RANDOMIZED CONTROLLED TRIALS

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Introduction

The criticism has been made of hyperbaric medicine that treatment is based on little or no good clinical evidence. Recently improved awareness among medical practitioners to the importance of evidence has highlighted this perception. In fact, many clinical randomized studies investigating the application of hyperbaric oxygen have been reported, although of variable quality.[1-150] It is the purpose of this section to describe the place of RCTs within the practice of Evidence-based Medicine (EBM), summarize the methods by which such trials were located, discuss the appraisal and performance of RCTs with specific reference to hyperbaric medicine, and promote further methodologically sound trials in the field. We will also discuss the generation of meta-analyses based on the individual trials with particular reference to the work of the Cochrane Collaboration.

It is generally accepted that results from well-designed RCTs are the gold-standard for directing clinical decision making.[151-163] The RCT is the most appropriate trial methodology for the investigation of causal relationships between therapy and clinical effects because of a low potential for systematic bias. A randomized methodology, properly concealed and blinded, eliminates systematic bias by removing all factors other than the vagaries of chance in determining to which arm of a study any individual subject will be allocated. No investigator or patient characteristic (e.g. prior belief in the effectiveness of HBO_2) can influence allocation between the therapeutic options under consideration. Avoiding the misinterpretation of random events as clinically meaningful is the realm of statistical analysis and appropriate empowerment of well-designed trials.

Discussions of the ethics of conducting RCTs are available.[151,164-167] Often it is difficult or impossible in life-threatening circumstances to obtain fully informed consent. The ethics of entering such patients in trials is complex and international standards may vary.

Many authorities have listed hierarchies of evidence by trial methodology. While there are minor differences in many of these tables, they all reflect a progression from single case reports or expert opinion (high possibility of bias) to appropriately powered RCTs (low possibility of bias). Table 1, modified from the Oxford Centre for Evidence-based Medicine web site, is an example of such a hierarchy.[168]

Evidence-Based Medicine

Evidence-based medicine (EBM) as a process by which to practice has only been possible since the development of electronic libraries and search engines. For the first time, rapid access to the vast medical literature published each year is possible, and EBM tools are designed to take advantage of this opportunity. EBM has been defined as "the conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients."[169] Despite recent enthusiasm expressed for the concept, many health care

professionals have been critical. Some practitioners feel the reference to evidence erodes clinical freedom and is designed by bean counters to control medical expenditure. There are fears that EBM is 'cookbook' medicine- requiring all individuals to receive the same diagnostic and therapeutic measures, regardless of individual needs. This is an unfortunate misconception. While health care providers often attempt to misuse the term 'EBM' to control expenditure, EBM is actually designed for the use of practitioners. It requires the synthesis of best evidence and clinical expertise/experience in order to arrive at the best diagnostic and therapeutic approaches for each individual under treatment.

In certain clinical situations, RCTs may be impractical and/or unnecessary for the rational institution of treatment. When dealing with rare conditions, or those with a universally poor outcome, a carefully constructed register of cases or even a retrospective case series may produce evidence powerful enough to drive practice (an 'all or none' result). The practice of EBM does not involve the slavish regard of RCT evidence only, but the critical appraisal of the best evidence available and the application of the most effective therapy available for the individual patient. The paucity of randomized evidence supporting the application of HBO_2 for many indications discussed elsewhere in this report should be interpreted carefully in this regard.

Table 1. An evidence hierarchy for therapeutic interventions (Adapted from the Oxford Centre for Evidence-based Medicine)

Level	Evidence source
1a	Systematic review of RCTs where the individual RCTs yield homogeneous results
1b	Individual RCT (with appropriate power)
2a	Systematic review of cohort studies where the individual studies yield homogeneous results
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
3a	Systematic review of case-control studies where the individual studies yield homogeneous results
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Single case report, expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. (Modified by author for this report).

The practice of EBM is not achieved without effort. Physicians need training to ask appropriate questions, execute efficient searching techniques, develop skills at critical appraisal of the evidence recovered, grasp some basic clinical statistical methods, and relate findings to individual patients. An excellent review of EBM was published in the Journal of the American Medical Society in 1992;[170] another major resource is the pocket guide to teaching and practice of EBM by Sackett and others.[171]

Search Strategy

To generate this list of RCTs, a systematic search of the literature was made using the following scheme. Yields are cumulative at each step:

1. Database of Randomised Controlled Trials in Hyperbaric Medicine (DORCTIHM) [www.hboevidence.com]. Yield: 144 reports of 123 trials.
2. The Cochrane Database of Systematic Reviews. Yield 16 meta-analyses, 1 protocol.
3. The Cochrane Central Register of Controlled Trials. Yield 2 reports of 2 trials.
4. Medline search (PubMed) using MeSH terms 'hyperbaric oxygenation' AND 'clinical trials'. Yield 120 hits, 0 new reports.
5. Hand searching of relevant journals published since 1965 (UHM, SPUMS Journal, EUBS), proceedings (UHMS ASM, EUBS, ICHM) and previous copies of this report. Yield 5 reports of 5 trials.
6. Review of citations form reports identified above. Yield 0 new reports.

The first step uses a specific database developed for the field of Diving and Hyperbaric Medicine. The database is available free over the Internet and is accessible from the UHMS website. It contains the citations and short, formalized critical appraisals of each study including the clinical impact of interventions tested.[164] It is updated frequently and includes a forum for general discussion and submission of new citations.

Critical Appraisal of RCTs

Table 2. Suggested checklist for appraising randomized trials in hyperbaric medicine (developed from teaching materials of the School of Public Health, Sydney University).

Important information that should be in the paper	Potential related problems	Threats to the internal and external validity of the study
1.1 What is the research question posed in the paper?	1.2 Is this question relevant to the clinical problem?	1.3 Does the question relate to a real clinical problem?
2.1a Define the population in which the authors are interested. Are the study subjects representative of this population?	2.2a Do the study subjects represent my patient population?	2.3a Can I apply the results to my patients?
2.1b Exactly how were the patients allocated to groups?	3.2b Was allocation made after a decision to enter the trial?	2.3b Possible bias if allocation not concealed.
2.1c How many reached final follow-up?	2.2c Less than 80% follow-up may reduce confidence in the result.	2.3c Problems relate to fate of those not followed-up. Would they affect the result?
3.1 What is being studied (study factor)? Usually a regimen of HBO_2T. How is it measured?	3.2 Is there any likely measurement error (not usually a problem!)?	4.3 Is there any likely important cause of bias? Not likely if we are confident the profile was actually delivered as stated.
4.1 What are the main outcomes assessed (outcome factors)?	4.2 Any important outcomes missed? Any likely measurement error?	4.3 Do missed outcomes reduce the applicability of this study? Is measurement different in the two groups?
5.1a What potential confounders are considered?	5.2a Any important confounders missing?	5.3 How likely is confounding to be a significant source of bias?
5.1b How were they dealt with?	5.2b Were they dealt with adequately?	
6.1a Is a point estimate of effect given (the actual difference between the groups)?	6.2a Is it reasonable to accept these results are not due to chance? Was analysis by intention to treat?	6.3 Is this study useful or inconclusive in answering the research question? Is a clinically significant effect inside or outside the 95%CI?
6.1b Are confidence intervals given? If not in a study with statistically non-significant findings, is power given?	6.2b Are the differences reported clinically significant? Was the sample size sufficient to detect a clinically significant difference?	
7.1 What are the author's conclusions?	7.2 Have the authors correctly interpreted the results?	7.3 Have the authors considered study limitations in their conclusions?

Some RCTs are more valuable than others. Identifying those depends on a careful examination of the trial report to identify any serious threats to internal or external validity. [Internal validity: are there any flaws in construction or execution of this trial that reduce the confidence we have in the results? External validity: are there elements in the patients studied or the trial execution that reduce our confidence that the results apply to our patient(s)?]. Table 2 summarizes the most important questions that should be answered in a study of high methodological quality. The use of a checklist such as this is invaluable in ensuring that all-important aspects of trial design and study execution are addressed.

Conducting RCTs

Table 2 identifies the more important features of a well-conducted and suitably powered RCT. Emphasis should be placed on sound assumptions concerning sample size, concealing allocation from the individual enrolling patients in the study, blinding of both outcome assessors and patients where possible, and appropriate statistical analysis. A detailed protocol should be written to state all the rules for conducting the RCT and include background information with the rationale for conducting the RCT. It is particularly important to analyze all participants entering the trial in the group where they were originally allocated, not on the basis of whether they actually received the trial therapy. This is known as '*intention to treat analysis*'. This approach tests the clinical application of a therapy, rather than the effect in the sub-group of patients who will comply with a therapeutic protocol.[159,160] A secondary analysis on the basis of treatment received can be performed should there be an important message to convey concerning the effect of compliance on therapeutic results.

Many of the trials in hyperbaric medicine are underpowered to show important clinical differences. Quite a number are labeled 'pilot studies'; although in most cases, the presumed 'definitive' study has never materialized. It is reasonable to conduct preliminary non-comparative clinical trials based upon an understanding of physiologic principles to determine how any given therapy might impact a specific disorder. As new information regarding fundamental mechanisms of HBO_2 are elucidated, new and prior applications for HBO_2 should be considered. If a preliminary study suggests therapeutic efficacy for HBO_2, careful consideration should be given to following with a pilot study and moving toward a definitive trial. While a pilot study may avoid the possibility of undertaking a full RCT without a realistic hope of finding (or eliminating) a clinically useful benefit, it may consume sufficient time and resources to prevent the launching of the full RCT. In the latter situation it may be more useful to perform a definitive RCT with regular formal interim analysis (sequential analysis).

Based upon the preliminary and pilot outcomes, a full RCT should be organized if the possibility remains of an important clinical effect. Without preliminary studies, the lack of information might lead to inappropriate administration of HBO_2 therapy or withholding of potentially efficacious treatment. Importantly, if HBO_2 becomes the accepted standard for a particular disorder without data from an RCT, the ability to conduct an RCT for the "indicated" disorder in the future may be compromised. The primary goal of the preliminary trial is to determine if HBO_2 alters the outcome of the disorder. If the natural history of the disorder is not well known, inferences drawn from the study may be compromised. The Placebo Effect[173] and Hawthorne Effect[174-176] can confound conclusions regarding a given treatment.

Sample size: Design characteristics of a full-scale RCT depend upon data obtained from previous investigation and clinical experience. In general, sample size calculation will require an accurate estimate of the minimum *clinically* significant difference between the groups, the base rate in the placebo or standard arm against which HBO_2 is to be tested, the errors acceptable to the investigators [traditionally most investigators accept a chance of 1:20 that they will interpret a difference as true when it is a random event (P=0.05) and accept a 4:1 chance of finding a difference if it exists in truth (power 80%)]. It is not unusual for putative sample sizes to be so large that only a cooperative multi-institutional study can provide sufficient numbers of patients within acceptable time limits.

Concealed allocation and blinding: Where possible, good trials mask three distinct groups as to the true nature of the therapy each individual subject receives during the course of the trial. 'Allocation concealment' indicates that the individual responsible for entering subjects into the trial cannot predict the group to which each potential subject would be allocated. Examples of failure to conceal allocation would be sequential entry into a trial (pseudo-randomization) and having the same individual in charge of randomization and entering subjects in the trial. 'Double-blinding' usually refers to the masking of group allocation to the subject and the group responsible for outcome assessment.

In the context of hyperbaric therapy, blinding usually entails a sham treatment of some kind. There are at least three common methods of providing a sham hyperbaric oxygen therapy session: 1) minimal chamber pressurization with the patient breathing air to simulate the experience of HBO_2, 2) chamber pressurization briefly, followed by return to 1ATA (air or 100% oxygen) for the bulk of the treatment, and a second brief descent to simulate decompression at the end of the treatment time, and 3) hyperbaric pressurization with the patient breathing a reduced fractional inspired concentration of oxygen to provide the same alveolar oxygen tension under hyperbaric conditions as the patient would have breathing normobaric air. Each method has advantages and disadvantages, not least of which relate to the clinical question being asked in the trial and the putative mechanism of action of the HBO_2 arm. It is very important that the minimally pressurized control patients are unable to determine their treatment allocation. The latter method controls for alveolar oxygen tension, but introduces potentially confounding variables, for example, increased blood and tissue partial pressures of nitrogen with an associated increased risk of decompression illness. Patient blinding using a minimal pressurization method of has been demonstrated to work in at least one previous trial.[177]

Statistical analysis: Trialists are *strongly advised* to seek the advice of a clinical statistician in the planning stages of any trial. Not only will this provide clear guidance on sample size calculation and the appropriate statistical tests to employ, but also the exercise of clearly and explicitly defining the trial protocol will be invaluable in the successful and efficient prosecution of the trial.

General help and advice: The Consolidated Standards of Reporting Trials (CONSORT)[159] is a valuable method that can assist with design of the study, help authors prepare manuscripts, and aid reviewers in critically examining results. Most high profile journals (including JAMA) require RCT manuscripts submitted for consideration for publication to include all the

information in the CONSORT checklist. The CONSORT statement, flow diagram, and checklist are available on the JAMA World Wide Web home page (http://www.ama-assn.org).

This section of the Committee Report has touched only briefly upon a few issues pertinent to the conduct of a rigorous RCT. The interested individual is encouraged to read further regarding design of RCTs.[160-163]

The Cochrane Collaboration

It is generally accepted that results from well designed double-blind, prospective RCTs are the gold-standard for directing clinical decision making.[151-161] Recently, the development of the Cochrane Collaboration Database of Systematic Reviews (CDSR) has made available explicit systematic reviews of randomized evidence through many areas of clinical medicine (http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME). To date, 17 such reviews have been made that examine the therapeutic use of hyperbaric oxygenation, and these can be viewed on the web site shown above.(178-194). Combined with economic data, such reviews of efficacy can be used to estimate the cost-effectiveness of HBO_2T for common indications; some of these have been examined in a recently published doctoral thesis.[195]

The Cochrane Collaboration is an international non-profit and independent organization, dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide. The aim is to assist health care workers and their patients to make decisions about health care. The Collaboration produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. Publication in the CDSR does not guarantee that a review is free of errors and biases. Cochrane reviews must be read with the same critical eye as any other research report. While the aim of reviews is to produce an unbiased summary of the highest level of evidence, those with the motivation and expertise to perform reviews often have strong opinions in the area they are reviewing. Supporters of the collaboration suggest that these problems are likely to be of greater magnitude in non-explicit reviews of the same material; there is some evidence that this is true.[196-197]

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