Original articles

Blinding the blinded – assessing the effectiveness of a sham treatment in a multiplace hyperbaric chamber trial

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Hyperbaric research, hyperbaric oxygen, profile, hyperbaric facilities

Abstract

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Hyperbaric oxygen therapy (HBOT) is used for a variety of problem wounds as an adjunctive treatment. The therapeutic impact of adding HBOT to a wound-healing regimen in many cases remains unclear and an ongoing need exists for additional randomised controlled trials. Many of these clinical studies require a sham group of study participants. To date, there has not been any published research on the concealment of sham treatments in multiplace hyperbaric chambers. The aim of this pilot project was to validate the existing blinding procedures used at one hyperbaric facility. Sixty-six volunteer recreational scuba divers, who had not previously been exposed to compression in a hyperbaric chamber, were recruited through local dive shops. One group was pressurised to 203 kPa and the other was minimally pressurised to 121 kPa, the minimum pressure required to cause middle ear pressure changes. Both protocols implemented continuous, though subtle, pressure variations toward the attainment of the final target pressure. A nearly identical number of subjects in both the 203 kPa (n = 32) and 121 kPa (n = 34) groups believed they had undergone a treatment pressure to 203 kPa (72% versus 71%) indicating a similarity of perception between the two groups.

Introduction

Hyperbaric oxygen therapy (HBOT) consists of the administration of 100% oxygen (O_2) at pressures above 101.3 kPa (1.0 ATA). The Undersea and Hyperbaric Medical Society, an important source of information for diving and hyperbaric medicine physiology worldwide, lists 13 indications for HBOT. Eleven of these are non-diving related, e.g., carbon monoxide poisoning, clostridial infections, acute traumatic ischaemias, and enhancement of healing in selected problem wounds. A common use for HBOT is as an adjunctive modality in the healing of chronic or hypoxic wounds. A typical session for wound healing requires the patient to breathe the increased partial pressure of oxygen (PPO_2) for periods of 90–120 minutes. Therapy can be delivered in either a monoplace or multiplace chamber and is typically given once a day for several weeks until the wound is either healed or healing.

To scientifically validate the purported benefits of adjunctive HBOT against existing wound-healing regimens, additional randomised controlled trials (RCTs) need to be undertaken. Exaggerated claims of the benefits of HBOT by some have increased scepticism towards hyperbaric medicine among many in the general medical community. This has further highlighted the need for carefully designed and conducted trials.

Historically, blinded hyperbaric trials have utilised one of two techniques for creating a sham treatment – either the breathing gas mixture is altered or the treatment pressure is maintained at or near 101.3 kPa. As the former technique has certain disadvantages related to cost, complexity and patient risk, it is more common for the pressure to be varied between the sham and treatment groups. The aim of this project was an attempt to validate the existing blinding procedure used at our facility, the Wesley Centre for Hyperbaric Medicine (WCHM). Since this is the first published trial of its kind, we believe it may offer other multiplace hyperbaric facilities a protocol for blinding subjects for their own research.

Techniques of blinding in a multiplace hyperbaric chamber

OPTION ONE

Both the treatment and sham groups are compressed to identical pressures but the sham group breathes a reduced PPO_2 thus breathing a normoxic mixture at pressure. An example of this technique would be to have the treatment group breathe 100% O_2 at 203 kPa (2.0 ATA) and the sham group breathe a 10% O_2 mix also at 203 kPa. This method has been effectively used in the past and has the advantage of ensuring both groups actually undergo identical pressurisations.[1] Some potential disadvantages with this method include the costs associated with providing the reduced-oxygen gas mixtures and the possibility of inadvertently supplying a hypoxic mixture when gas switches are made during treatment. A further concern is that as the percentage of O_2 is decreased there is an increasing

risk of decompression sickness (DCS) for patients in the sham group. In the above example the use of a 10% O_2 mix at 203 kPa gives an equivalent air depth (EAD) of 12.8 metres' sea water (msw). This allows for a no-decompression treatment of only 75 minutes. If the study were done at 243 kPa (a pressure commonly used in HBOT) then the EAD jumps to 17 msw and the risk of DCS rises accordingly.

OPTION TWO

In many hyperbaric studies the sham group is compressed to only 111–121 kPa.[2–4] The slight pressurisation of the chamber ensures the chamber door stays sealed. If the chamber door were to inadvertently open midway through the treatment it would reveal that the chamber had not actually been pressurised. Using a minimal change in pressure also reduces the risks of DCS and barotrauma to the sham group. A further benefit is realised in cost savings as this technique does not require expensive gas mixes described above in Option 1. This method does give the patient a feeling of pressurisation as even at 111 kPa the pressure change is felt on the middle ear by most people, requiring a Valsalva or similar ear-clearing technique.

The main disadvantage of this form of patient blinding is that the compression time, as compared with the typical compression rate of 5–10 minutes to achieve a pressure of 203–243 kPa, is quite quick, often just a few seconds. At first this may not seem to be a matter of great concern but it may not always be possible to ensure that the sham and the treatment group subjects do not come into contact with each other in a busy hyperbaric facility. If the two groups were to compare treatment times, they could reveal significant differences in compression times, an issue best avoided if possible.

OPTION THREE

A final option and the one we feel is most likely to truly blind the two groups, is to use multiple, small changes of pressurisation during compression/decompression. This is done for both the sham and the treatment groups. The advantages to this technique are that:

- overall, each group undergoes the experience of pressurisation for a similar duration;
- the compression/decompression profiles are fairly simple to achieve for trained chamber technicians;
- both sham and treatment groups feel the need to clear their ears during the compression phase; and
- costs are kept to a minimum.

The protocol had previously been tested at our facility in a very limited fashion but with the current study we hoped to validate its effectiveness.

Table 1
Demographics of the volunteer divers in the 'treatment' (T) group (pressurised to 203 kPa) and the 'sham' (S) group (pressurised to 121 kPa). Two divers in the sham group had over 500 dives each

Group	Subjects	Male	Female	Mean age (yrs)	Mean dives
T	30	19	11	32	65
S	34	22	12	33.4	125

Methods

The study was approved by the Uniting Healthcare Human Research Ethics Committee, Brisbane. Sixty-six volunteer, certified, recreational scuba divers from the local area, who had not previously been exposed to compression in a hyperbaric chamber, were recruited through local dive shops. The divers were not paid for their participation. The risks of participation, which were principally associated with barotrauma, were explained. Divers were chosen as test subjects as it was thought that they would be more likely than typical non-diver hyperbaric patients to assess accurately the pressure to which they are exposed.

After having the study explained to them and completing a signed consent form, the first group of divers to arrive on a study day was randomised (3–6 subjects per chamber run) to undergo a compression to either 203 kPa, the 'treatment' group, or to 121 kPa, the 'sham' group. The number of divers in each run was considered not to be relevant. The compression profile for each subsequent group on that day was then assigned in alternating fashion. All participants were instructed to avoid communication with each other during the study and this was strictly enforced by staff members.

Once all participants within a group were seated in the chamber and the inside attendant was satisfied everyone was ready, the pressurisation commenced. Initially all groups were pressurised to 111 kPa to seal the chamber door. After a brief stop, all groups did a 10 minute 'descent' procedure that used an up/down pressure profile to mask pressure changes. The ideal pressure–time profiles are shown in Figures 1 and 2 for both the sham and treatment groups.

Immediately after completing the assigned profile all test subjects were asked to fill out a form indicating whether they believed they had undergone pressurisation to a maximum of 121 kPa or 203 kPa, or they were unsure. We used a standard 'off the shelf' dive computer to capture the actual compression profiles. The computer used was found to have an error of over-calculation by 10 kPa (1 msw equivalent) at gauge pressures less than 40 kPa, when calibrated against our chamber gauge. Therefore, the real-time pressure recordings shown in Figures 3 and 4 exceed the actual pressure by 1 msw. Due to this error, the pressure tracings were viewed as representative only and not seen as exact mirrors of the pressures achieved.

Figure 1
Ideal sham profile for a dry-chamber pressurisation to 121 kPa

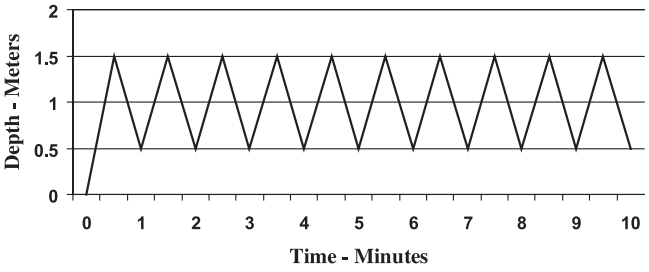
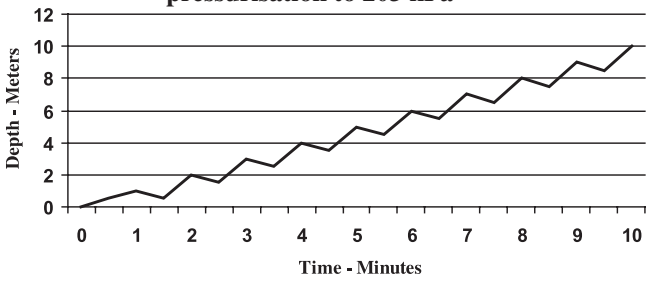


Figure 2
Ideal treatment profile for a dry-chamber pressurisation to 203 kPa



The study was an equivalence study with an aim to test whether two different treatments were equivalent.[5,6] As it is nearly impossible to blind people from the perception of pressurisation, our goal was to achieve a sham protocol that would be perceived as identical to the actual treatment protocol. The tolerance for testing in this study was set at ±15%, a figure the investigators felt was both reasonable to detect a variance between the two protocols and deemed to be clinically important. The Newcombe method was employed to calculate the confidence interval for the difference between two proportions from independent samples.[7]

For purposes of analysis the 'Not sure' group was collapsed within the group that had a perception of not being pressurised to 203 kPa. This was done in order to increase the expected value of each cell to above 5, which was required for a valid Chi-squared test. Thus, the proportion of patients who perceived they had definitely been pressurised in each group was compared.

Results

There were no significant differences in age or sex between the two groups. Divers were all between the ages of 21 and 44, having between 8 and 598 dives (Table 1). The mean number of dives in the sham group was nearly twice that of the treatment group, as two divers in the sham group had over 500 dives each. Correcting for these outliers, the average number of dives in the sham group was very similar to that of the treatment group (60 versus 65; rounded).

The perceptions of pressurisation of the two groups are

Figure 3
Tracing of an actual sham pressurisation to 121 kPa. There is an offset of 1 msw at low pressures in the gauge used, which thus over reads the actual pressure by this value

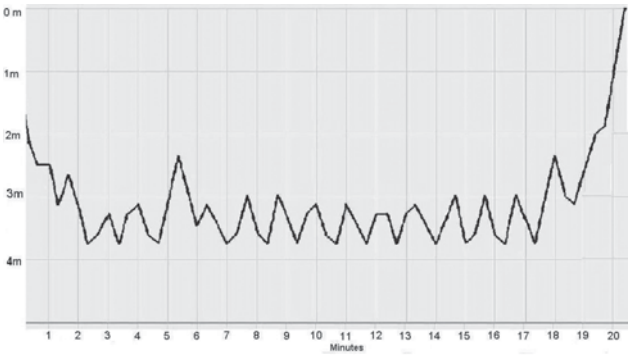


Figure 4
Tracing of an actual treatment pressurisation to 203 kPa. Despite the initial offset of 1 msw in the gauge used, it did not over read at depth

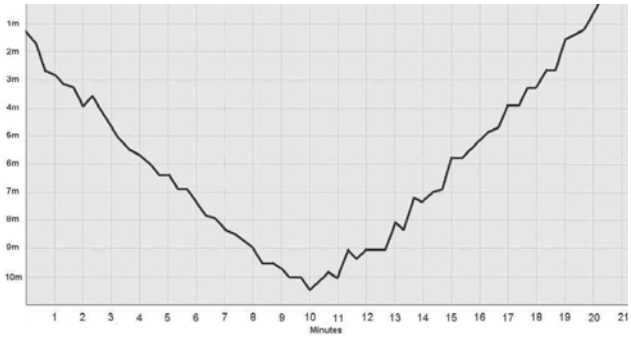
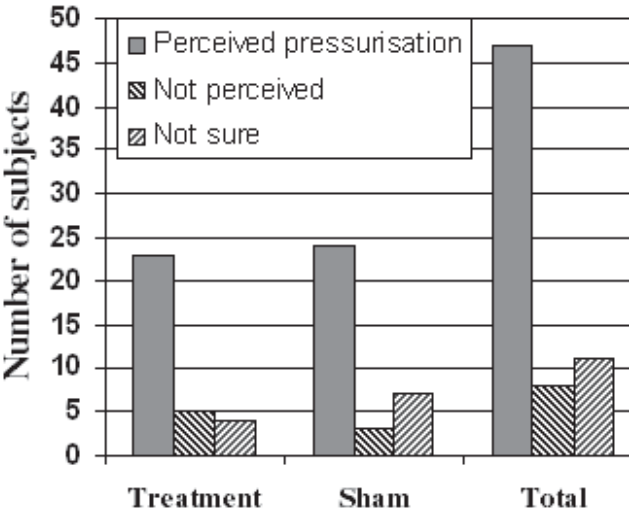


Figure 5
Perception of pressurisation for subjects undergoing 203 kPa of pressure or a sham group undergoing 121 kPa of pressure



presented in Figure 5. Interestingly the two divers in the sham group with over 500 dives each believed that they had been pressurised to 203 kPa.

Approximately 70% of subjects in each group reported that they had been pressurised to 203 kPa (71.9% and 70.6% for the treatment and sham groups respectively). The difference between these two groups is 1.3% (95% confidence interval of the difference in proportions -20.1% to +22.2%).

Discussion

When designing a randomised clinical trial it is important to consider how the control group will be handled. Although there may be debate as to the optimal method for blinding participants in a trial, the principle of blinding itself is a cornerstone of modern medicine, with its foundations laid over 250 years ago by British physician James Lind.[8–11] In modern medical trials, the goal is to reduce bias between groups to such a level that any differences observed between them can be said confidently to be related to the intervention itself and not to a placebo effect. In order to effectively assess the results of a particular intervention, it is important to utilise validated blinding techniques. For pharmaceutical studies this may involve a relatively simple and inexpensive process of using visually identical modes of drug delivery for both arms of the trial, but for other types of clinical trials blinding may be much harder to achieve.

Driven by both science and economics, there is an ever-increasing emphasis on the need for evidence-based medicine. It is rather difficult to blind participants to an intervention which itself cannot be concealed. An example might be a trial investigating the use of therapeutic massage for back strain. Blinding participants from knowing whether they were randomised to the massage group or the alternative is difficult, if not impossible. Further, the principles of informed consent may preclude concealment of the intended goals of the trial. Good-quality, blinded, hyperbaric trials have been hampered by these same difficulties. Optimally many clinical studies in hyperbaric medicine require a sham group of study participants and, unlike a trial of a new drug in which the costs of the placebo group are minimal, a single placebo hyperbaric treatment may cost hundreds of dollars. Partly as a result of these high costs, there have been relatively few double-blinded HBOT trials in the past.

Our interest in providing reliable blinding procedures in a multiplace hyperbaric facility began with our recent involvement in a large, multi-centre, blinded HBOT trial. The trial protocol specified that the sham group should be maintained as close to ambient pressure as possible. In order to keep the chamber at or near 101.3 kPa and maintain similar run times between the sham and treatment groups, we have used the option which utilises small yet perceptible pressure changes for both groups. These small pressure variations mean both groups of study subjects experience similar middle ear pressure changes. Further, both groups will have similar overall compression times. We believe this technique to be superior to protocols utilising a standard straight compression profile. Typically a straight compression to achieve 243 kPa requires 8–10 minutes in our eight-patient multiplace chamber compared with the 10–15 seconds to achieve the chamber-door seal of 121 kPa.

The confidence intervals in this study (95% CI -20.1% to +22.2%) are larger than the 15% tolerance limit determined by the investigators to test for equivalence. Since the lower and upper confidence limits exceeded these tolerances, the study does not provide unambiguous evidence that the treatment and the sham are equivalent. However, in an equivalence trial, unlike a typical study testing difference, a conventional significance test has little relevance and absolute equivalence can never be fully achieved.[6] Since true equivalence was not achieved, we cannot say categorically that the two arms of the trial provide identical perceptions of pressurisation, despite the difference between the two groups being only 1.3%.

Limitations of our study were the fact that the actual pressurisations deviated slightly from the ideal pressurisation protocol and also that we had a relatively small number of subjects for a study of equivalence. To definitively assess equivalence a much larger sample size, of over 350 per group, would be required. It should be noted that the results from our trial (performed at 203 kPa) may not be directly extrapolated for a pressurisation to 243 kPa (a treatment pressure used commonly in HBOT).

Before allowing any of our technicians to pressurise the test subjects, the ideal pressurisation pattern was described to them and they were subsequently observed to be following this ideal protocol. Actual pressure tracings were recorded for each technician but not for every compression. Although target depth was never exceeded, we did find some variability between the actual compression profiles and the ideal as described above; however, there was no evidence that this had an important influence on the results. It seems that the presence of frequent variations in pressure is more important than strict adherence to the actual pressures of the protocol.

Conclusions

The blinding pressure-variation protocol described here is cheaper, simpler, and safer than other multiplace sham options. The majority of subjects in both the treatment and sham groups believed they had undergone a therapeutic treatment pressure. Although the confidence intervals exceeded the tolerance limits set beforehand, the study supports the contention that the technique described here is likely to blind ‘sham treatment’ patients in equal proportion to ‘treatment’ patients when assessing their ultimate treatment pressure, and that, therefore, it can be used with reasonable confidence in hyperbaric RCTs to a treatment pressure of 203 kPa.

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Conflicts of interest

No conflict of interest was present.

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