Effective patient blinding during hyperbaric trials.

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Clarke D. Effective patient blinding during hyperbaric trials. Undersea Hyperb Med 2009 36(1):13-17. Hyperbaric medicine is applied for several disease states. Laboratory evidence is compelling but clinical efficacy remains incompletely validated. The standard by which supportive research is measured is termed evidence-based medicine, with results of randomized, blinded trials being most desirable. Blinding patients during hyperbaric exposure poses unique challenges. Few such studies are reported and confirmation of its success lacking. A study of patients suffering radiation-induced proctitis was conducted. It involved blinding of sham controls via a minimal air compression technique. Prior to unblinding 72 patients were surveyed using a standardized questionnaire to determine if they had been aware of their treatment allocation. Twenty of the 33 in the treatment group answered that they were in the treatment group, one answered sham and 12 did not know. Twenty-three of 39 in the sham group thought they were in the treatment group, two said sham and 14 did not know. A Chi-square analysis detected no relationship between what treatment was provided and what patients thought they received (p=0.9058). Eliminating those who did not know, a Kappa statistic was p=0.0299, indicating that there was no agreement beyond chance. Minimal air compression is an effective blinding tool for patients enrolled in hyperbaric trials.

INTRODUCTION

There is an increasing expectation on the practice of hyperbaric medicine, like a number of other therapeutic interventions, to improve its evidence of efficacy and to demonstrate its cost-effectiveness. This expectation is considerable because hyperbaric practice standards are supported by only modest amounts of high quality clinical research.

The standard by which efficacy and cost-effectiveness are assessed and evaluated for a given intervention is termed ‘Evidence-based Medicine’ (1). Modern EBM involves an integration of best clinical evidence with clinical expertise and patient values. Representing the highest and most desirable of several levels of supportive evidence are the results from randomized, controlled and blinded clinical trials. ‘Blinding’ is a key component of clinical trial design, and is employed in order to minimize the likelihood of bias. ‘Single blinding’ commonly refers to hiding the treatment allocation (active treatment or placebo/sham) from a study’s patients. This is considered important because patients may act differently if they know of their particular allocation. ‘Double-blinding’ hides allocation from both the patient and those who will assess their respective outcomes. Researchers, too, may behave differently as they evaluate subjects if they are aware of their allocation.

When evaluating the effects of hyperbaric oxygen therapy, blinding of investigators is relatively straightforward. They should be restricted from the hyperbaric facility while subjects are present, they should not be given access to hyperbaric treatment records prior to unblinding and care should be taken when discussing subjects in their presence. The blinding of the patient is more of a challenge, given the unique nature of the hyperbaric chamber, with its oxygen and pressure variables.
HISTORICAL PERSPECTIVE

Hyperbaric medicine’s first blinded trial occurred in 1955 (2). It was single blinded and involved the evaluation of hyperbaric oxygen as a radiation sensitizer. Eight patients with breast or chest wall malignancies and had tumors large enough to be divided into two halves were recruited. Each patient had one half of their tumor shielded before undergoing external beam radiotherapy during exposure to hyperbaric doses of oxygen. Upon removal of the patient from the monoplace chamber the shielding was reversed and the remaining half of the tumor was irradiated under conventional conditions.

The pathologist who assessed for any potential sensitizing effect of hyperbaric oxygen was blinded (not the patient in this case) as to which half of the tumor had been irradiated in hyperbaric oxygen and which in air. Following analysis and unblinding, it was apparent that tumor destruction was much greater when irradiation took place while patients breathed hyperbaric doses of oxygen in the hyperbaric chamber. Several other hyperbaric radiation sensitization trials followed over the ensuing decade although none reported employment of any patient and/or investigator blinding.

It was 12 years before another blinded hyperbaric trial was reported (3). This trial’s objective was to determine if hyperbaric oxygen could improve the ‘take’ of split thickness skin grafts applied to thermally burned patients. Reference to blinding was directed at the investigator side. The surgeon, who operated on all of the study patients, was unaware to which group each patient would be subsequently assigned (hyperbaric oxygen or control) post-operatively. No attempt was made to blind the patients and it is unclear if the surgeon had remained blinded at the time of his assessment of graft ‘take’, some four days post-operatively.

Using the monoplace hyperbaric delivery system, Hart and colleagues reported hyperbaric medicine’s first double-blind clinical trial, in 1974 (4). In order to determine if the addition of hyperbaric oxygen therapy to standard care improved outcome in thermal burns, acutely injured patients were randomized to receive oxygen at 2.0 ATA or a sham hyperbaric exposure. In order to ‘blind’ those randomized to sham, investigators provided a brief chamber compression to 5 psig, while these patients breathed air. Immediately upon arrival at 5 psig, patients underwent a slow decompression to approximately 1 psig, where they remained for the remainder of their ‘treatment’. This blinding technique served to produce pressure and temperature changes associated with such alterations in ambient pressure. None of the eight sham patients were reported to have experienced ear barotrauma while three of the eight treatment group (14.7 psig oxygen) did. No apparent attempt was made to determine the effectiveness of this method of patient blinding via a survey of patient beliefs. All of the physicians who evaluated outcomes and supervised hyperbaric treatments were likewise blinded as to patient allocation.

In 1982 the United States Air Force began a clinical investigation program designed to evaluate the role of HBO therapy in several conditions. Each separate investigation, conducted in a multiplace chamber, involved a double-blind study design, with patient selection (treatment or sham control) known only to the technologist who manipulated each patient’s breathing mixture. The approach to patient blinding was quite unique. It involved ‘sham’ patients being compressed all the way to standard treatment pressure (in this case 2.36 ATA), where they were then provided with an 8.9% oxygen mixture, in nitrogen. This resulted in an effective oxygen delivery pressure of 0.21 ATA (the equivalent of a normal atmospheric oxygen exposure of 21%) (5). The necessary
decompression procedure for such nitrogen exposures, however, mandated a ‘staged’ ascent to 1.0 ATA. Staged decompression was not required for active treatment patients as they breathed only oxygen and were not, therefore, at risk for decompression sickness. As this temporary halting of the chamber’s ascent may have served to unblind sham patients, these Air Force investigators elected to decompress sham patients by a gradual, rather than staged, 20 minute linear ascent, breathing oxygen. This approach to decompression, though non-standard, was considered preferable in order to minimize the risk of decompression sickness while maintaining patient blinding. It did, however, introduce an oxygen breathing element to the sham group, which was not ideal from a scientific purity perspective.

This approach to patient blinding served to control for pressure, *per se*. It did, however, involve a greater degree of technical complexity and introduced risks of hypoxia and anoxia (should inadvertent delivery of pure nitrogen occur) and iatrogenic decompression sickness. The hyperbaric and evaluating physicians were also blinded as to treatment allocation, thereby completing the double blind aspect of the study’s design.

This technique of compression all the way to standard treatment pressure was considered necessary because the minimal compression technique used by Hart’s group was thought to have been insufficient to produce adequate patient blinding. These USAF investigators felt that these patients might be able to sense the magnitude of pressure change differences and those modest changes in pressure would not prompt sufficient degrees of middle ear auto-inflation compared to standard treatment pressure. The failure to report any complaint of barotrauma in the Hart, *et al.*, trial’s sham patients did suggest that this potential study design flaw was a least a possibility. USAF patients were apparently not surveyed either, in order to determine how successful this alternative form of blinding had been.

In 1997 Weaver and colleagues, using monoplace hyperbaric chambers, reported successful blinding of patients during a randomized and controlled double-blind trial that investigated the role of HBO therapy in acute carbon monoxide poisoning. The Weaver group’s approach to patient blinding was similar to that of Hart, *et al.*, in that sham patients were briefly compressed to several psig while breathing air, then immediately decompressed to the minimum chamber operating pressure for the remainder of their ‘treatment’. A post-treatment survey of the last 26 patients enrolled in this trial determined that they were unable to determine their treatment allocation (6). Weaver, *et al.*, suggested, however, that this finding of apparent successful blinding needed to be interpreted with some caution. They felt it possible that CO poisoned patients might have suffered impaired recall regarding events that occurred immediately following their poisoning.

**PATIENT BLINDING SURVEY**

Our group has recently reported the results of a randomized and double-blind clinical trial that investigated hyperbaric medicine’s therapeutic role in the treatment of late radiation tissue injury (7). We employed the minimal and brief air compression (5 psig) technique in order to blind those patients allocated to sham, in both monoplace and multiplace hyperbaric delivery systems. Through the use of volunteer recreational SCUBA divers we were able to determine that it would be highly unlikely that study patients could detect differences between active treatment (2.0 ATA O₂) and sham chamber treatment pressures (1.1-1.34 ATA air). All references to chamber pressure and oxygen content were obscured from view and care
was taken not to comment regarding treatment allocation by unblinded clinical personnel in the presence of study patients and their family members. Hyperbaric team members, including the physicians, remained unblinded. Physicians who were assigned to evaluate outcomes, however, were blinded. Upon completion of the treatment period, and prior to unblinding, 72 patients were asked if they knew which arm of the trial they had been assigned to. They were asked not to guess, but to respond with either a ‘Yes’, ‘No’, or ‘Don’t Know’. If they answered yes they were then asked to state why they felt this answer to be correct. From the results shown in Table 1 it is clear that these patients did not know of their allocation. A Chi-square analysis detected no relationship between the actual treatment provided and what patients thought they had received (p = 0.9058). When patients who ‘did not know’ were ignored, a Kappa statistic (an index used to compare agreement against that which might be expected by chance) was p = 0.0299, indicating essentially no agreement beyond chance. Apart from a majority of patients believing they had received HBO therapy, no other relationships could be seen.

An analysis of the incidence of barotrauma between the groups in our trial certainly suggests that the selected ‘sham’ pressure of 5 psig (1.1-1.34 ATA air) was sufficient an increase in pressure for blinding purposes. Auto-inflation of the middle ear spaces was clearly necessary during the compression period and Table 2 records those attempts that were not entirely successful. It was concluded, therefore, that, as observed in the Weaver trial, brief and minimal air compression is an effective blinding technique during hyperbaric trials.

### Table 2 Incidence of Ear Pain/Ear Discomfort, and its Management

<table>
<thead>
<tr>
<th></th>
<th>HBO (2.0 ATA)</th>
<th>Sham (1.34 ATA)</th>
<th>Sham to HBO (2.0 ATA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear pain/discomfort</td>
<td>11</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decongestants</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ventilation tubes</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

### SUMMARY

Successful patient blinding can be accomplished during clinical trials that incorporate hyperbaric medicine using the minimal and brief air compression technique. It eliminates any risk of iatrogenic decompression sickness in sham patients and minimizes technical complexity and is, therefore, preferred to compression to standard treatment pressure and delivery normobaric normoxic equivalent oxygen inhalation.

### REFERENCES

