EDITORIAL

Hyperbaric oxygen therapy, multiple sclerosis, and unapproved indications: Taking a stand

As the field of hyperbaric medicine has grown over the last three decades, the interest in using hyperbaric oxygen therapy (HBO₂,T) has grown as well. Unfortunately, that interest has grown not just for those “approved” indications which are well justified in the literature, such as DCS, arterial gas embolism, wound healing, among others, but for an increasing number of “unapproved” indications. Some have called these “off-label” indications, trying to make a parallel to pharmaceuticals, the Food and Drug Administration (FDA)-approval process, and the right of physicians to use a medication any way they see fit, once it has been approved for a single indication.

The Hyperbaric Therapy Committee of our Society reviews indications for use of HBO₂,T. Its recommendations have been published on an approximately tri-annual schedule to update the medical community about what has been decided in terms of old and new indications, based on the medical literature, after presentations before the Committee. Approval is by majority vote of the Committee, after hearing an invited speaker for each side of the debate. The Committee usually looks for three demonstrated kinds of support: 1) physiologic reasons or models to account for possible effects; 2) existence of an animal model for the clinical situation, with data which demonstrate a positive effect on some outcome; and 3) human studies, preferably randomized, controlled studies, which show significant benefits to patients for that indication. A few case reports or a case series is not usually enough to merit approval.

For these other non-approved indications, the Committee has been relatively silent, as has the Society itself. Other than minutes of the committee, presented to the Executive Committee, it has not been common knowledge what has been presented to but not approved by the Committee. However, some have felt that, as the preeminent medical society comprised of researchers and practitioners of undersea and hyperbaric medicine from around the world, the UHMS should take positions on these unapproved conditions for HBO₂,T.

The current issue of Undersea & Hyperbaric Medicine contains two papers that respond in very different ways to the call. The first is the result of a request for an Ethics Review by the President of the Society that goes back to the fall of 1998, while the second is a UHMS Position Paper on the treatment of Multiple Sclerosis (MS).

Ethical dilemmas: In their paper “Ethical dilemmas in hyperbaric medicine,” which appears in this issue (1), Chan and Brody review how they were charged with the task of studying the issue of “off-label” indications for HBO₂,T, and how they engaged representative experts to examine ethical issues in the field. The current societal forces that have created a demand for unapproved indications for HBO₂,T are listed. They then propose, for a number of reasons, several sets of criteria related to these therapies. They have three sets of proposals, and each should be looked at separately.

First, they propose criteria for “potentially therapeutic off-label use of hyperbaric oxygen”. The first criteria is that alternative treatments are neither cost effective nor successful. This should eliminate routine muscle strains and sprains, since these conditions usually heal by themselves, and the symptoms are usually treated with medications available over the counter. However, in professional sports, if a player can get back to “work” even one day sooner, a multimillion dollar superstar might be available for a weekend game that he might otherwise miss. Thus that could theoretically be interpreted as “cost effective” in such a setting.

The next criterion is that human or animal study data support its use, with which most would agree. Third, the benefits are greater than the risks, considering any patient co-morbid conditions and the technical capability and safety of the facility. Presumably this last point relates to the ability of the chamber and its tenders to manage the kind of problem presented by the patient. Although such criteria appear to be reasonable, they could also be used to justify creating a loophole around a specific non-approved indication. As an example, let us look at the indication of increased intracranial pressure following head injury. This was formerly an approved indication, but after the studies by Rockswold (2), it was removed from the list of approved indications. HBO₂,T did dramatically reduce the mortality rate among severely head-injured patients with Glasgow Coma Scores of 4 to 6, patients with mass lesions, and in those patients with intracranial pressures of >20 mmHg. However, the functional recovery of the salvaged patients was not satisfactory, causing increased utilization of medical care dollars, without a commensurate increase in quality of life. Thus the proposed three criteria do not go far enough to protect hyperbaricists from having to approve HBO₂,T when the benefits are controversial. To some physicians and patients, saving a life is more important than the quality of that life, while others may look to the quality of life as the definition of whether an outcome is truly “successful”.

The second group of criteria are for inclusion in a National Registry. These include the same three criteria as above, but add the following: Significant incidence of disease; public pressure or demand; well-defined protocol with defined measures for outcomes; informed consent forms; and funding. However, the authors do not go far enough in maximizing the return on investment in a National Registry. For example, let us look at mucormycosis as a proposed indication for HBO₂,T.

Mucormycosis is an infrequent cause of infection of the
sinuses and nasopharynx, and can extend to the cranial bones and to central neural structures. It is most often seen in patients who are diabetic and acidotic. This indication has been presented to the Hyperbaric Oxygen Therapy Committee on at least two occasions, once in 1989 and once in 1998. Each time, the indication was not approved by the Committee because of the paucity of published cases reported in the literature. Both times, there was concern for not approving this indication since it is very difficult to get data on a series of patients when the incidence of the condition is so low. Control groups would be nearly impossible to generate. This is an ideal situation wherein a National Registry would be of great benefit. It would allow a nationwide experience to be tracked, and data could then be obtained which might be of significant weight to allow this indication to be accepted, since it is unlikely that a single center would see enough cases to generate significant data. The inclusion of the criteria of a “significant incidence of the disease”, is thus not justified. Responding to public pressure could certainly be used to generate a registry, but what about when there is public pressure despite the lack of evidence for effectiveness in the literature, such as appears to be the case with MS?

The third set of guidelines is for physicians responding to requests for the off-label use of HBO₂T. These guidelines are quite straightforward, and require that the physician check to see if there are any medical treatments for the proposed indication that are “cost-efficient” and “successful”. It does not require that the “treatments” be FDA approved. It also guides the physician to consider risks and benefits, on a patient-specific basis, and to assess the facility delivering the treatments regarding their ability to handle any complications from the treatments. Also included as a guideline is an “offer” to have the patient participate in a Registry, which is proposed in their manuscript, but which does not currently exist. The creation, then, of such a Registry appears to be proffered as a challenge to the hyperbaric community, although a comparison to how the Cancer registries work would be to allow barophysicians to see how such a system might work.

Finally, although the authors mention the potential risks of home, garage, and non-medical installations having hyperbaric chambers in this age of affluence, justifiable concern for home chambers is not adequately addressed. Surely there is an ethical issue in their proliferation, for it is only the hyperbaric medicine community that must understand the risks of such devices in untrained hands. If a patient has a seizure in a chamber, and the local EMS system, through a 911 call, responds, there is a risk to the responder, not knowing how and when to decompress a patient out of a chamber. The first responder may not know what the issues are for pressure chambers, may not have been informed of the presence of such a site, and may not have had any training at all on how to deal with a patient inside a chamber. These issues are very relevant, since ethically we are not bound to reach out in our communities if we are aware of the existence of home chambers, to bring up the safety issues and supervisory medical issues to our local Health Departments, Fire Departments, and EMS agencies? Should home chambers be allowed at all, if not supervised by a medical presence? Who controls quality control issues regarding the operation of home chambers? Perhaps there should be some form of licensing, if they are to be allowed. Perhaps they should be pronounced illegal unless they are under the direct supervision of a hyperbaric technologist, and the patient is under the direct supervision of an identified physician, at a licensed medical facility. This is of course the position of the UHMS. Perhaps chamber manufacturers should be prohibited from selling to the general public. Can we allow such circumstances to exist in our communities without speaking out on safety and quality issues to our lawmakers and health care regulators? Of course not. The ethical imperative of taking a position is thus even larger than that delineated by the authors. Still, this discussion is, overall, an excellent start to establishment of an ethical basis for considering if and when to support hyperbaric treatments that are not approved.

Multiple sclerosis: MS is the “unapproved” disease that perhaps generates the most intense emotional response on the part of practitioners and sufferers of the disease, who “believe” in HBO₂T for this indication. The disease is currently considered to be “incurable”. It manifests with several clinical patterns, and may in fact be a catch-all for two or more different diseases.

The recognized clinical patterns include: Relapsing–Remitting MS; Secondary Progressive MS, and Primary Progressive MS.

In the first common scenario, the patient experiences a single, transient episode of loss of neurologic function, followed by a period of recovery and remission for variable lengths of time, often months or years. If only one episode occurs, it is often considered to be “Possible MS” at that point after the first episode, since the diagnosis of MS requires second events to occur. This scenario, which accounts for 80% of MS, is frequently studied. In a second form of the disease, so-called secondary progressive, persistent signs of CNS dysfunction may develop after a relapse, and the disease may progress between relapses. Signs and symptoms of the disease have a significant differential diagnosis, as numerous entities can mimic such MS. A third form of the disease is that of primary progressive MS, characterized by a gradually progressive clinical course.

The position paper in this journal reviews the level of evidence and conclusions of 18 published papers, including 2 meta-analyses of HBO₂T, when used for MS. More specifically, it targets studies designed to modify disease progression and reduce relapse rates. After review and categorization of these papers, the authors conclude that there is no significant beneficial effect on MS from the administration of HBO₂T.

Although a case could be argued from perhaps one or two of the papers that there may be small niches where HBO₂ may have some very limited temporary utility, such as with the transient symptomatic sphincter tone improvement noted by Barnes et al. (3), the case is even stronger that, considering the natural history of this disease, all observations of minimal, transient effect are irrelevant to the overall clinical course from this disease. Examination of the outstanding review by Noseworthy et al. (4) in the New England Journal of Medicine only
reinforces how trivial even these observations are. None of these trials are truly Phase III, as they do not compare hyperbaric therapy to any of the newer, more accepted therapies, at least three [Interferon beta-1b (Betaseron, Berlex Laboratories), Interferon beta-1a (Avonex, Biogen) and glatirimer acetate (Copaxone, Teva Pharmaceutical Industries)] of which have demonstrated reduction of the frequency of relapse by 30% (5–8).

The significant benefit of placebos is noted throughout the series of HBO₂, studies, and the observation that claiming effects based on trends that are non-statistically significant appears more than once in some of these papers, are both points that must be emphasized.

None of the HBO₂, studies included a 3-yr follow-up to identify biologically meaningful effects of treatment, as recommended by the Noseworthy review (4). Additionally, the issue is raised by Noseworthy et al. of whether it is even ethical anymore to evaluate new treatments for relapsing–remitting MS in a placebo-controlled study, because of the demonstrated efficacy of currently available immune modulators.

One basis for the attempt at rationalizing the mainstreaming of HBO₂, for MS appears to be a theoretical paper speculating that hypoxia may be the ultimate cause of MS, due to the proximity of many of the lesions of MS to vascular structures, based on observational histology (9). Without direct supporting data, this hypothesis should be ignored, when considering the numerous strides in the understanding of the entity or entities that comprise MS since the publication of that paper over 10 yr ago.

Putting the two together: If we examine the MS paper, in the context of the ethical guidelines, what would we come up with regarding the use of HBO₂, for MS? We would find an inexcusable entity for which the overwhelming published literature does not support any lasting benefit from hyperbaric therapy, and rarely any temporary benefit. We would find also a disease that has new immunologic therapy that appears to reduce the incidence of relapses, in the relapsing–remitting form of the disease, by 30%. This is far better than anything ever reported with HBO₂, Since there ARE alternative treatments which are more successful than HBO₂, and since there are NO animal models which support its use, and the benefits are not greater than risks, the ethical guidelines would support the position of the Society position paper that HBO₂, cannot be recommended or approved at the present time. Additionally, since the criteria for inclusion in a National Registry are not present either, the guidelines would support not including MS cases in such a registry, if it existed. Finally, the guidelines would support the physician responding negatively to a request for HBO₂ for a case of MS. Perhaps these papers, taken together, will finally put to rest the ineffective use of HBO₂ for MS. Finally it is critical to note that the treatment of MS with HBO₂ is now contrary to the standards of the UHMS.

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REFERENCES