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Hyperbaric Oxygen Therapy for Brain Injury, Cerebral Palsy, and Stroke

Summary

Overview

Hyperbaric oxygen therapy (HBOT) is the inhalation of 100 percent oxygen inside a hyperbaric chamber that is pressurized to greater than 1 atmosphere (atm). HBOT causes both mechanical and physiologic effects by inducing a state of increased pressure and hyperoxia. HBOT is typically administered at 1 to 3 atm. While the duration of an HBOT session is typically 90 to 120 minutes, the duration, frequency, and cumulative number of sessions have not been standardized.

HBOT is administered in two primary ways, using a monoplace chamber or a multiplace chamber. The monoplace chamber is the less-costly option for initial setup and operation but provides less opportunity for patient interaction while in the chamber. Multiplace chambers allow medical personnel to work in the chamber and care for acute patients to some extent. The entire multiplace chamber is pressurized, so medical personnel may require a controlled decompression, depending on how long they were exposed to the hyperbaric air environment.

The purpose of this report is to provide a guide to the strengths and limitations of the evidence about the use of HBOT to treat patients who have brain injury, cerebral palsy, and stroke. Brain injury can be caused by an external physical force (also known as traumatic brain injury, or TBI); rapid acceleration or deceleration of the head; bleeding within or around the brain; lack of sufficient oxygen to the brain; or toxic substances passing through the blood-brain barrier. Brain injury results in temporary or permanent impairment of cognitive, emotional, and/or physical functioning. Cerebral palsy refers to a motor deficit that usually manifests itself by 2 years of age and is secondary to an abnormality of at least the part of the brain that relates to motor function. Stroke refers to a sudden interruption of the blood supply to the brain, usually caused by a blocked artery or a ruptured blood vessel, leading to an interruption of homeostasis of cells, and symptoms such as loss of speech and loss of motor function.

While these conditions have different etiologies, prognostic factors, and outcomes, they also have important similarities. Each condition represents a broad spectrum, from barely perceptible or mild disabilities to devastating ones. All three are characterized by acute and chronic phases and by changes over time in the type and degree of disability. Another similarity is that the outcome of conventional treatment is often unsatisfactory. For brain injury in particular, there is a strong sense that conventional treatment has made little impact on outcomes.

Predicting the outcome of brain injury, cerebral palsy, and stroke is difficult. Prognostic instruments, such as the Glasgow Coma Scale (GCS) for brain injury, are not precise enough to reliably predict an individual patient's mortality and long-term functional status. Various prognostic criteria for the cerebral palsy patient's function have been developed over the years. For example, if a patient is not sitting independently when placed by age 2, then one can predict with approximately 95 percent confidence that he/she never will be able to walk. However, it is not possible to predict precisely when an individual patient is likely to acquire a particular ability, such

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as smiling, recognizing other individuals, or saying or understanding a new word.

Mortality and morbidity from a stroke are related to older age, history of myocardial infarction, cardiac arrhythmias, diabetes mellitus, and the number of stroke deficits. Functional recovery is dependent on numerous variables, including age, neurologic deficit, comorbidities, psychosocial factors, educational level, vocational status, and characteristics of the stroke survivor's environment.

The report focuses on the quality and consistency of studies reporting clinical outcomes of the use of HBOT in humans who have brain injury, cerebral palsy, or stroke. This information can be used to help providers counsel patients who use this therapy and to identify future research needs.

Reporting the Evidence

This review addresses the following questions:

1. Does HBOT improve mortality and morbidity in patients who have traumatic brain injury or nontraumatic brain injury, such as anoxic ischemic encephalopathy?
2. Does HBOT improve functional outcomes in patients who have cerebral palsy? (Examples of improved functional outcomes are decreased spasticity, improved speech, increased alertness, increased cognitive abilities, and improved visual functioning.)
3. Does HBOT improve mortality and morbidity in patients who have suffered a stroke?
4. What are the adverse effects of using HBOT in these conditions?

To identify the patient groups, interventions, and outcomes that should be included in the review, we read background material from diverse sources including textbooks, government reports, proceedings of scientific meetings, and Web sites. We also conducted focus groups and interviews to improve our understanding of the clinical logic underlying the rationale for the use of HBOT. In the focus groups, we identified outcomes of treatment with HBOT that are important to patients, caregivers, and clinicians and examined whether patients, caregivers, and clinicians who have experience with HBOT value certain outcomes differently from those who have not used HBOT. A broader goal of the focus groups was to better understand the disagreement between supporters and non-supporters of HBOT.

The following interventions, populations, outcomes, and study design criteria were used to formulate the literature search strategy and to assess eligibility of studies.

- **Intervention.** Hyperbaric oxygen therapy: any treatment using 100 percent oxygen supplied to a patient inside a hyperbaric chamber that is pressurized to greater than 1 atm.
- **Population**. Patients with:
  - o brain injury from any cause and in any stage (acute, subacute, or chronic).
  - o cerebral palsy of any etiology.
  - o thrombotic stroke.
- **Outcomes.** We sought articles reporting any clinical endpoint. We focused on health outcomes, including mortality and functional changes that a patient would experience, rather than intermediate outcomes. Intermediate outcomes include physiologic measures, such as intracranial pressure, cerebrospinal fluid lactate levels, or changes in cerebral blood flow, or results of imaging studies. Some clinical measures, such as neuropsychiatric and cognitive tests, are also intermediate measures. We did not assume that any of these intermediate measures of the effect of HBOT on patients with brain injury, cerebral palsy, or stroke was proven to be an indicator of the long-term outcome. Instead, in reviewing articles for inclusion in this report, we were particularly interested in studies that reported both intermediate measures and health outcomes, to assess the strength of evidence about their correlation.
- **Design.** We included original studies of human subjects that reported original data (no reviews). All study designs except for case reports and small case series were eligible for inclusion. Before-after or time-series studies with no independent control group were included if a) five or more cases were reported, and b) outcome measures were reported for both the pre- and post-HBOT period.

Methodology

Technical Expert Advisory Group (TEAG)

We identified technical experts to assist us in formulating the research questions and identifying relevant databases for the literature search. The expert panelists included a neurologist specializing in stroke, a neurosurgeon specializing in severe brain injury, a pediatric neurologist with expertise in treating patients with cerebral palsy, and a physician with an HBOT practice. Throughout the project period, we consulted individual members of the TEAG on issues that arose in the course of identifying and reviewing the literature.

Literature Search, Study Selection, and Data Extraction

We searched a broad range of databases to identify published and unpublished studies of the effectiveness and harms of HBOT in patients with brain injury, cerebral palsy, and stroke. Each database was searched from its starting date to March 2001. The databases searched were:

- MEDLINE®
- PreMEDLINE®

- EMBASE
- HealthSTAR (Health Service Technology, Administration and Research)
- CINAHL® (Cumulative Index to Nursing & Allied Health)
- Cochrane Database of Systematic Reviews
- Cochrane Controlled Trials Register
- DARE (Database of Abstracts of Reviews of Effectiveness)
- AltHealthWatch
- MANTIS™ (Manual, Alternative and Natural Therapy)
- Health Technology Assessment Database

TEAG members identified the following additional databases as potential sources of other material that may not be indexed in other electronic databases:

- The Undersea & Hyperbaric Medical Society: a large bibliographic database
- The Database of Randomised Controlled Trials In Hyperbaric Medicine
- European Underwater and Baromedical Society
- International Congress on Hyperbaric Medicine
- National Baromedical Services, Inc.

Update literature searching of the electronic databases MEDLINE, PreMEDLINE, EMBASE, CINAHL, the Cochrane Library, and the Health Technology Assessment Database was completed on February 26, 2002, using the same search strategy as used for the initial searches. Eight additional references submitted by a peer reviewer were added in May 2003. Finally, a supplemental search of MEDLINE, PreMEDLINE, EMBASE, and CINAHL was conducted in July 2003.

The references of all included papers were hand searched. In addition, two reviewers independently conducted hand searches of the references from the *Textbook of Hyperbaric Medicine*.[1] One TEAG member provided articles and meeting abstracts from his personal library.

Two reviewers independently assessed each title and abstract located through the literature searches for relevance to the review, based on the intervention, population, outcome, and study design criteria. The full-text articles, reports, or meeting abstracts that met the criteria listed above were retrieved and reviewed independently by two reviewers who reapplied the eligibility criteria. Disagreements were resolved through consensus.

Extraction of data from studies was performed by one reviewer and checked by a second reviewer. Disagreements were resolved through consensus.

Internal and External Validity and Quality Rating

The quality of all trials in the review was assessed using a list of items indicating components of internal validity. We modified the standard checklists to address issues of particular importance in studies of HBOT. For randomized controlled trials (RCTs) and nonrandomized controlled trials (NRCTs), the items assessed for internal validity were: randomization/allocation concealment, baseline comparability of groups, timing of baseline measures, intervention, outcome measures, timing of followup measurements (long enough to assess effects), loss to followup, handling of dropouts or missing data, masking, statistical analysis (if any), and general reviewer comments.

For the observational studies, items assessed for internal validity were exposure measurement (whether all subjects were given the same HBOT treatment), other interventions, differences in baseline factors among the groups of subjects compared (if a comparison group was included), discussion of or control for potential confounding, masking, evidence of stable baseline, timing of baseline survey, timing of followup measures, outcome measures used, and general comments of the reviewer.

Each study was then assigned an overall rating (good, fair or poor) according to the US Preventive Services Task Force method:

- **Good:** Comparable groups assembled initially (adequate randomization and concealment, and potential confounders distributed equally among groups) and maintained throughout the study; followup at least 80 percent; reliable and valid measurement instruments applied equally to the groups; outcome assessment masked; interventions defined clearly; all important outcomes considered; appropriate attention to confounders in analysis; for RCTs, intention-to-treat analysis.
- **Fair:** Generally comparable groups assembled initially (inadequate or unstated randomization and concealment methods) but some question remains whether some (although not major) differences occurred with followup; measurement instruments acceptable (although not the best) and generally applied equally; outcome assessment masked; some, but not all, important outcomes considered; appropriate attention to some, but not all, potential confounders; for RCTs, intention-to-treat analysis.
- **Poor:** Groups assembled initially not close to being comparable or not maintained throughout the study; measurement instruments unreliable or invalid or not

[1] Jain K, editor. Textbook of hyperbaric medicine. 3rd rev. ed. Kirkland, WA: Hogrefe & Huber Publishers, Inc; 1999.

applied equally among groups; outcome assessment not masked; key confounders given little or no attention; for RCTs, no intention-to-treat analysis.

For each study, the reviewer's assessment of external validity is given, including an assessment of the evidence that the study population reflects the underlying patient population (age-range, co-morbidities, co-interventions, etc.). External validity indicates the applicability of the results of the study to clinical practice. For example, if the study recruited a narrowly defined group of patients, the results may not be generalizable to a broader spectrum of patients. A study can have high internal validity but low external validity. There are no well-defined criteria for assessing external validity, and clinicians must assess the applicability of the results to the patient population for which the intervention is intended.

Findings

Brain Injury

- For traumatic brain injury, one randomized trial provided fair evidence that HBOT might reduce mortality or the duration of coma in severely injured TBI (traumatic brain injuries) patients. However, in this trial, HBOT also increased the chance of a poor functional outcome. A second fair quality randomized trial found no difference in mortality or morbidity overall, but a significant reduction in mortality in one subgroup. Therefore, they provide insufficient evidence to determine whether the benefits of HBOT outweigh the potential harms.
- The quality of the controlled trials was fair, meaning that deficiencies in the design add to uncertainty about the validity of results.
- Due to flaws in design or small size, the observational studies of HBOT in TBI do not establish a clear, consistent relationship between physiologic changes after HBOT sessions and measures of clinical improvement.
- The evidence for use of HBOT in other types of brain injury is inconclusive. No good- or fair-quality studies were found.

Cerebral Palsy

- There is insufficient evidence to determine whether the use of HBOT improves functional outcomes in children with cerebral palsy. The results of the only truly randomized trial were difficult to interpret because of the use of pressurized room air in the control group. As both groups improved, the benefit of pressurized air and of HBOT at 1.3 to 1.5 atm should both be examined in future studies.
- The only other controlled study compared HBOT treatments with 1.5 atm to delaying treatment for 6 months. As in the placebo-controlled study, significant improvements were seen, but there was not a significant difference between groups.
- Two fair-quality uncontrolled studies (one time-series, one before-after) found improvements in functional status comparable to the degree of improvement seen in both groups in the controlled trial.
- Although none of the studies adequately measured caregiver burden, study participants often noted meaningful reductions in caregiver burden as an outcome of treatment.

Stroke

- Although a large number of studies address HBOT for the treatment of stroke, the evidence is insufficient to determine whether HBOT reduces mortality in any subgroup of stroke patients because no controlled trial assessed was designed to assess mortality.
- Among controlled trials, the evidence about morbidity is conflicting. The three best-quality trials found no difference in neurological measures in patients treated with HBOT versus patients treated with pressurized room air.
- Two other controlled trials, one randomized and one nonrandomized, found that HBOT improved neurological outcomes on some measures. However, both were rated poor-quality.
- Most observational studies reported favorable, and sometimes dramatic, results, but failed to prove that these results can be attributed to HBOT. For example, one retrospective study found better mortality rates in patients who received HBOT than a comparison group of patients from a different hospital who did not. The study did not provide information on mortality rates from other causes in each hospital; this information would have made it easier to judge whether the improved survival was due to HBOT or to differences in overall quality of care at the HBOT hospital.
- The observational studies of HBOT provided insufficient evidence to establish a clear relationship between physiologic changes after HBOT sessions and measures of clinical improvement. Few studies established that patients were stable at baseline.

Adverse Events

- Evidence about the type, frequency, and severity of adverse events in actual practice is inadequate. Reporting of adverse effects was limited, and no study was designed specifically to assess adverse effects.
- The few data that are available from controlled trials and cohort studies of TBI suggest that the risk of seizure may be higher in patients with brain injuries treated with HBOT.

- No study of HBOT for brain injury, cerebral palsy, or stroke has been designed to identify the chronic neurologic complications.
- Pulmonary complications were relatively common in the trials of brain-injured patients. There are no reliable data on the incidence of aspiration in children treated for cerebral palsy with hyperbaric oxygen.
- Ear problems are a known potential adverse effect of HBOT. While ear problems were reported in brain injury, cerebral palsy, and stroke studies the incidence, severity and effect on outcome are not clear. However, the rates reported among cerebral palsy patients were higher (up to 47 percent experiencing a problem) than reported with brain injury or stroke. However, the data in brain injury are limited by the use of prophylactic myringotomies.

Supplemental Qualitative Analysis

- Opinions about the frequency and severity of risks of HBOT vary widely.
- Several participants emphasized the importance of continued treatments to maximize results.
- Patients and caregivers value any degree of benefit from HBOT highly. An improvement that may appear small on a standard measure of motor, language, or cognitive function can have a very large impact on caregiver burden and quality of life.

Future Research

Outcome Studies

We identified several barriers to conducting controlled clinical trials of HBOT for brain injury, particularly cerebral palsy:

- Lack of agreement on the dosage and the duration of treatment.
- Need for better measures of relevant outcome measures, such as caregiver burden.
- Lack of independent, reliable data on the frequency and severity of adverse events.
- Patients' unwillingness to be assigned to a placebo or sham treatment group.

As described below, strategies can be developed to conduct good-quality studies to overcome each of these barriers.

Dose and duration of treatment. Oxygen, the "active ingredient" in HBOT, is fundamentally a drug. As for any drug, dose and duration of treatment must be determined in carefully designed dose-ranging studies before definitive studies demonstrating clinical efficacy can be started. Good-quality dose-ranging studies of HBOT for brain injury can be done, based on the model used by pharmaceutical manufacturers and the FDA. It is likely that the dosage of HBOT needs to be individualized based on the patient's age, clinical condition, and other factors. This is the case for many other drugs and does not pose an insurmountable barrier to designing dose-finding trials. In fact, the need to individualize therapy makes it essential to base the design of long-term studies of clinical outcomes on the results of dose-ranging studies.

Better outcome measures. In describing the course of their patients, experienced clinicians who use HBOT to treat patients with brain injury, cerebral palsy, and stroke refer to improvements that may be ignored in standardized measures of motor and neuro-cognitive dysfunction. These measures do not seem to capture the impact of the changes that clinicians and parents perceive. Caregivers' perceptions should be given more weight in evaluating the significance of objective improvements in a patient's function. Unfortunately, studies have not consistently measured caregiver burden, or have assessed it only by self-report. Studies in which the caregivers' burden was directly observed would provide much stronger evidence than is currently available about treatment outcome.

Adverse events. Uncertainty about the frequency and severity of serious adverse events underlies much of the controversy about HBOT. The case against HBOT is based on the reasoning that, because HBOT may be harmful, it must be held to the highest standard of proof. A corollary is that, if HBOT can be shown to be as safe as its supporters believe it to be, the standard of proof of its efficacy can be lowered.

Good-quality studies of adverse effects are designed to assess harms that may not be known or even suspected. The most common strategy is to use a standard template of several dozen potential adverse effects affecting each organ system. Other characteristics of a good study of adverse events are a clear description of patient selection factors, independent assessment of events by a neutral observer, and the use of measures for the severity (rather than just the occurrence) of each event.

Unwillingness to be in a placebo group. The issue of placebo groups has been the subject of a great deal of debate. Participants on both sides make the assumption that an "evidence-based" approach implies devotion to double blind, placebo-controlled trials without regard to practical or ethical considerations. This assumption is false. Double blind, placebo-controlled trials are the "gold standard" for government regulators overseeing the approval of new pharmaceuticals, but not for clinical decision making or for insurance coverage decisions. Evidence-based clinical decisions rely more heavily on comparisons of a treatment to other potentially effective therapies than to placebos.

Several alternatives to the double blind, placebo-controlled trial can be used to examine effectiveness. One approach is to compare immediate to delayed treatment with HBOT, as was done in the Cornell trial. Another is to design a trial in which patients are randomly assigned to several alternative HBOT regimens. Because of uncertainty about the dosage and

duration of treatment, such a trial would be preferable to a trial that offered a choice between one particular regimen and no treatment at all. It is also easier to incorporate a sham therapy arm in such a trial: patients may be more willing to enter a trial if they have a 10 percent or 20 percent chance of being assigned to sham treatment instead of a 50 percent chance. Other alternatives to a placebo include conventional physical, occupational, and recreational therapy, or another alternative therapy, such as patterning.

The Canadian trial of HBOT for cerebral palsy has important implications for the design of future research. In the trial there was a clinically significant benefit in the control group. Debate about the trial centers largely on how the response in the control group should be interpreted. The trial investigators believe that the beneficial effect was the result of the psychological effect of participating in the trial and extra attention paid the children in and out of the hyperbaric chamber. Alternatively, the slightly pressurized air (that is, "mild" hyperbaric oxygen) may have caused the improvement. A third possibility is that the slightly increased oxygen concentration, not the pressure per se, was responsible for the benefit.

A trial that could sort out which of these explanations was true would have a major impact on clinical practice. Such a trial might compare (1) room air under slightly elevated pressure, delivered in a hyperbaric chamber, to (2) elevated oxygen concentration alone, delivered in a hyperbaric chamber, and to (3) an equal amount of time in a hyperbaric chamber, with room air at atmospheric pressure. From the perspective of a neutral observer, the third group is not a "sham" but rather an attempt to isolate the effect of the social and psychological intervention cited by the Canadian investigators.

In addition to needing improved design, future trials of HBOT need better reporting. This would aid interpretation and the application of the research results. Two types of information are essential: a clear description of the research design, particularly of the control and comparison groups, and a detailed description of the patient sample. It is frequently difficult to tell from published studies how comparable the patient populations are, not only demographically but also clinically, in order to interpret the diagnosis and prognosis.

Studies of Diagnosis and Nonclinical Endpoints

An independent, critical assessment of the body of animal experiments and human case studies supporting the "idling neuron" theory of brain injury and recovery should have been done. A large body of studies supports the theory underlying the use of HBOT, but the interpretation of these studies is also disputed. Most of these studies use experimental animal models of brain injury and are designed to provide support for the hypothesis that HBOT redirects blood flow to, and promotes recovery and growth of, "idling neurons" at the border of the damaged brain tissue.

There is sharp disagreement in the medical literature over the validity of these experimental models. One major issue is the significance of improvements in patterns of cerebral blood flow. The principle that redirecting flow toward ischemic areas can help damaged tissue recover is well established in cardiology. However, in critical care generally, drugs and maneuvers that redirect flow to ischemic organs (e.g., brain and kidney) do not always improve recovery at the cellular level. For this reason, improved blood flow must be linked to other measures of cellular and organ recovery.

HBOT for brain injury is not likely to gain acceptance in routine clinical use until a clinical method of assessing its effectiveness in the individual patient is validated.Specifically, the diagnostic value of SPECT scans and of other intermediate indicators of the effects of HBOT should be examined in good-quality studies. Like all other diagnostic tests, SPECT scans have a measurable false positive and false negative rate in relation to clinical outcomes. Controlled trials are not needed as the ideal study design to measure the accuracy of a diagnostic test. Rather, a longitudinal cohort study in which all patients undergo scans as well as standardized followup tests would be a feasible and ideal approach.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Oregon Health & Science University Evidence-based Practice Center, under Contract No. 290-97-0018. It is expected to be available in September 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 85, *Hyperbaric Oxygen Therapy for Brain Injury, Cerebral Palsy, and Stroke,* (AHRQ Publication No. 04-E003). In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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