REVIEW ARTICLE

Hyperbaric Oxygen Therapy for Traumatic Brain Injury: A Systematic Review of the Evidence

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ABSTRACT. McDonagh M, Helfand M, Carson S, Russman BS. Hyperbaric oxygen therapy for traumatic brain injury: a systematic review of the evidence. Arch Phys Med Rehabil 2004;85:1198-204.

Objective: To identify the benefits and harms of hyperbaric oxygen therapy (HBOT) to treat traumatic brain injury (TBI).

Data Sources: MEDLINE, EMBASE, the Cochrane Library, HealthSTAR, CINAHL, MANTIS, professional society databases, and reference lists. Databases were searched from inception through December 2003.

Study Selection: We included English-language studies of patients with TBI given HBOT and evaluating functional health outcomes.

Data Extraction: Data were abstracted by 1 reviewer and checked by a second. Study quality was rated as good, fair, or poor.

Data Synthesis: Two fair-quality randomized controlled trials of patients with severe brain injury reported conflicting results. One found no difference in mortality (48% HBOT vs 55% control) or morbidity at 1 year. In young patients with brainstem contusion, significantly more regained consciousness at 1 month with HBOT (67%) than control (11%) (P<.03). The other found a significant decrease in mortality in the HBOT group at 1 year (17%) compared with controls (31%) (P=.037). This decrease in mortality was accompanied by an increase in proportion of patients with severe disability. Patients with intracranial pressure (ICP) greater than 20mmHg or a Glasgow Coma Scale score of 4 to 6 had significantly lower mortality at 1 year than controls. Five observational studies did not provide better evidence of effectiveness or adverse events. Two indicated a potential for initially reducing elevated ICP in some patients. However, rebound elevations higher than pretreatment levels occurred in some patients. Adverse events, including seizures, pulmonary symptoms, and neurologic deterioration, were reported; however, no study systematically assessed adverse events, and none reported adverse events in control groups.

Conclusions: The evidence for HBOT for TBI is insufficient to prove effectiveness or ineffectiveness, and more high-quality studies are needed. The evidence indicates that there is a small chance of a mortality benefit, which may depend on subgroup selection. The effect on functional status and the incidence and clinical significance of adverse effects are unclear.

Key Words: Brain injuries; Hyperbaric oxygenation; Intracranial pressure; Rehabilitation; Review (publication type).

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USE OF HYPERBARIC OXYGEN therapy (HBOT) to treat traumatic brain injury (TBI) is controversial, with implications for clinicians, patients, and health care systems. Proponents are actively lobbying to expand Medicaid coverage to include HBOT for TBI, and the number of private HBOT centers is increasing.[1] As awareness of HBOT increases through these efforts, patients and their families may increasingly ask their clinicians' opinions on the benefits of HBOT for TBI. In 2000, the US Government Accounting Office reported that the cost of HBOT was estimated at $405 per session, with a mean total treatment cost of $12,000 per patient. The costs associated with its use in TBI may be different, because this report was restricted to outpatient use, most commonly for wound-related problems.[1]

HBOT is defined as the inhalation of 100% oxygen inside a hyperbaric chamber that is pressurized to greater than 1 atmosphere (atm).[2] Typical HBOT regimens use 1.5 to 2.5atm pressure for durations of 30 to 90 minutes, repeated multiple times. The time between and the total number of repeat sessions varies widely.

HBOT is used to treat patients with TBI at some hyperbaric centers around the United States, but it is not widely accepted as effective for this indication. The potential mechanism of action of HBOT in treating TBI has not been fully elucidated. Its use in TBI is based on the theory that damaged cells are "idling neurons" in the ischemic penumbra (the border between healthy and damaged brain tissue), which may have the potential to be recovered.[3-5] Improving oxygen availability to these cells may stimulate the cells to function normally, reactivating them metabolically or electrically, resulting ultimately in angiogenesis and other signs of healing.[5] However, the potential for recovery may be diminished as the time postinjury increases.[5] This theory is controversial, even though there is evidence that secondary ischemia and oxygen deficiency are important mechanisms of cell death in TBI.[6]

Studies in humans showing improvements in blood flow to injured areas, as documented by serial single proton emission computed tomography (SPECT) scans, and changes in cerebral metabolism in patients with TBI after HBOT help to support this theory.[5,7,8] Ultimately, the proof of the theory depends on improvements in functional outcomes.

We conducted a systematic review of the effectiveness of HBOT for TBI as part of a broader-scope evidence report for

the Agency for Healthcare Research and Quality.[9] Our purpose was to identify the benefits and harms of HBOT in treating acute or subacute TBI or the chronic effects of TBI.

METHODS

We searched the following databases: MEDLINE, EMBASE, CINAHL, the Cochrane Library, HealthSTAR, DARE, AltHealthWatch, and MANTIS by using medical subject heading terms and text words for *hyperbaric oxygen therapy* and *brain injury*. Each database was searched from its starting date through February 2002. Searches were updated in December 2003 by using the 4 databases with the highest yield in the original search (MEDLINE, EMBASE, CINAHL, Cochrane Library). We also searched a bibliographic database from the Undersea & Hyperbaric Medical Society; the Database of Randomized Controlled Trials in Hyperbaric Medicine; and the libraries of the European Underwater and Baromedical Society, International Congress on Hyperbaric Medicine, and the National Baromedical Services Inc. Additionally, we searched the references of all included papers, reviews, and the *Textbook of Hyperbaric Medicine*.[5] Finally, some references were suggested by technical experts whom we consulted.

We included studies published in the English language that reported original data from patients with TBI, using any HBOT protocol and evaluating functional health outcomes, including mortality and measures of functional status. In general, we excluded studies that reported only intermediate outcomes, such as changes in cerebral metabolism or electroencephalographic findings. However, we included studies that reported the effect of HBOT on elevated intracranial pressure (ICP), an intermediate outcome that is currently a main determinant of treatment in current clinical practice. Our rationale was that, by reducing ICP, the use of HBOT might reduce the use of invasive or potentially dangerous approaches to monitoring and controlling ICP.

Several other physiologic parameters have been proposed as intermediate measures of the effect of HBOT in TBI. Cerebral blood flow (CBF), the arteriovenous oxygen difference, the cerebral metabolic rate of oxygen, and the distribution of CBF as visualized by SPECT scan are examples. The correlation of clinical outcomes with these measures has not been examined in controlled trials of HBOT for TBI, and we did not include studies reporting only these measures.

Case reports and animal studies were excluded. Before-after and time-series studies with no control group were included if (1) 10 or more cases (authors' arbitrary breakpoint) were reported and (2) outcome measures were reported for both pre- and post-HBOT periods.

Two reviewers (MM, SC) independently assessed for inclusion each title and abstract located through the literature searches, based on the intervention, population, outcome, and study design criteria. Full-text articles, reports, and meeting abstracts that met inclusion criteria were retrieved and again reviewed independently by 2 reviewers (MM, SC). Extraction of data from studies that met eligibility criteria was performed by 1 reviewer (MM) and checked by a second (MH or SC). Disagreements about eligibility or data extraction were resolved through consensus.

The quality assessment of the included studies was based on checklists developed by the National Health Service Centre for Reviews and Dissemination[10] and by the US Preventive Services Task Force (USPSTF).[11] We modified the standard checklists to address issues of particular importance in studies of HBOT. For controlled trials (randomized or nonrandomized), the items assessed were randomization and allocation concealment, baseline comparability of groups, timing of base-line measures, intervention, outcome measures, timing of follow-up measurements (long enough to assess effects), loss to follow-up, handling of dropouts or missing data, masking, and statistical analysis (if any). For observational studies, items assessed were exposure measurement (Were all subjects given the same HBOT treatment?), other interventions, differences in baseline factors among the groups of subjects compared (if a comparison group was included), discussion or control for potential confounding, masking of outcome assessors, evidence of stable baseline, timing of baseline survey, timing of follow-up measures, and outcome measures used. Each study was then assigned an overall rating (good, fair, poor), according to the USPSTF methods.[11]

RESULTS

The searches resulted in 400 citations. Only 7 met inclusion criteria for HBOT treatment of TBI (fig 1): 2 randomized controlled trials (RCTs) and 5 observational studies.

Controlled Trials

The best evidence of the effect of HBOT on mortality and morbidity in TBI comes from 2 fair-quality RCTs (table 1).

Artru et al[12] studied 60 patients with coma because of head injury. These patients were stratified into 9 subgroups, based on the severity of coma and the presence of mass lesions, and were then randomized to HBOT or to standard therapy. Artru did not report whether the resulting subgroups were similar in other important prognostic variables. The HBOT regimen was 2.5atm for 60 minutes daily for 10 days, then 4 days off, repeating this schedule until the patient died or recovered consciousness. Timing of admission to the study in relation to the injury was not reported. The average time between onset of coma and treatment was 4.5 days. This study was rated fair quality, because randomization and allocation concealment were not reported, there were differences in HBOT intervention depending on other medical factors, and masking of outcome assessors was not reported.

After 12 months of follow-up, overall mortality was similar in both groups (48.3% HBOT vs 55.2% control). The rate of recovery of consciousness at 1 month was higher in the HBOT group (42% HBOT vs 28% control), but this finding was not statistically significant.[12] The mean duration of coma was also shorter in the HBOT group but did not differ statistically significantly from the control group (28.2d vs 32.7d). In 1 of 9 subgroups, patients younger than 30 years with brainstem contusion were more likely to recover consciousness by 1 month if they received HBOT. There were 9 patients in each group; 1 died in each group, and there were 6 conscious in the HBOT group and 1 conscious in the control group at 1 month (67% HBOT vs 11% control, $P<.03$).

In the second trial, Rockswold et al[13] studied 168 patients with acute closed-head trauma. Patients had Glasgow Coma Scale (GCS) scores of 9 or less, 6 to 24 hours after admission with a severe head injury or 6 to 24 hours after deterioration after admission for what appeared to be a mild or moderate injury.[13-15] Patients randomized to HBOT were treated with 1.5atm for 60 minutes every 8 hours for 2 weeks or until the patient was brain dead or could consistently follow simple commands. An average of 21 treatments per patient were given. There were several differences between the HBOT and the control groups at baseline. Although not statistically significant, the differences appeared large on some potentially important factors. For example, more patients in the control group than in the HBOT group (49% vs 39%) had an operative mass lesion, and more patients in the HBOT group than in the control group (52% vs 46%) had ICP above 20mmHg. Overall,

N=400
Citations identified through
electronic and hand searches

n=232
Excluded*

n=168
Full-text articles considered for
inclusion

n=11
Unable to retrieve full article
n=12
Available as abstract only

n=145
Full-text articles reviewed for
inclusion

n=138
Excluded*

2 controlled trials
5 observational studies
Included

* Exclusion criteria:
    1. No patients with TBI.
    2. No HBOT.
    3. Opinion, letter, or short review with
       no patient data.
    4. Fewer than 10 patients or baseline
       not established for before-after
       studies and time series.
    5. Data from anoxic brain injury or
       HBOT not discernable, or abstract
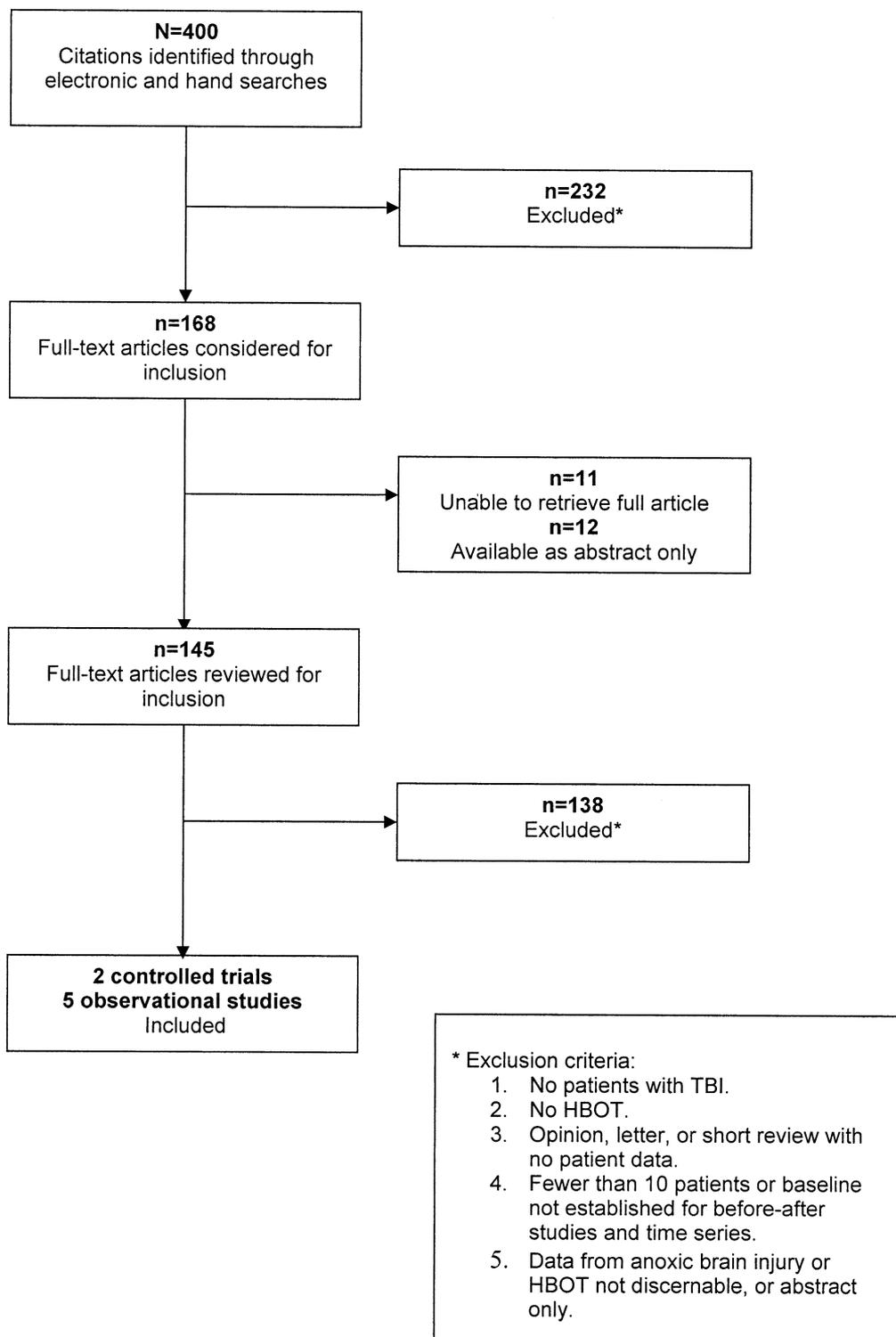   only.

Fig 1. Study eligibility flow-
chart.

Table 1: Study Characteristics of RCTs of HBOT for TBI

Study, Location, and Quality	Population	HBOT Protocol (type of chamber)	Other Interventions	Baseline Differences Between Groups	No. of Patients
Artru et al[12] France Fair	Patients with severe head injuries in a coma (mean Jouvet scale score, 9.5). Time from injury not reported; mean time from onset of coma to treatment, 4.5d.	2.5atm × 60min daily × 10d of treatment alternating with 4d off until patient regained consciousness or died. (Type of chamber not specified.)	Standard therapeutic measures were the same in both groups.	No information on factors other than those on which they matched participants. Severity of coma (based on Jouvet scale) was 9.39 for HBOT and 9.59 for control group (NS). Types of brain lesions similar except acute subdural hematoma (7 in HBOT, 3 in control group). Age similar (HBOT, 29.9y; control, 29.7y).	31 HBOT, 29 control
Rockswold and Ford,[15] Rockswold et al,[13] Rockswold[14] Minnesota Fair	Patients with severe head injury admitted 1983-1989. GCS score of ≤9 for at least 6h within 24h of admission or deterioration.	1.5atm × 60min every 8h × 2wk or until the patient was brain dead or could consistently follow simple commands. Average 21 treatments per patient. (Monoplace chamber.)	All patients received intensive neurosurgical care, according to standard medical practice covering stabilization in the ED, surgical management, medical treatment, and the management of ICP. However, HBOT patients received closer ICP monitoring. All study patients received phenytoin.	Small differences in proportion with operable mass lesions, multiple trauma, elevated ICPs, and "poor outcome BAEPs" and "SSEPs."	84 HBOT, 84 control

Abbreviations: BAEPs, brainstem auditory-evoked potentials; ED, emergency department; GCS, Glasgow Coma Scale; NS, not significant; SSEPs, somatosensory evoked potentials.

differences in prognostic variables did not seem to favor either the HBOT group or the control group.

Rockswold[13-15] did not report whether patients enrolled after deterioration were distributed evenly, and because these patients may have a worse prognosis, the results of the trial could be biased if they were not distributed equally in the 2 groups. The outcomes for this subgroup were not reported separately. After 38 patients received HBOT, the protocol was changed to require prophylactic myringotomy, because the researchers thought that ear pain caused by HBOT was contributing to a lack of effect in reducing elevated ICP. This study was rated fair quality, because randomization and allocation concealment were not described; some differences between groups existed at baseline; the intervention was not consistent across all patients in the HBOT group; and although long-term outcomes were assessed by masked neurologists, the analysis of ICP data did not seem to be masked, as evidenced by the change in protocol because of a lack of response.

The main results of the trial are summarized in table 2. After 1 year, patients who were assigned to HBOT treatment had lower mortality than those in the control group (17% vs 31%, $P=.037$), but there was no difference in the proportion of patients who were either dead or severely disabled (48% HBOT vs 46% control, $P=.871$). Additional analysis showed that HBOT reduced mortality in patients who had a GCS score

of 4 to 6 or ICP greater than 20mmHg, but it did not reduce mortality in other subgroups of patients.

In the Rockswold trial, ICP measurements were taken every 15 minutes during HBOT and then hourly until the next treatment and hourly in the control group.[13-15] The mean peak ICP values in controls and HBOT patients did not differ significantly. However, mean peak ICP was significantly lower for patients who received HBOT and myringotomy (22mmHg) versus patients who received only HBOT (33mmHg) and versus controls (30mmHg) ($P<.05$). Baseline ICP, time to the mean peak, duration of the effect, and treatments given for elevated ICP stratified by subgroup were not reported. Interpretation of these findings without these data is superficial. Without baseline data, the size of the effect cannot be accurately assessed; without the time to mean peak ICP, the relationship of these findings to HBOT cannot be assessed, and the treatments given may introduce confounding.

Neither controlled trial adequately reported adverse events. In the Artru trial, which used 2.5atm of pressure, treatment was stopped in 35% (11/31) of sessions because of pulmonary symptoms.[12] No information was presented on outcomes of these patients or on whether treatment was restarted later. In the Rockswold trial,[13-15] which used 1.5atm of pressure, HBOT had to be permanently stopped because of adverse effects in 12% (10/84) of the patients. The reasons for withdrawal of therapy were not described clearly. By protocol, HBOT was discontinued when a patient's GCS motor score decreased by 1 point without apparent explanation, but the investigators did not say how often this occurred. Two patients had seizures. Pulmonary complications (increasing fraction of inspired oxygen requirement and/or infiltrates detected on chest radiograph) were described as the most frequent complication, but the number, severity, and outcome of these adverse events were not reported. After 2 patients had hemotympanum, prophylactic myringotomies were performed on the last 46 patients enrolled in the HBOT arm. Neither study reported rates of similar adverse events in control groups.

Observational Studies

We found 5 observational studies of HBOT in patients with TBI. Four of these studies[16-19] compared the conditions of a

Table 2: Morbidity and Mortality Results From RCTs of HBOT for TBI

	HBOT Group, n/n (%)	Control Group, n/n (%)	P Value
Artru et al[12]			
Died within 1y	15/31 (48)	16/29 (55)	NS
Conscious at 1mo	13/31 (42)	8/31 (26)	NS
Independent in daily activities at 1y	14/31 (45)	12/29 (41)	NS
Rockswold et al[13]			
Died within 1y	14/84 (17)	26/84 (31)	.04
Dead or severely disabled at 1y	40/84 (48)	40/84 (48)	.99

single group of patients before and after HBOT treatment. The other study[20] compared 2 groups of patients, 1 of which was treated with HBOT. Two were of fair quality and 3 were of poor quality.

In most of these studies, the main research goal was to examine the short-term effect of HBOT on physiologic parameters (eg, ICP), sometimes with the goal of examining whether a correlation between physiologic parameters and patients' outcomes was observed. These studies reported outcomes incompletely and often provided no information on how assessments were made. None of the studies masked the assessment of prognostic measures or clinical outcomes.

Two fair-quality studies[16,17] primarily examined physiologic changes associated with HBOT, with little or no emphasis on clinical outcomes. Hayakawa et al[16] studied 13 comatose brain-injured patients, 9 with TBI. Because these 9 were not reported separately, we used data from all 13 subjects. Hayakawa described the patients as being in the acute postinjury period. Cerebrospinal fluid pressure (CSFP) was measured before, during, and after a single treatment with 2atm pressure for 1 hour. On the basis of the description in the methods, it appears that ICP was measured; however, because CSFP can also refer to measurement of pressure outside the intracranial space, there is some uncertainty about the comparability to other studies. The baseline CSFP ranged from 20 to 40mmHg. After treatment, CSFP was 5mmHg higher than the pre-HBOT level in 2 patients, 5mmHg lower in 2 other patients, and similar to the pre-HBOT level in the remainder of patients. The investigators provided no information about the clinical responses of these patients, but they stated, "When [HBOT] produced a major change in CSFP, the neurological deficit of the patient was mild and the clinical improvement with OHP [oxygen under hyperbaric pressure] was remarkable. On the other hand, when CSFP was little changed by OHP, there was little clinical improvement and the patient commonly had extensive brain damage."[16] It is impossible to determine how the investigators decided that a subject improved clinically or if the CSFP response to HBOT was a cause of a good prognosis or simply a marker of it.

Rockswold et al[17] measured cerebral metabolism, CBF, and ICP before and up to 6 hours after HBOT treatment in 37 TBI patients with severe closed-head injury (defined as a GCS score ≤8), admitted to a trauma center. Time since injury was not reported. The investigators did not report clinical outcomes. The protocol specified that each subject would be treated for 60 minutes at 1.5atm of pressure daily for up to 6 days. All patients in this study received prophylactic myringotomies before treatment.

In patients with pretreatment ICP greater than 15mmHg, ICP rose during the HBOT session by an average of 7mmHg, and then fell 1 hour after treatment by an average of 2mmHg. By 6 hours after treatment, the average reduction in ICP was 4mmHg. In patients with pretreatment ICP less than 15mmHg, there was a small (2–4mmHg) increase during and up to 6 hours after HBOT. At some point during their stay, 44% of the subjects had an episode of intracranial hypertension (ICP >20mmHg) for 20 minutes or longer. It is unknown whether the proportion would have been higher or lower in a group of similar subjects who did not receive HBOT.

The effect of HBOT on CBF and metabolic measures was complex, with low CBF increasing, high CBF decreasing, CSF lactate levels decreasing (where it could be measured), and no effect on arteriovenous oxygen difference found. Correlations between these changes and either ICP or clinical outcomes were not reported.

The 3 poor-quality studies[18-20] are summarized briefly below to show the serious limitations.

Mogami et al[19] did a retrospective before-after study of 66 brain-injured patients, 51 of whom had TBI. The study results are uninterpretable, because prognostic information about the subjects before treatment was inadequate. Patients were described as severe, but no definition was given, and the time since injury was not reported. The main outcome measure was whether the patient improved. Improvement was classified as "great," "some," or "none." The timing of assessment and the criteria used to classify patients' conditions were not described, other than to say that the assessment included mental as well as neurologic function. Notably, only patients who had mild deficits improved.

In a retrospective cohort study, Ren et al[20] examined the effect of HBOT on 35 subjects with severe TBI (GCS score <8); 20 control subjects with TBI did not receive HBOT. All patients were admitted to the hospital within 24 hours of injury, but HBOT was not administered until the patient was stable for 3 days. The main outcome measure was functional status, measured by the Glasgow Outcome Scale (GOS) score 6 months after treatment. We rated the study as one of poor quality, because it lacked a well-defined inception cohort and excluded subjects who died after the analysis. Because the study was not randomized, selection bias could be a confounding factor. The investigators did not explain why there were uneven numbers of patients in the groups (35 vs 20) and provided no details on how patients were selected.

This study found significant improvement in the mean GCS after 1 and 3 treatments (both $P<.01$) in the HBOT-treated group, with a mean GCS score of 5.1 at baseline and 14.6 after 3 treatments. No significant difference in mean score was found in the control group, with a mean GCS score of 5.3 at baseline and 9.5 at 6 months. This result corresponded to a significant difference between the 2 groups in the proportion with good recovery or mild disability (based on the GOS score) at 6 months ($P<.001$). However, this analysis is not based on change in mean score but on a comparison of scores at 6 months.

Sukoff and Ragatz[18] did a retrospective study of HBOT in 50 patients with traumatic encephalopathy, 10 of whom underwent continuous ICP monitoring. Severity and time since injury were not reported. In the ICP-monitored patients, HBOT treatments at 2atm of pressure for 45 minutes were given every 8 hours for 48 hours or every 4 hours if the ICP remained above 15mmHg. In patients without ICP monitoring, HBOT was given every 8 hours for 2 to 4 days, depending on the clinical response.[18] The study was rated of poor quality, because potential confounding factors were not addressed, outcome assessors were not masked, and data were presented selectively rather than according to a protocol.

Detailed case descriptions were provided for the 10 patients who had ICP monitoring. A review of these case histories suggests that the ICP levels for 8 subjects decreased during their hospital course, whereas 2 had ICP values near or higher than pretreatment at 2 hours. For the other 40 subjects, Sukoff and Ragatz[18] reported that 22 "improved while undergoing their treatments," but they provided no information about the criteria used to assess the response.

Adverse Events

None of these studies adequately reported adverse events. Seizures were reported in 4 HBOT patients in 3 studies,[13-15,18,19] and pulmonary symptoms impeded therapy in 2 studies.[12,13-15] In 1 study, 4 myringotomies were required, and

increased restlessness was seen in some comatose HBOT patients.[18] Adverse effects were not reported in 3 studies.[16-18]

DISCUSSION

The evidence supporting the use of HBOT to treat TBI is insufficient to clearly establish the risks and benefits. The best evidence, from 2 fair-quality randomized trials, is conflicting. One trial found that HBOT reduced mortality but did not improve outcomes after 1 year of follow-up.[13-15] Specifically, the proportion of completely disabled and severely disabled survivors was much higher in the HBOT group than in the control group. The other trial found no difference in mortality after 1 year of follow-up.[12]

Differences between these 2 studies might explain the discrepant mortality results. First, Artru et al[12] was a much smaller study and could have missed an important difference in mortality. Second, the HBOT protocols differed among these studies. The Rockswold[13-15] trial used 1.5atm, whereas the Artru study used 2.5atm.[12] In the Rockswold trial, patients were treated for 60 minutes every 8 hours for 2 weeks or until the patient regained consciousness or died.[13-15] In the Artru trial,[12] treatments were given daily for 10 days, followed by 4 days without treatment, followed by 10 days of treatment until the patient regained consciousness or died. These differences can be seen as differences in dosage and regimen, which could affect the results. In both trials, there were a substantial number of protocol violations. Third, in most cases, Rockswold began treatment within 24 hours of injury, whereas in Artru's patients there was an average delay of 4.5 days between the onset of coma and the start of HBOT. It is possible that Artru's patients were treated beyond a window of time in which the penumbra was still recoverable, but this theory cannot be substantiated from a comparison of these 2 studies because of other potentially important differences.

It is important to note that Artru's control patients had higher mortality ($\approx$50%)[12] than Rockswold's control patients (34%).[13-15] This could be because of differences in baseline prognosis or to differences in the standard treatments given to control patients. Unfortunately, it is difficult to compare the prognoses of the patients in the 2 studies, because they used different scales to assess the prognosis of the head injury and provided different information about associated injuries and other comorbidities. Rockswold used the GCS, whereas Artru used a modified Jouvet scale.[21] The 2 scales are thought to be poorly correlated.[22] Because of the spread in the years of publication (1976 and 1994) and the different countries involved, it can be assumed that the standard treatments given to patients varied considerably. For example, in the more recent Rockswold trial, all patients had ICP monitoring and received phenytoin. In the Artru study, most patients in both groups received furosemide and mannitol.

Differences in study quality are unlikely to explain the discrepant results of the trials, but the limitations of both trials make their results uncertain. Neither study described the methods used to randomize patients. Some methods of randomization cannot prevent investigators from (knowingly or unknowingly) placing patients with a more favorable prognosis into the treatment group. Empirical evidence has shown that studies that do not describe the method of randomization report exaggerated effects.[23] This flaw is particularly important in studies of comatose trauma patients, because an experienced clinician can predict prognosis within groups of patients who have a similar severity-of-illness score.

Of the 2 trials, Rockswold's had slightly better validity, because it masked outcome assessors (although assessment of ICP data appear to have been unmasked) and reported how the patients were selected from the potential pool of eligible patients and how many refused enrollment.[13-15] This study enrolled 168 of 272 eligible patients (62%). Of the 272 potentially eligible patients, 18% died within 6 hours of admission, 8% had contraindications to HBOT, 6% were not identified as potential subjects in time for randomization within 6 hours of admission, and 6% did not give consent (no details were given on the baseline characteristics or outcome of these patients).

In the Rockswold trial, nearly all the observed reduction in mortality occurred in the subgroup of patients who had ICP of 20mmHg or higher before treatment.[13-15] One important question is whether this benefit corresponded to a reduction in ICP in these subjects. Rockswold theorized that (1) the pain caused by increased otic pressure contributed to the maintenance of elevated ICP, and (2) the effect of HBOT can be seen once prophylactic myringotomies are performed. Although a lower mean peak ICP was reported in patients who received both HBOT and myringotomy, it is unclear whether these are the same patients who had ICP of 20mmHg or higher at baseline and subsequently had a lower mortality rate.

The observational studies of HBOT in TBI provided insufficient evidence to establish a clear relationship between physiologic changes after HBOT sessions and measures of clinical improvement. Most did not include a control group, and baseline data regarding patient severity and prognosis were missing or poorly reported. The important quality problems were lack of establishing a stable baseline before taking measurements, failure to mask outcome assessors, and lack of objective outcome measures. The best observational study, that of Rockswold et al,[17] did not report clinical outcomes. Those that did report them were inadequately controlled, used subjective (or did not describe) methods to assess clinical outcomes, and provided insufficient information to determine whether the observed outcomes were attributable to HBOT or could have been expected from the severity of injury and other prognostic characteristics of subjects. Without adequate control groups, these studies may suffer from both bias and confounding and have very limited ability to clarify the role of HBOT in TBI. A well-designed cohort or case-control study would add meaningful insight into the balance between benefits and harms of HBOT for TBI.

The evidence on adverse effects of HBOT in the setting of acute TBI is also insufficient. None of the studies was designed to identify adverse effects adequately. It appears that events were detected and reported selectively. No study included a process for identifying adverse events or provided definitions for what was considered an adverse event, and none used a standardized method to rate the severity and clinical significance of adverse effects. Seizures, pulmonary symptoms, and neurologic deterioration were the most serious adverse events reported. However, because this population is at risk for these adverse events without HBOT, and the reporting in the 2 controlled trials was inadequate, it is not possible to assess the additional risk contributed by HBOT.

CONCLUSIONS

A small number of studies on HBOT for TBI were found, and these studies had multiple internal and external validity problems. The best evidence comes from 2 fair-quality RCTs, which found disparate effects on mortality in TBI patients on the whole. Adverse events were reported only sporadically for HBOT-treated groups, and consideration of adverse events in control groups was disregarded.

Taken together, the results of the studies indicate that there is small chance of a mortality benefit, which may be dependent on appropriate selection of patients with specific prognostic

characteristics. The effect on the functional status of survivors and the incidence and clinical significance of adverse effects are unclear. The evidence is insufficient to prove the effectiveness or ineffectiveness of HBOT for TBI, and other, high-quality studies are needed.

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