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Double-blind trials in hyperbaric medicine: A narrative review on past experiences and considerations in designing sham hyperbaric treatment

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Abstract

Background: Hyperbaric oxygen therapy, which consists of breathing 100% oxygen under a higher atmospheric pressure than normal, is utilized worldwide in the treatment of several diseases. With the growing demand for evidence-based research, hyperbaric oxygen therapy has been criticized for delivering too little high-quality research, mainly in the form of randomized controlled trials. While not always indispensable, the addition of a sham-controlled group to such a trial can contribute to the quality of the research. However, the design of a sham (hyperbaric) treatment is associated with several considerations regarding adequate blinding and the use of pressure and oxygen. This narrative review discusses information on the sham profile and the blinding and safety of double-blind trials in hyperbaric medicine, irrespective of the indication for treatment.

Methods: MEDLINE, Embase and CENTRAL were searched for sham-controlled trials on hyperbaric oxygen therapy. The control treatment was considered sham if patients were blinded to their allocation and treatment took place in a hyperbaric chamber, with no restrictions regarding pressurization, oxygen levels or indication. Studies involving children or only one session of hyperbaric oxygen were excluded. Information on (the choice of) treatment profile, blinding measures, patient's perception regarding allocation and safety issues was extracted from eligible studies.

Results: A total of 42 eligible trials were included. The main strategies for sham treatment were (1) use of a lower pressure than that of the hyperbaric oxygen group, while breathing 21% oxygen; (2) use of the same pressure as the hyperbaric oxygen group, while breathing an adjusted percentage of oxygen; and (3) use of the same pressure as the hyperbaric oxygen group, while breathing 21% oxygen. The advantages and disadvantages of each strategy are discussed using the information provided by the trials.

Conclusion: Based on this review, using a lower pressure than the hyperbaric oxygen group while breathing 21% oxygen best matches the inertness of the placebo. Although studies show that use of a lower pressure does allow adequate blinding, this is associated with more practical issues than with the other strategies. The choice of which sham profile to use requires careful consideration; moreover, to ensure proper performance, a clear and detailed protocol is also required.

Keywords

Hyperbaric oxygen therapy, sham, placebo, double-blind, methodology, randomized controlled trial, narrative review, safety, complications, blinding

Introduction

Hyperbaric oxygen (HBO) therapy, which consists of breathing 100% oxygen under a higher atmospheric pressure than normal (i.e. above 1.0 atmosphere absolute (ATA)), is utilized worldwide in the treatment of several diseases. The Undersea and Hyperbaric Medical Society, a nonprofit organization that plays an important role in providing scientific and medical information

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on hyperbaric medicine, lists 14 indications for HBO therapy. These include late radiation tissue injuries, diabetic foot ulcers and carbon monoxide poisoning.[1] Treatment for chronic problems (e.g. wound healing) usually involves giving daily sessions for several weeks, at pressures between 2.0 and 2.5 ATA. These sessions can be given in either a monoplace chamber (in which only one patient is treated per session) or in a multiplace chamber (where several patients are treated simultaneously, with the possibility of an attendant joining them to supervise treatment). The therapy is generally considered safe with few complications, with barotrauma of the ears or sinuses and transient myopia being the most common.[2]

HBO therapy has been controversial from the start. For example, in 1987, Gabb et al.[3] stated in *Chest* that HBO was "... a therapy in search of diseases." The currently available scientific research is still criticized. Although the theoretical basis for the use of HBO therapy seems rational, and well-performed studies in animals and humans show positive effects, a large proportion of the evidence is anecdotal, retrospective, uncontrolled and underpowered. The increased application of evidence-based medicine has raised concerns about the overtreatment of patients, possibly causing unnecessary risks and higher costs in health care. Despite efforts by the Undersea and Hyperbaric Medical Society and (recently) the European Committee for Hyperbaric Medicine to establish recognized clinical indications, a need still exists for more and better research, particularly in the form of randomized controlled trials.[4] Because the outcome of such a trial can be biased by a placebo effect (especially in the case of subjective parameters), a sham treatment for the control group can be a valuable addition.

However, the design of such a trial is associated with several considerations regarding the sham treatment. The goal of a sham treatment is to ensure that patients and investigators are unable to distinguish sham from actual HBO therapy (thus filtering out a potential placebo effect), while the sham procedure must not have any effect on the disease being treated. Because patients have to auto-inflate their ears when pressure is increased in HBO therapy, sham therapy also has to use pressure to create/mimic this experience. However, every increase in pressure has an effect on the partial pressures of gases, potentially causing the sham treatment to become an active agent.

This dilemma, together with considerations regarding practicality, safety and blinding, has resulted in different strategies being used in various trials over the years, each with their own advantages and disadvantages. The aim of this narrative review is to provide a structured overview of all past randomized controlled trials that included sham (hyperbaric) treatment. The methodology is examined and, if available, the authors' considerations for the choice and the results of this methodology (regarding treatment profiles, blinding and safety) are presented. The findings of this review may help researchers to make a more balanced decision regarding the design of their specific trial.

Being a narrative review on the methodology of trials investigating hyperbaric medicine, there is no discussion on the indications for which HBO was applied, or on the efficacy and/or outcome of each trial.

Methods

Our aim was to provide a summary of past studies involving HBO therapy using a sham treatment. A systematic search of the literature was conducted using the following protocol.

Eligibility criteria

Included were all studies comparing actual HBO therapy with sham treatment, irrespective of the indication for treatment. It was expected that most of these studies would be randomized, but if any non-randomized controlled trial were encountered, these were also considered for inclusion. The control treatment was considered sham if no additional therapeutic effect to standard care was intended, and patients were blinded to their allocation. The minimum criterion for the blinding of patients was that the patients were located in a hyperbaric chamber (either monoplace or multiplace) during sham treatment; no restrictions were made regarding pressure or oxygen levels. Studies that did not meet this criteria (e.g. if patients were allowed to choose their own allocation, or if they received a gas mixture in a normal room) were excluded. Studies on children were excluded, because their treatment regimens (generally using a lower pressure) and blinding measures can differ from those applied in adults. Studies with only one session of HBO were also excluded, because that treatment regimen is dissimilar to a typical hyperbaric treatment which (generally) consists of multiple sessions, often administered over several weeks.

Database search

MEDLINE via PubMed, Embase via Ovid and the Cochrane Central Register of Controlled Trials were searched (up to April 2017) for sham-controlled studies on hyperbaric medicine. Medical subject heading (MeSH and Emtree) terms were used, in combination with keywords. Searches were limited to randomized controlled trials and trials including human adults and published in English. Details of the search strategies are presented in Appendix 1.

Other sources

The reference lists of the included studies and identified (systematic) reviews were screened to identify additional eligible studies. Also, the Database of Randomized Controlled Trials in Diving and Hyperbaric Medicine was searched by hand for articles on HBO.

Data collection

Data collection was performed by the first author (N.C.A.L.). Abstracts were screened for eligibility following the criteria mentioned above. After screening, information on the study sample, and on the sham and HBO profile (pressure, time, oxygen levels), was extracted from the full-text article.

The full text was also searched for considerations regarding the choice for a certain sham treatment profile, for information on blinding procedures and for the use of questionnaires on patients' perceived allocation. Information on the safety of the sham procedure was also collected, including details on any type of complications.

Results

The search of the databases and other sources yielded 477 articles. After removal of duplicates (including separate articles reporting on the same trial) and initial screening, 45 articles remained. After assessing the eligibility based on the full-text articles, 42 studies were finally included in the present review (Figure 1). All of these studies were randomized controlled trials.

Of the 42 included studies, analysis of the sham profiles revealed the use of three main strategies. Presented in chronological order as described in the literature, these are (1) use of a lower pressure than the HBO group, while breathing 21% oxygen; (2) use of the same pressure as the HBO group, while breathing a mixture with an adjusted percentage of oxygen; and (3) use of the same pressure as the HBO group, while breathing 21% oxygen.

The first strategy was used in 23 studies, with pressures in the sham group ranging from 1.1 to 1.5 ATA. An overview of these studies including considerations for the choice of profile, blinding measures and complications in the sham group as provided in the articles is presented in Table 1. The second strategy, using an adjusted percentage of oxygen for sham therapy while maintaining the same pressure as the HBO group, was used in 11 studies. Adjusted oxygen levels ranged from 7% to 41%. An overview is provided in Table 2. The third and last strategy (use of the same pressure with 21% oxygen in the sham group) was used in eight studies, of which the information is presented in Table 3. The advantages and disadvantages of all three strategies, using the information provided in the articles, are discussed separately below.

Discussion

Sham treatment using lower pressure than the HBO group while breathing 21% oxygen

The first documented trial that involved patient blinding using a sham treatment was a study performed by Hart et al.[5] in 1974. In that study, patients were exposed to either real HBO therapy (at 2.0 ATA) or to a sham therapy consisting of breathing 21% oxygen (i.e. normal air) at a considerably lower pressure (1.1 ATA) than the active treatment. The choice for this profile was not explained by the authors.

The advantage of using only a slight increase in pressure is that the partial pressure of oxygen also increases only slightly. Normally, at atmospheric pressure (1.0 ATA), 21% of the air consists of oxygen; this is equal to a partial pressure of oxygen of 0.21 ATA. If the atmospheric pressure is doubled to 2.0 ATA, the partial pressure of oxygen also doubles to 0.42 ATA. This is the equivalent of 42% oxygen under normal circumstances (i.e. 1.0 ATA).

In the study by Hart et al.,[5] 21% oxygen was used under a pressure of 1.1 ATA. This is the equivalent of breathing 23% oxygen under atmospheric pressure and, therefore, minimizes the effect on the inertness of the placebo. However, some claim that even a slight increase in the partial pressure of oxygen, or the mere use of pressure alone (irrespective of the partial pressures of the gases), could inflict changes in the body and interfere with the realization of an inert placebo. Although a small number of animal and cell culture studies support this claim, it is debatable whether these results are substantial enough to be used as an argument for clinical practice.[49,50]

Following the trial by Hart et al.,[5] concerns were raised about the effectiveness of blinding, given that no ear barotrauma occurred in the sham control group. If the use of 1.1–1.3 ATA had resulted in patients having to equalize their ears, one would also have expected more reports of complications.

Using a lower pressure for the sham treatment group has some practical implications related to blinding. Apart from masking the gas mixture that is being applied, care should also be taken to blind the interior/exterior of the chamber to prevent gauges or other devices being seen that might indicate the pressure. If the chamber operator or hyperbaric physician is unblinded, they should be instructed not to refer to the pressure used when in close vicinity to the patients and investigators and to use a percentage of pressure (rather than the actual pressure) when communicating with an (inside) chamber attendant. Using a different pressure also requires a separate daily session,

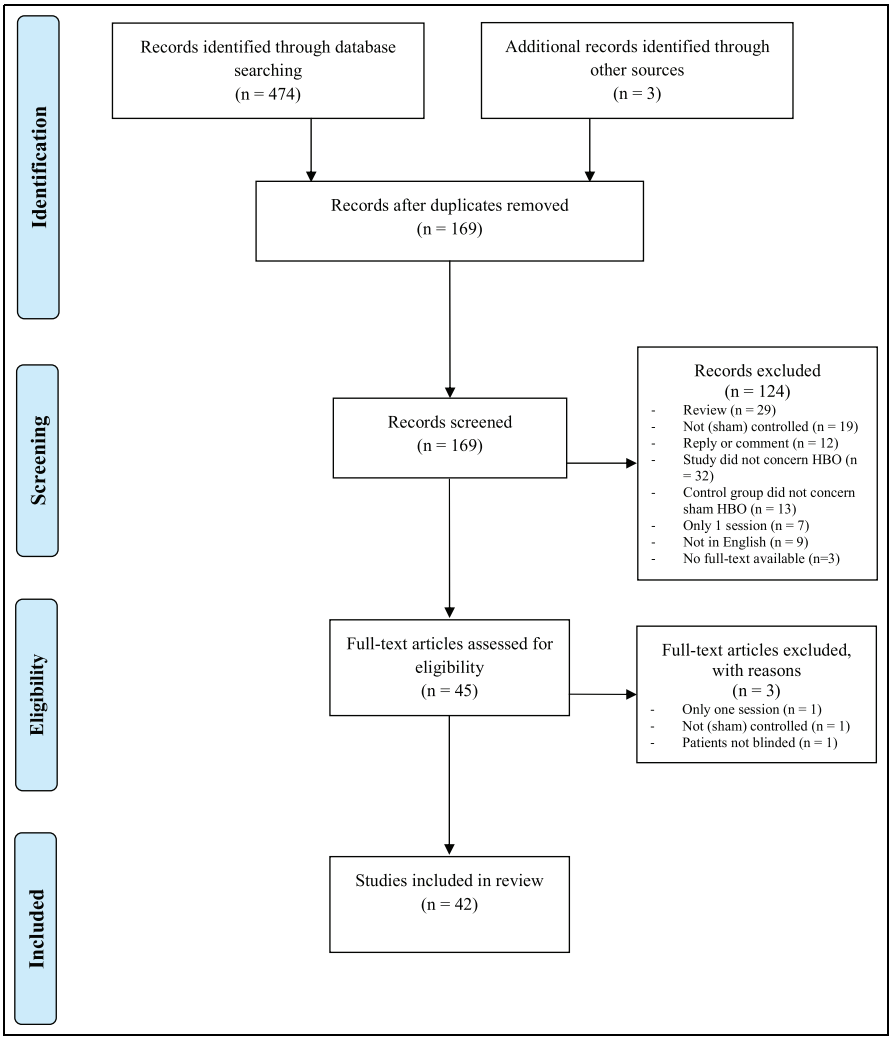

Figure 1. Flowchart showing identification of the eligible studies.

preferably scheduled so that the two groups cannot meet and compare experiences. The use of cluster or block randomization can minimize the impact of these precautions on daily practice. Additional practical measures used to prevent unblinding in these trials are presented in Table 1.

Sham treatment using the same pressure as the HBO group while breathing a mixture with an adjusted percentage of oxygen

The second documented double-blind trial used a different strategy and was performed in 1983 by Fischer et al.[30] In that study, the same pressure was used for both the HBO and the control groups (2.0 ATA). This reduced concerns about patients' perception of their allocation due to differences in pressure between the groups and made blinding easier because only the breathing mixture was different.

To correct for the increase in partial pressure of oxygen to 0.42 ATA for the control group, the breathing mixture for the control group was lowered in oxygen content by adding nitrogen. This resulted in a mixture of 10% oxygen and 90% nitrogen, allowing the control group to be exposed to about the same partial pressure of oxygen as normal (0.2 ATA). However, an increase in the nitrogen percentage in the breathing mixture also increases the risk for decompression sickness. In decompression sickness, nitrogen bubbles are formed inside the body once the patient is decompressed, resulting in symptoms ranging from joint pain and rashes to other neurological symptoms such as paresthesia and paresis. To prevent this, after the treatment, the period of time in which the pressure is lowered to normal has to be prolonged, by stopping once (or multiple times) during decompression; patients in the control group have to breathe 100% oxygen during decompression to get rid of any excess nitrogen.

Table 1. Studies using lower pressure and 21% oxygen for sham treatment, and information on choice of profile, blinding and safety provided by these studies.

Authors	Sample size (n)	Sessions	Active treatment	Sham treatment	Considerations for choice of profile	Information on blinding procedures	Information on safety of sham group
Hart et al.[5]	8 HBO 8 sham	At least three sessions, monoplace	100% oxygen at 2.0 ATA	21% oxygen, compression to 1.3 ATA, then reduced to 1.0 ATA, sequence repeated at end	Profile was chosen to give the illusion of having been under pressure	Physicians and patients were blinded and chamber operators were control officers	No ear barotrauma. One transient viremia during the course of sham treatment
Barnes et al.[6]	60 HBO 60 sham	20 sessions, multiplace	100% oxygen at 2.0 ATA	21% oxygen, compression to 1.1 ATA in 2 min, maintained for 10 min and then reduced to 1.0 ATA	None provided	Separate pipe-work system for air and oxygen, not visible to patients. Schedules were arranged so that the two groups could not meet	One case of claustrophobia, no other complications. No mention of procedures to record/score complications
Wiles et al.[7]	42 HBO 42 sham	20 sessions, monoplace	100% oxygen at 2.0 ATA	21% oxygen at 1.1 ATA	Sham profile was found to be virtually indistinguishable subjectively to actual treatment in preliminary experiments (no reference provided)	Patients could not see gas controls or delivery lines. Limited number of patients each day due to monoplace chambers, reducing opportunity for patients to compare experiences	Fourteen patients experienced complaints due to changes in pressure (10 ear discomfort, 3 deafness and 1 sinus pain). Other complaints were headache (4), leg pain (4), visual disturbance (3), nausea (1), fatigue (20) and anxiety (5). No mention of procedures to record/score complications
Neiman et al.[8]	10 HBO 9 sham	20 sessions, multiplace	100% oxygen at 2.0 ATA	21% oxygen, compression to 1.2 ATA, maintained for 5 min and then reduced to 1.0 ATA	None provided	Chamber operator unblinded	None provided (complications were mentioned but not separated for HBO and control groups)
Nigho-ghossian et al.[9]	17 HBO 17 sham	10 sessions, monoplace	100% oxygen at 1.5 ATA	21% oxygen at 1.2 ATA	Pressure was raised 0.2 ATA to mimic HBO pressure effect, no details provided	None provided	"Special attention was paid to recording side-effects usually expected with HBO treatment," no mention of actual procedure. No major side-effects related to therapy were observed in sham group
Boua chour et al.[10]	18 HBO 18 sham	12 sessions, multiplace	100% oxygen at 2.5 ATA	21% oxygen at 1.1 ATA	Sham profile was chosen to simulate compression and its effects on the ears	Patient and assessor of outcome were blinded	No complications were observed
Borromeo et al.[11]	16 HBO 16 sham	3 sessions, monoplace	100% oxygen at 2.0 ATA	21% oxygen at 1.1 ATA	None provided	"Patients experienced sensation of pressure increase in their ears." Chamber operator was unblinded, but did not let others know allocation. Pressure gauges were not visible	None provided
Staples et al.[12]	9 HBO 9 sham	3–5 sessions, chamber unknown	100% oxygen at 2.0 ATA	21% oxygen at 1.2 ATA	Use of minimal pressure for sham therapy was necessary for the breathing apparatus to function properly	None provided	None provided
Schein-kestel, 1999[13]	104 HBO 87 sham	3–6 sessions, multiplace	100% oxygen at 2.8 ATA	21% oxygen at 1.0 ATA	Chamber door was closed and chamber flushed with air regularly to simulate pressurization, but the chamber was not pressurized	Cluster randomization to minimize impact on daily practice. Hyperbaric technicians and nursing staff had knowledge of treatment groups but patients and outcome assessor did not	One patient with severe claustrophobia, no other complications for sham group. No information provided on procedures to record/score complications
Webster et al.[14]	6 HBO 6 sham	3 sessions, monoplace	100% oxygen at 2.5 ATA	21% oxygen at 1.3 ATA	1.3 ATA deemed sufficient enough to ensure symptoms of external pressure changes, but does not result in marked increases in oxygen tension	Gas supply to the chambers was covered with drapes. Protocol and sham procedures were the same, apart from the partial pressure of oxygen	Otoscopy was performed before and after each session in both groups to ensure no pathology was present, no mention of outcome

(continued)

Table 1. Continued

Authors	Sample size (n)	Sessions	Active treatment	Sham treatment	Considerations for choice of profile	Information on blinding procedures	Information on safety of sham group
Weaver et al.[15]	*76 HBO* *76 sham*	*3 sessions, monoplace*	*100% oxygen at 2.0–3.0 ATA*	*21%–100% oxygen at 1.0 ATA*	*First session on 100% oxygen as part of standard care. Ambient pressure outside was 0.85 ATA (hospital was situated at altitude), so difference in pressure was 0.15 ATA. Pressure was used to maintain blinding of patients and investigators*	*Pressure gauges visible only to respiratory therapist, who maintained separate confidential records of the chamber sessions to ensure that others were unaware of the treatment group assignments*	*Three patients failed to complete treatment in the sham group, no subdivision into reasons for failure*
Babul et al.[16]	*8 HBO* *8 sham*	*4 sessions, monoplace*	*100% oxygen at 2.0 ATA*	*21% oxygen, compression to 1.2 ATA and then reduced to 1.0 ATA*	*Patients were instructed to remove the mask while decompression was initiated, no mention of pressure changes during decompression*	*Authors deemed it unlikely for patients to determine their group designation, since the use of 1.2 ATA pressure is sufficient for equalization of ears (no reference provided)*	*None provided*
Yildiz et al.[17]	*26 HBO* *24 sham*	*15 sessions, chamber unknown*	*100% oxygen at 2.4 ATA*	*21% oxygen at 1.0 ATA*	*None provided; specifically no information on the use of 1.0 ATA for sham group and implications for blinding*	*Only physician administering therapy not blinded*	*Unblinding of treating physician was deemed necessary for evacuation purposes in the event of an emergency. No information on complications provided*
Vila et al.[18]	*18 HBO* *8 sham*	*10 sessions, multiplace*	*100% oxygen at 2.5 ATA*	*21% oxygen at 1.1 ATA*	*After sham treatment cross-over to HBO*	*Blinding of patients but not investigators*	*No complications in sham groups, no information on procedures to record/score complications*
Alex et al.[19]	*33 HBO* *31 sham*	*3 sessions, chamber unknown*	*100% oxygen at 2.4 ATA*	*21% oxygen at 1.5 ATA*	*Profiles for both groups based on "the optimum effect noted in previous studies and patient safety considerations." Authors refer to several articles showing no significant effect of air at 2.0 ATA on the indication being treated in this trial*	*Authors acknowledge the sham profile was not a true placebo, but found the use of 1.5 ATA necessary for blinding of patients. Patients and investigators were blinded, no mention of hyperbaric personnel*	*Lowering the oxygen content of the breathing mixture was not done because it would increase the risk of decompression sickness. Authors deemed the use of this sham protocol to be safe. No information on complications provided*
Van Ophoven et al.[20]	*14 HBO* *7 sham*	*30 sessions, multiplace*	*100% oxygen at 2.4 ATA*	*21% oxygen at 1.3 ATA*	*The chamber valves that regulate the air supply are pressure sensitive; therefore, providing patients with air is technically linked to a slight increase of chamber pressure*	*Only chamber operator unblinded. Instruments accessible or visible to patients were blinded. Authors claim distinction between mild and intense pressure is not easily achieved, no reference provided. Response rate for sham group was 0%; therefore, the authors question the blinding procedure, but hesitate to attribute this to potential unblinding*	*Some information on complications available, however, not separated completely for both groups and no mention of procedures to record/score complications*
Clarke et al.[21a]	*64 HBO* *56 sham*	*30–40 sessions, multiplace*	*100% oxygen at 2.0 ATA*	*21% oxygen, compression to 1.34 ATA and then reduced to 1.1 ATA*	*Higher pressure during initial compression was used for blinding purposes. Through the use of volunteer recreational SCUBA divers, it was found to be highly unlikely that differences between groups could be detected (no reference provided)*	*All references to chamber pressure and oxygen content were obscured from view. Hyperbaric team was unblinded, but care was taken not to comment on treatment allocation in the presence of others. Survey to determine perception of allocation (60% response), no significant differences*	*Information on complications not presented separately for the groups, except for ear barotrauma: five incidences of ear pain/discomfort, for which two decongestants, one ventilation tube and two no interventions. No complication compromised participation in the study. No information provided on procedures to record/score complications*
Kiralp et al.[22]	*20 HBO* *10 sham*	*10 sessions, multiplace*	*100% oxygen at 2.4 ATA*	*100% oxygen at 1.3 ATA*	*None provided, specifically no considerations concerning the use of 100% oxygen*	*Hyperbaric medicine physician not blinded for safety reasons*	*None provided*
Yuan et al.[23]	*12 HBO* *12 sham*	*14 sessions, multiplace*	*100% oxygen at 2.0 ATA*	*21% oxygen at 1.0 ATA*	*"Patients were administered ineffective oxygenation," no other information*	*None provided, specifically no information regarding the lack of increased pressure*	*No severe side-effects were observed. No mention of procedures to record/score complications*

(continued)

Table 1. Continued

Authors	Sample size (n)	Sessions	Active treatment	Sham treatment	Considerations for choice of profile	Information on blinding procedures	Information on safety of sham group
Miller et al.[24]	*24 HBO 23 sham*	*40 sessions, multiplace*	*100% oxygen at 1.5 ATA*	*21% oxygen at 1.2 ATA*	*Authors recognize that this sham is not inert and cannot completely discount the physiologic effects of increases in O_2/N_2 from pressurized room air, but believe it is biologically implausible that air at 1.2 ATA has a beneficial effect. The use of 1.2 ATA is able to provide adequate blinding (reference provided)*	*Chamber technician unblinded and kept a separate work area from other study personnel. Dive console hidden by a curtain so that gauges were not visible to other staff, and interior chamber gauges were covered. Extra chamber venting cycles to match hyperbaric session. Questionnaire to assess blinding at the end of trial, no results presented*	*Single hyperbaric exposure for all participants prior to randomization in order to assess claustrophobia and ability to equalize ear pressure. One claustrophobia/ anxiety (with discontinuation of chamber sessions), three sinus pain and one middle ear pain. No mention of procedures to record/score complications*
Wolf et al. [25a]	*25 HBO 25 sham*	*30 sessions, multiplace*	*100% oxygen at 2.4 ATA*	*21% oxygen, compression to 1.3 ATA and then reduced to 1.2 ATA*	*Based on earlier studies, authors found this profile minimized any "treatment" effect, with the blinding validated. The partial pressure resembles 27% oxygen at sea level, making it "even less of a consideration."*	*Chamber operator and attendant unblinded, medical monitors were not. Nondisclosure agreements were signed, Inside observers were instructed to perform a Valsalva maneuver every 10–30 s. Chamber operator would refer to percentage of pressure achieved. Venting was done in both groups to create similar temperature and noise levels. All clocks and pressure gauges were removed from inside the chamber, no watches or electronics were allowed inside the chamber. Pre-compression checklist including breathing gas mixture was confirmed by the inside observer where the subjects could hear; however, all 1.3 ATA exposures used air and all 2.4 ATA exposures 100% O_2. Survey to determine perception of allocation (32% response), no significant differences*	*Inside observers breathed oxygen three times during every exposure, regardless of the profile, to avoid decompression sickness. To track complications as defined by the Undersea and Hyperbaric Medical Society, monitors interviewed each subject daily, checked tympanic membranes and auscultated heart and lungs. Findings were annotated on a subject daily log. In addition, any medical or physical complaint was annotated in the dive record by the chamber operator; four patients had ear blocks (none of which required removal from the chamber) and one confinement anxiety. Myopia (defined as worsening of two or more Snellen lines) was not reported. Snellen was performed before, after and 6 weeks after treatment. Five sham eyes had a one-line decrease at 6-week follow-up. Interestingly, 25 eyes had a one-line increase, 7 a two-line increase and 1 eye a three-line increase at 6-week follow-up*
Glover et al.[26]	*55 HBO 29 sham*	*40 sessions, multiplace*	*100% oxygen at 2.4 ATA*	*21% oxygen at 1.3 ATA*	*None provided*	*Staff at the hyperbaric medicine facility unblinded. It was disallowed for a non-trial patient to share the chamber with a trial patient as the most important precaution in blinding*	*Three eye refractive changes, three increased fatigue or tiredness, six ear pain or barotrauma. No mention of procedures to record/score complications*
Fedorko et al.[27]	*49 HBO 54 sham*	*30 sessions, monoplace*	*100% oxygen at 2.4 ATA*	*21% oxygen at 1.25 ATA*	*Authors used this strategy because using a placebo of 21% oxygen at 2.5 ATA is "extreme with regards to decompression stress" and provide references to other studies on negative effects of single, shorter exposures, concluding that using this does not satisfy the criteria for an inert placebo*	*Only chamber operator was unblinded*	*Solicited and unsolicited complications were recorded. Solicited events were barotrauma (three patients) and visual changes (three patients). Unsolicited events were nausea (two patients) and hypoglycemic episode (two patients). No unsolicited barotraumas were observed. One patient was "unable to tolerate chambers."*

HBO: hyperbaric oxygen; ATA: atmosphere absolute pressure.
[a]Additional information on complications and blinding was found in later publications.[28,29]

Table 2. Studies using the same pressure and adjusted oxygen level for sham treatment, and information on choice of profile, blinding and safety provided by these studies.

Authors	Sample size (n)	Sessions	HBO profile*	Sham profile	Considerations in methodology of sham group	Information on blinding procedures	Information on safety of sham group
Fischer et al.[30]	*17 HBO* *20 sham*	*20 sessions, multiplace*	*100% oxygen at 2.0 ATA*	*10% oxygen at 2.0 ATA*	*None provided*	*Chief chamber operator unblinded. Separate team measured arterial oxygen via puncture, results were recorded and sealed afterwards to ensure effective blinding. It was visually impossible to trace the piping leading from the oxygen and air storage compartment to the actual oxygen and air outlets inside the chamber. Air and oxygen are indistinguishable to the breather. Authors suggest that myopia in a patient might unblind an investigator, since no myopia was found in this trial in the sham group*	*Three patients had minor and transient ear discomfort, with none of them having direct damage to the tympanic membrane. No myopia in the control group (assessed by patients history, and if myopia was present based on the complaints serial fundoscopic examinations were made, without changes). No other mention of procedures to record/ score complications*
Wood et al.[31]	*21 HBO* 20 sham	*20 sessions, multiplace*	*100% oxygen at 2.0 ATA*	*10% oxygen at 2.0 ATA*	*None provided*	*Gas mixtures were breathed through identical apparatus*	*All masks were removed before decompression to prevent hypoxia in the placebo group. Random end-expired oxygen levels and transcutaneous oxygen analyses to measure oxygen delivery. Patients were seen daily and questioned about possible complications. Three withdrawals in sham group due to equalization problems. Several patients complained of blurring of vision, no subdivision between the groups*
Harpur et al.[32]	*41 HBO,* *41 sham*	*20 sessions + boosters, multiplace*	*100% oxygen at 1.75 ATA*	*12.5% oxygen at 1.75 ATA*	*None provided.*	*Gas supply to mask by concealed piping from coded connectors. Tender responsible for connecting equipment was blind to the gas delivered. Chamber operator responsible for control of the gas mixture was unblinded. Survey to determine perception of allocation after 12th exposure and completion of trial: blind was preserved, with most patients thinking they received air after completion (most likely due to the lack of anticipated benefit).*	*Percentage of oxygen in the expired gas was monitored, as well as transcutaneous oximetry. No information on complications provided (complications were mentioned but not separately for HBO and control group).*
Bojic et al.[33]	*31 HBO* *20 sham*	*30 sessions, chamber unknown*	*100% oxygen at 2.0 ATA*	*10.5% oxygen at 2.0 ATA*	*None provided*	*None provided*	*None provided*
Niezgoda et al.[34]	*6 HBO* *6 sham*	*6 sessions, multiplace*	*100% oxygen at 2.4 ATA*	*8.75% oxygen at 2.4 ATA, 100% oxygen during decompression*	*Oxygen during decompression may have decreased differences between groups*	*Hyperbaric facility was equipped to conduct blinded hyperbaric treatments. All participants in study blinded, including chamber operator*	*Single hyperbaric exposure for all participants prior to inclusion. 100% oxygen during decompression to prevent decompression sickness. No information on complications provided.*
Racic et al.[35]	*37 HBO* *42 sham*	*Average of 18 sessions, multiplace*	*100% oxygen at 2.8 ATA*	*7% oxygen at 2.8 ATA*	*Relatively high pressure considered acceptable during preliminary study, but no reference provided*	*None provided*	*Decompression stop for both groups to prevent decompression sickness. No information on complications provided*

(continued)

Table 2. Continued

Authors	Sample size (n)	Sessions	HBO profile*	Sham profile	Considerations in methodology of sham group	Information on blinding procedures	Information on safety of sham group
Mekjavic et al.[36]	*12 HBO* *12 sham*	*7 sessions, multiplace*	*100% oxygen at 2.5 ATA*	*8% oxygen at 2.5 ATA*	*None provided*	*One of four investigators was blinded + all patients, no details provided*	*Decompression stops to prevent decompression sickness for both groups. No information on complications provided*
Pritchard et al.[37]	*17 HBO* *17 sham*	*30 sessions, multiplace*	*100% oxygen at 2.4 ATA*	*41% oxygen at 2.4 ATA*	*Enrichment of the gas mixture to avoid risk of decompression sickness with no effect on the indication being investigated (reference provided), making it a "reliable comparator"*	*Breathing system of hyperbaric chamber was configured so that patients were unaware of the group to which they were allocated. Chamber operator and statistician unblinded*	*None provided*
Nilsson et al.[38]	*8 HBO* *8 sham*	*2 sessions, multiplace*	*100% oxygen at 2.5 ATA*	*10% oxygen at 2.5 ATA*	*None provided*	*Gases administered from paired blinded gas cylinders*	*Decompression on air using "equivalent N2-pressure" to calculate safe tables. No information on complications provided*
Annane et al.[39]	*31 HBO* *37 sham*	*30 sessions, multiplace*	*100% oxygen at 2.4 ATA*	*9% oxygen at 2.4 ATA*	*Authors found no previous data suggesting that high pressure itself or a high concentration of nitrogen may impact the healing process*	*Only chamber operators unblinded*	*Arterial oxygen tension was monitored and pharmacist checked fraction of inspired oxygen during each session to ensure correct treatment. One patient with seizures (due to brain metastasis), six patients with otic barotrauma. No mention of procedures to record/score complications. "Technical problems" in two patients, no details provided*
Cifu et al.[40]	*40 HBO* *21 sham*	*40 sessions, multiplace*	*75%–100% oxygen at 2.0 ATA*	*10.5% oxygen at 2.0 ATA*	*2.0 ATA for all three groups was chosen to minimize patients noting differential pressures*	*None provided*	*None provided*

*HBO: hyperbaric oxygen; ATA: atmosphere absolute.

Table 3. Studies using the same pressure and 21% oxygen for sham treatment, and information on choice of profile, blinding and safety provided by these studies.

Authors	Sample size (n)	Sessions	HBO profile*	Sham profile	Considerations in methodology of sham group	Information on blinding procedures	Information on safety of sham group
Oriani et al.[41]	*22 HBO* *22 sham*	*20 sessions + boosters, multiplace*	*100% oxygen at 2.5 ATA*	*20% oxygen at 2.5 ATA*	*None provided, specifically no explanation for 20% oxygen instead of 21%*	*Air and oxygen piping leading systems were indistinguishable to the patients*	*"Problems related to pressurization were of minor importance, consisting mainly of ear discomfort and anxiety." Not reported separately for each group. No mention of procedures to record/score complications.*
Anderson et al.[42]	*20 HBO* *19 sham*	*15 sessions, monoplace*	*15 sessions of 100% oxygen at 1.5 ATA*	*15 sessions of 21% oxygen at 1.5 ATA*	*None provided*	*None provided*	*None provided (complications were mentioned but not separately for the HBO and control group)*
Hammar lund and Sundberg[43]	*8 HBO* *8 sham*	*30 sessions, multiplace*	*100% oxygen at 2.5 ATA*	*21% oxygen at 2.5 ATA*	*Oxygen percentage was not adjusted to avoid risk of decompression sickness. Authors feel that if the increase in oxygen partial pressure would have affected the wound healing, it would likely be in the same manner as in the oxygen group, with the differences shown between groups consequently smaller. No significant changes in wound area in the control group, although minor changes were seen in some wounds*	*Two extra pipes were arranged to penetrate the chamber wall, marked "gold-gas" and "silver-gas."Gas supplies were blinded for all persons involved, except for the technician who connected the gas pipes (on the basis of a tossed coin). Due to the separate pipes, patients from both groups could be treated at the same time. A reduction valve was installed to exactly match the air pressure to the oxygen pressure*	*None provided*
Abidia et al.[44]	*9 HBO* *9 sham*	*30 sessions, multiplace*	*100% oxygen at 2.4 ATA*	*21% oxygen at 2.4 ATA*	*Authors acknowledge that the control group received an amount of oxygen equal to 50% at sea level, but claim "this is generally considered to be insufficient to produce any clinical effect in this group of patients."*	*Chamber operator unblinded. Patients were questioned about their allocation at the end of the study: the majority of patients believed that they received the active treatment, the remainder were unable to guess. No patients believed that they were in the control group*	*Decompression time was extended in both groups to avoid giving oxygen to the sham group in order to prevent decompression sickness. No complications in either of the groups, no mention of procedures to record/score complications*
Kiralp et al.[45]	*37 HBO* *34 sham*	*15 sessions, chamber unknown*	*100% oxygen at 2.4 ATA*	*21% oxygen at 2.4 ATA*	*None provided*	*Only the physician administering treatment was unblinded*	*The administering physician was unblinded to enhance safety. No information was provided on complications*
Eftedal et al.[46]	*19 HBO* *15 sham*	*3 sessions, monoplace*	*100% oxygen at 2.0 ATA*	*21% oxygen at 2.0 ATA*	*21% oxygen was chosen over 10.5% oxygen to minimize the risk of decompression sickness. Authors acknowledge that the control treatment was not strictly placebo as the oxygen partial pressure was twice that of breathing air at sea level*	*Only chamber operator had knowledge of treatment allocation and arterial oxygen levels. Chamber operator was specifically instructed not to discuss the topic of treatment gas with patients or any other study participants*	*Arterial oxygen levels were assessed using a transcutaneous oximeter. No information on complications was provided: only two withdrawals due to claustrophobia were mentioned, but not reported separately for the two groups*
Camporesi et al.[47]	*10 HBO* *10 sham*	*30 sessions, multiplace*	*100% oxygen at 2.5 ATA*	*21% oxygen at 2.5 ATA*	*None provided*	*Physician overseeing daily treatments was unblinded*	*Oxygen concentration in the mask was measured every 5 min to ensure adequacy of the gas supply. Treatment was well tolerated by both groups; no cerebral complications, otalgia or other complications. No mention of procedures to record/score complications*
Londähl et al.[48]	*49 HBO* *45 sham*	*40 sessions, multiplace*	*100% oxygen at 2.5 ATA*	*21% oxygen at 2.5 ATA*	*None provided*	*Study gases administered through separate double-blinded pipes*	*Two patients required ventilation tubes due to inability to equalize ears. Other complications were hypoglycemia (four patients), anxiety (one patient), temporary loss of consciousness after sessions (one patient) and minor head injury after a fall in the chamber (one patient). No mention was made of procedures to record/score complications*

*HBO: hyperbaric oxygen; ATA: atmosphere absolute.

In the present review, of the 11 trials applying this strategy, 3 used stops in the decompression to prevent decompression sickness,[35,36,38] and 1 trial administered 100% oxygen during decompression.[34] Other trials did not mention the risk of decompression sickness or the way that this risk was minimalized. The authors of the study using 100% oxygen during decompression acknowledged that the use of this strategy may have negatively influenced the inertness of the placebo, possibly decreasing the differences in outcome between the groups.[34]

When blinding measures are limited to the breathing gas alone, patients of the two groups can receive treatment during the same session (in case of a multichamber). Separate piping systems for air and oxygen can be installed relatively easily, as long as the systems are (visibly) indistinguishable from one another. To ensure that the appropriate breathing mixture is applied, oxygen concentration in the mask, or arterial oxygen tension, can be measured. For this reason and for other safety reasons (e.g. in case of an evacuation) in most studies, the chamber operator and/or the hyperbaric physician was unblinded. As mentioned, unblinded staff should be instructed not to discuss the topic of treatment gas with the patients or any other study participants.

Sham treatment using the same pressure as the HBO group while breathing 21% oxygen

In 1990, Oriani et al.[41] introduced a third strategy: 2.0 ATA for both groups, with the control group breathing 21% oxygen, instead of correcting the percentage of oxygen to keep the partial pressure of oxygen at 0.21 ATA. As mentioned, this resulted in the control group breathing the equivalent of 42% oxygen under atmospheric pressure. In the present review, seven other trials used this same strategy, with a maximal partial pressure of oxygen of 0.53 ATA. However, it is debatable whether this strategy can be considered to deliver a true placebo. For example, Greif et al.[51] showed that patients receiving 80% oxygen during and 2 h after colorectal resection had 50% fewer surgical wound infections than patients receiving 30% oxygen. The amount of oxygen that can be therapeutic is likely to depend on the disease being treated; however, in the absence of sufficient evidence regarding the different oxygen fractions in relation to (patho)physiology, the use of 53% oxygen for a placebo might be incorrect. Of the 42 studies in the present review, only two cited previous studies that showed no effect of an increased oxygen partial pressure on the condition being investigated, to justify their choice of a sham profile.[19,37] In contrast, in 2016, Fedorko et al.[27] stated that using a placebo of 21% oxygen is "... extreme regarding decompression stress" and cited earlier studies reporting the negative effects (endothelial injury, proinflammatory changes and significant venous gas emboli) of single, shorter exposures; these authors concluded that using this particular profile does not satisfy the criteria for an inert placebo.

Of the eight trials that used 21% oxygen at the same pressure as the actual treatment, only three discussed the choice for this sham profile. Two groups preferred the use of 21% oxygen over an adjusted percentage to avoid the risk of decompression sickness,[43,46] and the other claimed that the equivalent of 50% oxygen "... is generally considered to be insufficient to produce any clinical effect in this group of patients."[44] Unfortunately, the authors presented no evidence for this claim.

Blinding perception as reported by patients

In the first double-blind trial (performed by Hart et al.[5]), the lack of barotrauma raised questions about the adequacy of blinding measures, especially regarding the use of a lower pressure. However, sequential trials using the same strategy reported problems with equalization: even the use of ventilation tubes in the sham group was reported.[28] This would imply that blinding was adequate.

To further investigate blinding perception by patients, in some trials, the patients were asked about their allocation: at the end of treatment, patients were asked whether they thought they had received HBO therapy, sham treatment or if they did not know. In the present review, for each of the three strategies identified, at least one randomized controlled trial had provided information on this topic. All studies concluded that there was no relationship between patients' perception and their actual allocation, thereby concluding that blinding had been adequate.[25,28,32,44] In addition, in 2008, Clarke[28] stated that "... through the use of volunteer recreational Scuba divers it was found to be highly unlikely that differences between groups could be detected." Unfortunately, no reference was provided to support their statement.

Apart from the information emerging from the trials in the present review, concerns were raised by others about the blinding perception of patients when using sham treatment. For example, in 2008, Rainolds and Long[52] used experienced scuba divers to assess whether they could differentiate between the use of 1.2 and 2.0 ATA; their study showed that even the most experienced divers (>500 dives) were unable to make this distinction. It is important to mention that this latter study used "... subtle pressure variations toward the attainment of the final target pressure" to ensure that patients in both groups had to constantly auto-inflate their ears during the first 10 min of compression. In the present review, none of the trials reported use of this latter strategy.

In 2009, Jansen et al. investigated the blinding of volunteers who had no prior experience in hyperbaric treatment or diving. They were asked to guess if they were pressurized to 1.2 or 2.5 ATA and how certain they were about this. Most volunteers reported to be quite certain they were exposed to 2.5 ATA, even though this opinion proved to be (statistically) invalid.[53]

In 2012, Weaver et al. asked divers and experienced chamber attendants to estimate the pressure (1.2 or 1.5 ATA) and breathing gas (air or oxygen) that was being applied. Again, the conclusion was that no distinction could be made.[54] In 2015, this latter study was cited by Miller et al.[24] to justify the choice for 1.2 ATA in their sham group.

Based on the present research and the data from patient questionnaires in various randomized controlled trials, it can be concluded that adequate blinding of patients is possible, even when using a pressure lower than that of the actual treatment.

Complications in the sham group

A possible consequence of using pressure for the sham group to ensure adequate patient blinding is the occurrence of barotrauma. In our 42 studies, barotrauma was observed with the use of each of the three strategies. Even the use of minimal pressure resulted in complications: for example, in 1986, Wiles et al.[7] used 1.1 ATA for the sham group, with 14 patients experiencing complaints due to changes in pressure (10 ear discomfort, 3 deafness and 1 sinus pain). As mentioned, even the use of ventilation tubes was reported in sham treatment using lower pressures.[28] Two trials mentioned giving a single hyperbaric exposure to each participant prior to inclusion in the trial to prevent barotrauma during the study.[24,34] Moreover, the manner in which barotrauma is scored and reported is often unclear: most studies seem to rely on patients' complaints, with only two studies mentioning that patients were explicitly questioned about the occurrence of the most common complications.[27,31] Only three studies mentioned the use of otoscopy to objectively assess barotrauma of the ears.[14,29,30]

With regard to another common complication, myopia, in 1983, Fischer et al.[30] suggested that the fact that no myopia was seen in their sham group might potentially unblind an investigator. However, later research showed that myopia appeared in the sham group with the use of each of the three strategies. This could either be an effect of the (slight) increase in pressure and/or oxygen partial pressure or a placebo effect. Unfortunately, information on the method used to determine myopia is often missing and is most likely based on patients' complaints only. One study made a routine eye examination using a Snellen chart before, immediately after and 6 weeks after treatment to determine visual changes. No myopia (defined as a decrease of $\geq$2 Snellen lines) was seen in either the HBO or sham group. Interestingly, an increase in vision was reported in some patients, with up to three Snellen lines in one patient in the control group.[29] However, since the pathophysiology of myopia in HBO therapy remains unclear, it is uncertain how these results can best be interpreted.

Apart from barotrauma and myopia, claustrophobia was also reported in sham therapy. However, this can be expected, since the environment for patients in the sham group is similar to that for the HBO therapy group, in which claustrophobia is a well-known complication.[2] There were no reports of serious complications, such as oxygen toxicity (not expected with the partial pressures of oxygen used for sham treatment), decompression sickness or lung barotrauma.

Conclusion

This review examined different strategies used in the past to create a sham (hyperbaric) treatment. This is important because with the increased application of evidence-based medicine, randomized controlled trials are a frequently requested type of research. In such a trial, the addition of a sham treatment implies a considerable burden for patients not receiving actual treatment, including the time involved and the risk of complications (e.g. barotrauma of the ears). This means that performing such a trial is associated with ethical considerations, especially if performed with a vulnerable patient population, such as the elderly or the critically ill. However, especially in research where outcomes are patient reported, the inclusion of sham treatment can be a valuable addition to a trial.

All trials included in this review followed one of the three sham profiles: use of a lower pressure than the HBO group, while breathing 21% oxygen; use of the same pressure as the HBO group, while breathing a mixture with an adjusted percentage of oxygen; and use of the same pressure as the HBO group, while breathing 21% oxygen. The advantages and disadvantages of these strategies concerning blinding procedures, practicality, safety and inertness of placebo have been discussed.

The use of minimal pressurization and 21% oxygen was found to provide adequate blinding and cause the least interference on partial pressure of gases and, therefore, in creating an inert placebo. Although this strategy is associated with additional considerations regarding practicality and blinding measures, it is the most frequently used and documented profile. Considerable care is required when deciding which sham procedure to use; moreover, researchers need to report in detail the measures that were taken to ensure adequate performance of the chosen strategy.

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References

1. Lindell K and Weaver MD. *Hyperbaric oxygen therapy indications*. 13th ed. North Palm Beach, FL: Best Publishing Company, 2014.
2. Camporesi EM. Side effects of hyperbaric oxygen therapy. *Undersea Hyperb Med* 2014; 41: 253–257.
3. Gabb G and Robin ED. Hyperbaric oxygen. A therapy in search of diseases. *Chest* 1987; 92: 1074–1082.
4. Mathieu D, Marroni A and Kot J. Tenth European consensus conference on hyperbaric medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb Med* 2017; 47: 24–32.
5. Hart GB, O'Reilly RR, Broussard ND, et al. Treatment of burns with hyperbaric oxygen. *Surg Gynecol Obstet* 1974; 139: 693–696.
6. Barnes MP, Bates D, Cartlidge NE, et al. Hyperbaric oxygen and multiple sclerosis: short-term results of a placebo-controlled, double-blind trial. *Lancet* 1985; 1: 297–300.
7. Wiles CM, Clarke CR, Irwin HP, et al. Hyperbaric oxygen in multiple sclerosis: a double blind trial. *Br Med J* 1986; 292: 367–371.
8. Neiman J, Nilsson BY, Barr PO, et al. Hyperbaric oxygen in chronic progressive multiple sclerosis: visual evoked potentials and clinical effects. *J Neurol Neurosurg Psychiatry* 1985; 48: 497–500.
9. Nighoghossian N, Trouillas P, Adeleine P, et al. Hyperbaric oxygen in the treatment of acute ischemic stroke. A double-blind pilot study. *Stroke* 1995; 26: 1369–1372.
10. Bouachour G, Cronier P, Gouello JP, et al. Hyperbaric oxygen therapy in the management of crush injuries: a randomized double-blind placebo-controlled clinical trial. *J Trauma* 1996; 41: 333–339.
11. Borromeo CN, Ryan JL, Marchetto PA, et al. Hyperbaric oxygen therapy for acute ankle sprains. *Am J Sports Med* 1997; 25: 619–625.
12. Staples JR, Clement DB, Taunton JE, et al. Effects of hyperbaric oxygen on a human model of injury. *Am J Sports Med* 1999; 27: 600–605.
13. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled trial. *Med J Aust* 1999; 170(5): 203–10
14. Webster A, Syrotuik D, Bell G, et al. Effects of hyperbaric oxygen on recovery from exercise-induced muscle damage in humans. *Clin J Sport Med* 2002; 12: 139–150.
15. Weaver L, Hopkins R, Chan K, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med* 2002; 347: 1057–1067.
16. Babul S, Rhodes E, Taunton J, et al. Effects of intermittent exposure to hyperbaric oxygen for the treatment of an acute soft tissue injury. *Clin J Sport Med* 2003; 13: 138–147.
17. Yildiz S, Kiralp MZ, Akin A, et al. A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy. *J Int Med Res* 2004; 32: 263–267.
18. Vila J, Balcarce P, Abiusi G, et al. Improvement in motor and cognitive impairment after hyperbaric oxygen therapy in a selected group of patients with cerebrovascular disease: a prospective single-blind controlled trial. *Undersea Hyperb Med* 2005; 32: 341–349.
19. Alex J, Laden G, Cale ARJ, et al. Pretreatment with hyperbaric oxygen and its effect on neuropsychometric dysfunction and systemic inflammatory response after cardiopulmonary bypass: a prospective randomized double-blind trial. *J Thorac Cardiovasc Surg* 2005; 130: 1623–1630.
20. Van Ophoven A, Rossbach G, Pajonk F, et al. Safety and efficacy of hyperbaric oxygen therapy for the treatment of interstitial cystitis: a randomized, sham controlled, double-blind trial. *J Urol* 2006; 176: 1442–1446.
21. Clarke RE, Tenorio LM, Hussey JR, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; 72: 134–143.
22. Kiralp M, Uzun G, Dinçer O, et al. A novel treatment modality for myofascial pain syndrome: hyperbaric oxygen therapy. *J Natl Med Assoc* 2009; 101: 77–80.
23. Yuan JB, Yang LY, Wang YH, et al. Hyperbaric oxygen therapy for recovery of erectile function after posterior urethral reconstruction. *Int Urol Nephrol* 2011; 43: 755–761.
24. Miller RS, Weaver LK, Bahraini N, et al. Effects of hyperbaric oxygen on symptoms and quality of life among service members with persistent postconcussion symptoms: a randomized clinical trial. *JAMA Intern Med* 2015; 175: 43–52.
25. Wolf G, Cifu D, Baugh L, et al. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. *J Neurotrauma* 2012; 29: 2606–2612.
26. Glover M, Smerdon GR, Andreyev HJ, et al. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial. *Lancet Oncol* 2016; 17: 224–233.
27. Fedorko L, Bowen JM, Jones W, et al. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. *Diabetes Care* 2016; 39: 392–399.
28. Clarke D. Effective patient blinding during hyperbaric trials. *Undersea Hyperb Med* 2009; 36: 13–17.
29. Wolf EG, Prye J, Michaelson R, et al. Hyperbaric side effects in a traumatic brain injury randomized clinical trial. *Undersea Hyperb Med* 2012; 39: 1075–1082.
30. Fischer BH, Marks M and Reich T. Hyperbaric-oxygen treatment of multiple sclerosis. A randomized, placebo-controlled, double-blind study. *N Engl J Med* 1983; 308: 181–186.

31. Wood J, Stell R, Unsworth I, et al. A double-blind trial of hyperbaric oxygen in the treatment of multiple sclerosis. *Med J Aust* 1985; 143: 238–240.
32. Harpur GD, Suke R, Bass BH, et al. Hyperbaric oxygen therapy in chronic stable multiple sclerosis: double-blind study. *Neurology* 1986; 36: 988–991.
33. Bojic L, Racic G, Gosovic S, et al. The effect of hyperbaric oxygen breathing on the visual field in glaucoma. *Acta Ophthalmol* 1993; 71: 315–319.
34. Niezgoda JA, Cianci P, Folden BW, et al. The effect of hyperbaric oxygen therapy on a burn wound model in human volunteers. *Plast Reconstr Surg* 1997; 99: 1620–1625.
35. Racic G, Denoble P, Sprem N, et al. Hyperbaric oxygen as a therapy of Bell's palsy. *Undersea Hyperb Med* 1997; 24: 35–38.
36. Mekjavic I, Exner J, Tesch P, et al. Hyperbaric oxygen therapy does not affect recovery from delayed onset muscle soreness. *Med Sci Sports Exerc* 2000; 32: 558–563.
37. Pritchard J, Anand P, Broome J, et al. Double-blind randomized phase II study of hyperbaric oxygen in patients with radiation-induced brachial plexopathy. *Radiother Oncol* 2001; 58: 279–286.
38. Nilsson RAI, Ansjon R, Lind F, et al. Hyperbaric oxygen treatment of active cluster headache: a double-blind placebo-controlled cross-over study. *Cephalalgia* 2002; 22: 730–739.
39. Annane D, Depondt J, Aubert P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004; 22: 4893–4900.
40. Cifu DX, Hart BB, West SL, et al. The effect of hyperbaric oxygen on persistent postconcussion symptoms. *J Head Trauma Rehabil* 2014; 29: 11–20.
41. Oriani G, Barbieri S and Cislaghi G. Long-term hyperbaric oxygen in multiple sclerosis: a placebo-controlled, double-blind trial with evoked potentials study. *J Hyper Med* 1990; 5: 237–245.
42. Anderson DC, Bottini AG, Jagiella WM, et al. A pilot study of hyperbaric oxygen in the treatment of human stroke. *Stroke* 1991; 22: 1137–1142.
43. Hammarlund C and Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. *Plast Reconstr Surg* 1994; 93: 829–833.
44. Abidia A, Laden G, Kuhan G, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomized-controlled trial. *Eur J Vasc Endovasc Surg* 2003; 25: 513–518.
45. Kiralp MZ, Yildiz S, Vural D, et al. Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome. *J Int Med Res* 2004; 32: 258–262.
46. Eftedal OS, Lydersen S, Helde G, et al. A randomized, double blind study of the prophylactic effect of hyperbaric oxygen therapy on migraine. *Cephalalgia* 2004; 24: 639–644.
47. Camporesi EM, Vezzani G, Bosco G, et al. Hyperbaric oxygen therapy in femoral head necrosis. *J Arthroplasty* 2010; 25(6 Suppl.): 118–123.
48. Löndahl M, Katzman P, Nilsson A, et al. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010; 33: 998–1003.
49. Figueroa XA and Wright JK. Hyperbaric oxygen: B-level evidence in mild traumatic brain injury clinical trials. *Neurology* 2016; 87: 1400–1406.
50. Mitchell SJ and Bennett MH. Unestablished indications for hyperbaric oxygen therapy. *Diving Hyperb Med* 2014; 44: 228–234.
51. Greif R, Akca O, Horn EP, et al. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 2000; 342: 161–167.
52. Rainolds D and Long R. Blinding the blinded—assessing the effectiveness of a sham treatment in a multiplace hyperbaric chamber trial. *Diving Hyperb Med* 2008; 38: 3–7.
53. Jansen T, Mortensen CR and Tvede MF. It is possible to perform a double-blind hyperbaric session: a double-blinded randomized trial performed on healthy volunteers. *Undersea Hyperb Med* 2009; 36: 347–351.
54. Weaver LK, Churchill SK, Bell J, et al. A blinded trial to investigate whether "pressure-familiar" individuals can determine chamber pressure. *Undersea Hyperb Med* 2012; 39: 801–805.

Appendix 1

Search strategies used to search electronic databases.

Electronic database	Search strategy used	Restrictions	No. of hits up to April 2017
MEDLINE searched via PubMed (https://www.ncbi.nlm.nih.gov/pubmed)	("Hyperbaric Oxygenation"[MAJR] OR "HBO" OR "HBOT" OR "hyperbaric oxygen therapy" OR "hyperbaric oxygen") AND ("Placebos" [MeSH] OR placebo*[tiab] OR sham*[tiab] OR double-blin*[tiab]) NOT "Child"[MeSH]	Humans only; Randomized controlled trials; Published in English	67
EMBASE searched via Ovid (https://ovidsp.ovid.com/)	exp hyperbaric oxygen/or exp hyperbaric oxygen therapy/or HBO*.mp or hyperbaric oxygen*.mp and (exp placebo/ or placebo*.mp. or sham*.mp. or double-blin*.mp.) not child*.mp	Humans only; Randomized controlled trials; Published in English	118
CENTRAL searched via Cochrane Library (www.thecochranelibrary.com)	#1: MeSH descriptor: [Hyperbaric oxygenation] explode all trees #2: MeSH descriptor: [Placebos] explode all trees (#1 or HBO* or hyperbaric oxygen*) and (#2 or sham* or double-blind* or placebo*) not (child*)	Trials only	289