischemic acute wounds such as crush injuries, HBOT can be effective in overcoming an initial period of local ischemia underlying the problematic healing of these wounds. On the other hand, acute wounds

are more difficult to treat with HBOT because of their urgency and the limited availability of HBOT facilities. Thus, the application of HBOT can be justified only if the cost is acceptable and HBOT facilities are available at the time of presentation. Hence, it would be bold to advocate the routine use of HBOT for such wounds. In addition, patient selection should be done carefully and according to local guidelines for recognized and reimbursed indications for HBOT [22, 23] (Table 3). On the other hand, HBOT is rather widely available in North America—with more than 300 facilities registered with the Undersea and Hyperbaric Medical Society (UHMS)—Russia, China, and Cuba; it is less well established in Europe and Australasia [24].

Further evaluation through well designed and well conducted RCTs is needed to corroborate clinically relevant effects of HBOT. Patients suitable for HBOT require repeated treatments and depend on availability. These appear to be predominant reasons why RCTs on HBOT, particularly for acute wounds, may be difficult to perform. However, the number of HBO chambers is increasing, which expands the availability of the treatment. Acute conditions possibly of interest for future studies are flaps used in plastic surgery, calciphylaxis, and jaw surgery because in these circumstances oxygen perfusion can be severely hampered. In such cases, wound healing is at risk, and wound infections are more likely to occur. Currently, an RCT is ongoing to investigate the efficacy of adding HBOT to the treatment of late radiation damage of the lower jaw (osteoradionecrosis) (http:\\www.clinicaltrials. gov/, NCT00989820). Present-day reality is that cost-effectiveness studies are lacking [25], and transportation logistics may preclude the use of HBOT during an early phase of wound healing of acute surgical and traumatic wounds. Nevertheless, if a HBOT facility is at hand, the evidence found in this review supports its application for acute, difficult to heal wounds.

Conflicts of interest None.

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Table 3 Recognized indications for HBOT in the Netherlands (www. cvz.nl)

Acute indications
Decompression sickness
Air or gas embolism
CO poisoning
Necrotizing soft tissue infections
Crush lesions, compartment syndrome, and other acute traumatic ischemia
Skin grafts and flaps (compromised)
Limb reimplantation
Chronic indications
Diabetic ulcer
Delayed radiation injury (soft tissue and bony necrosis)
Radiocystitis, proctitis, enteritis
Osteomyelitis (refractory)

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