Results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen

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The authors enrolled 168 patients with closed-head trauma into a prospective trial to evaluate the effect of hyperbaric oxygen in the treatment of brain injury. Patients were included if they had a total Glasgow Coma Scale (GCS) score of 9 or less for at least 6 hours. After the GCS score was established and consent obtained, the patient was randomly assigned, stratified by GCS score and age, to either a treatment or a control group. Hyperbaric oxygen was administered to the treatment group in a monoplace chamber every 8 hours for 1 hour at 1.5 atm absolute; this treatment course continued for 2 weeks or until the patient was either brain dead or awake. An average of 21 treatments per patient was given.

Outcome was assessed by blinded independent examiners. The entire group of 168 patients was followed for 12 months, with two patients lost to follow-up study. The mortality rate was 17% for the 84 hyperbaric oxygen-treated patients and 32% for the 82 control patients (chi-squared test, 1 df, p = 0.037). Among the 80 patients with an initial GCS score of 4, 5, or 6, the mortality rate was 17% for the hyperbaric oxygen-treated group and 42% for the controls (chi-squared test, 1 df, p = 0.04). Analysis of the 87 patients with peak intracranial pressures (ICP) greater than 20 mm Hg revealed a 21% mortality rate for the hyperbaric oxygen-treated patients, as opposed to 48% for the control group (chi-squared test, 1 df, p = 0.02). Myringotomy to reduce pain during hyperbaric oxygen treatment helped to reduce ICP. Analysis of the outcome of survivors reveals that hyperbaric oxygen treatment did not increase the number of patients in the favorable outcome categories (good recovery and moderate disability). The possibility that a different hyperbaric oxygen treatment paradigm or the addition of other agents, such as a 21-aminosteroid, may improve quality of survival is being explored.

Key Words • head injury • hyperbaric oxygen • intracranial pressure • clinical trial

Head injury is the leading cause of death in people between the ages of 2 and 42 years, with 15- to 24-year-olds having the highest mortality rate.2,24,26 The toll on society, financial and otherwise, is immense. Our review of the literature suggested that hyperbaric oxygen may have some value in the treatment of severe head injury.5,9,11,19,30 In 1983, we began a clinical trial at the Hennepin County Medical Center to learn if severely head-injured patients would benefit from treatment with hyperbaric oxygen.

Clinical Material and Methods

Patient Population

Potential study candidates included all victims of acute severe head injury admitted to our Level I Trauma Center. Severe head injury was defined as a Glasgow Coma Scale (GCS) score of 9 or less. The GCS score for entry into the study was determined between 6 and 24 hours after hospital admission. Patients were not accepted into the study during the 6 hours following hospital admission because rapid neurological improvement or deterioration often occurs at this time.

Patients who entered the hospital with a seemingly mild or moderate head injury but subsequently deteriorated to a GCS score of 9 or less also became candidates for the study. In this situation, the same procedure was followed to determine eligibility and the randomization category, except that the 6- to 24-hour window for determining the entry GCS score was measured from the time of deterioration.
After eligibility and the GCS score were established, informed consent was obtained. Random assignment of the patient to either the hyperbaric oxygen-treated group or the control group then occurred. Controls were not sham-treated. Approval of this study had been granted by our institution's Human Subjects Research Committee.

**Patient Management**

All patients received intensive neurosurgical care according to a protocol covering stabilization in the Emergency Department, surgical management, medical treatment, and the management of intracranial pressure (ICP). Medical management was consistent with standardized management practices in institutions that routinely treat severely head-injured patients. In the hyperbaric oxygen-treated group, ICP data were collected every 15 minutes during the 60-minute treatment, and then hourly for the next 7 hours, when it became time for the next treatment. In the control group, ICP data were collected hourly. Data collected in both groups continued for 2 weeks, until the monitoring device was removed, or until hyperbaric oxygen treatments were discontinued. Brain-stem auditory evoked potentials (BAEP) and short-latency somatosensory evoked potentials (SSEP) were obtained within the first few days of injury and again in 2 weeks. Standard recording procedures were used with results graded blindly.

**Hyperbaric Oxygen Treatment**

Hyperbaric oxygen treatments were given in a Sechrist monoplace hyperbaric chamber. Compression with 100% oxygen to 1.5 atm absolute (ATA) occurred at a rate of 1 psf/min. The patient was kept at depth for 60 minutes and was decompressed at the same rate. Treatments were given every 8 hours for 2 weeks or until the patient was brain dead or could consistently obey simple commands.

Patient monitoring and safety within the hyperbaric oxygen chamber were of the utmost importance. Arterial blood pressure, electrocardiograms, and ICP were routinely monitored. Chest tubes and nasogastric tubes were frequently present in these patients. Although physical access to the patient is limited during hyperbaric oxygen treatment, in an emergency the chamber can be ventilated less than 10 seconds. Bilateral myringotomies were performed on the last 46 of the 84 patients in the hyperbaric oxygen group.

Oxygen toxicity is always a potential problem with hyperbaric oxygen therapy. It is a function of both partial pressure and exposure time and is often manifested in the pulmonary system and central nervous system (CNS). Since pulmonary oxygen toxicity is most often characterized by a progressively decreased level of oxygen tension (pO2) after repeated exposure to hyperbaric oxygen, we established and adhered to the following guidelines. If a patient required a fraction of inspired oxygen (FIO2) of 50% or greater to maintain adequate oxygenation (pO2 > 70 mm Hg), hyperbaric oxygen therapy was temporarily discontinued. If the patient’s condition improved and the FIO2 requirement dropped to 40% or less, treatment resumed; however, if the oxygen requirement again increased to an FIO2 greater than 50%, treatment was permanently terminated. At the frequency and depth of hyperbaric oxygen treatment used in this study, clinical CNS oxygen toxicity has usually been manifested by seizure. If the patient’s GCS motor score decreased by 1 point without apparent explanation, hyperbaric oxygen treatment was discontinued.

Tocopherol (vitamin E, 400 mg) was given via nasogastric tube every 8 hours as an antioxidant agent. This is considered a standard treatment with repetitive use of hyperbaric oxygen, and this dosage would result in insignificant brain levels. Both hyperbaric oxygen-treated and control patients received prophylactic phenytoin sodium.

**Outcome Measurement**

**Glasgow Outcome Scale.** We chose the Glasgow Outcome Scale as our primary tool for assessing recovery since it is simple, standardized, widely used, and facilitates comparisons between different series. At 6, 12, and 18 months after injury, each patient was assigned by a neurologist unaware of the patient’s treatment group to one of five categories: 1) good recovery (independent, but minor physical or mental deficits may be present); 2) moderately disabled (independent but disabled); 3) severely disabled (dependent upon others); 4) vegetative (no evidence of meaningful responsiveness); or 5) dead. Patients in Categories 1 and 2 were considered to have “favorable” outcomes while those in Categories 3, 4, and 5 were considered to have “unfavorable” results.

**Statistical Analysis.** The subjects were divided into broad age categories: 0 to 29 years, 30 to 59 years, and 60 years and older. The GCS strata included individual entry scores of 3 through 9. This preassigned stratification gave some protection against the chance development of a significant imbalance between the hyperbaric oxygen and the control groups in terms of age and initial severity of injury. Although the subjects were examined several times during their recovery, comparisons were based on the 12-month follow-up examination. We conducted separate statistical analyses for treatment effect on subjects with “entry” GCS scores of 3, 4, 5, 6, and the group with 7 to 9 values. The stratum of subjects with initial entry GCS scores of 4 to 6 was expected to be more sensitive to the potential benefits of the hyperbaric oxygen treatment because of the high mortality rate for patients with a GCS score of 3 and the relatively consistent good outcome for patients with GCS scores of 7 to 9. For patients with GCS scores of 4, 5, and 6, an increase by 30% in the survival or favorable recovery rate would be detected (with a one-tailed α of 0.05) 80% of the time with 40 hyperbaric oxygen-treated subjects and 40 controls. This was the key comparison of the study.
Brain injury and hyperbaric oxygen

TABLE 1
Characteristics of 168 head-injured patients in this series

<table>
<thead>
<tr>
<th>Factor</th>
<th>Treatment Group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperbaric O₂</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>no. of patients</td>
<td>84</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>average age (yrs)</td>
<td>32</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>sex (males)</td>
<td>77%</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>average entry GCS score</td>
<td>6.2</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>operative mass lesion(s)</td>
<td>39%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>multiple trauma</td>
<td>37%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>15 to 24 years old</td>
<td>33%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>ICP persistently &gt; 20 mm Hg</td>
<td>52%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>unreactive pupils</td>
<td>29%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>unilateral</td>
<td>8%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>bilateral</td>
<td>22%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>poor-outcome BAEP</td>
<td>6%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>poor-outcome SSEP</td>
<td>44%</td>
<td>37%</td>
<td></td>
</tr>
</tbody>
</table>

* Abbreviations: GCS = Glasgow Coma Scale; ICP = intracranial pressure; BAEP = brain-stem auditory evoked potentials; SSEP = somatosensory evoked potentials.

Results

Patient Population

Patient enrollment began in December, 1983, and ended in August, 1989. During this period, 272 patients with severe head injury were admitted to our center, 168 of whom were assigned to the study. The other 104 patients were excluded for the following reasons: 49 died within 6 hours of admission, 22 had contraindications to hyperbaric oxygen treatment, 16 were not recognized or reported to the study coordinator in time for randomization, and consent could not be obtained for 17. A total of 168 patients were entered into the study: 84 into the hyperbaric oxygen treatment group and 84 into the control group (Table 1). The two groups were very similar in terms of severity of injury. Interpretable baseline BAEP data were available within 7 days of injury for 48 hyperbaric oxygen-treated patients and 50 control patients, and SSEP data were available for 48 hyperbaric oxygen-treated patients and 51 controls. There was no significant difference between the hyperbaric oxygen and control groups in the proportion of patients showing poor-prognosis evoked potentials (Table 1). Evaluation for discrepancies in standard treatment for the control and treated patients revealed no significant difference in the usage of mannitol or barbiturates in all Glasgow Outcome Scale groups.

Hyperbaric Oxygen Treatments

The average amount of time from injury to the first hyperbaric oxygen treatment was 26 hours; the average time from randomization to the first hyperbaric oxygen treatment was 9.1 hours. Eighty patients received a total of 1688 hyperbaric oxygen treatments, for an average of 21 treatments per patient. Twenty-two patients experienced 24 protocol deviations; the most frequent deviation was in the administration of the hyperbaric oxygen (Table 2).

Intracranial Pressure

We postulated that inner ear pain, which is commonly experienced during hyperbaric oxygen therapy, might have contributed to higher-than-expected ICP's in the chamber, so we performed bilateral myringotomies on the last 46 of the 84 hyperbaric oxygen-treated patients.

Table 3 presents the mean observed peak ICP by...
Treatment group. A simple t-test comparing peak ICP between hyperbaric oxygen-treated and control subjects found no statistically significant difference (t = 0.92, 154 df). However, when the group of subjects treated with hyperbaric oxygen plus myringotomy are separated, some significant differences can be detected. It can be seen that the group with the lowest average peak ICP is the hyperbaric oxygen plus myringotomy group, which was significantly smaller than either the hyperbaric oxygen-only group (t = 2.84, p < 0.05) or the control group (t = 2.48, p < 0.05). The hyperbaric oxygen plus myringotomy group also showed the least variability in these peak values (standard deviation 11.7).

Outcome

Two control patients were lost to follow-up study; therefore, the 12-month outcome analyses are based on data from 84 hyperbaric oxygen-treated patients and 82 controls, for a total of 166 patients.

Mortality Rate. The difference in the overall mortality rate between the hyperbaric oxygen and control groups was statistically significant, with comparisons between certain subgroups revealing significant differences (Table 4). The mortality rate was 17% for the 84 hyperbaric oxygen-treated patients and 32% for the 82 control patients (chi-squared test, 1 df, p = 0.037). The log-rank (Mantel-Haensel) test for comparing the difference between two survival curves indicated a difference with a p value of 0.017. Of the 40 patients who died (both groups), 90% died of cerebral causes. If the patient was vegetative, death was attributed to a neurological cause even if the patient died from intercurrent illness, such as pulmonary embolus.

Hyperbaric oxygen treatment was related to a significant difference in mortality rate for two specific subgroups: patients with entry GCS scores of 4 to 6 and patients with ICP's greater than 20 mm Hg for over 20 minutes. The difference in mortality rate between the hyperbaric oxygen-treated and control patients with GCS scores of 4 to 6 was significant by the chi-squared test (1 df, p = 0.04) and by the log-rank (Mantel-Haensel) test for equality of survival curves (p = 0.02). Hyperbaric oxygen-treated patients with ICP's higher than 20 mm Hg for over 20 minutes had a mortality rate of 21%, as compared to 48% for the control group (chi-squared test, 1 df, p = 0.02).

Although the difference in mortality rates between the hyperbaric oxygen-treated and control patients with surgical mass lesions was not statistically significant by two-tailed chi-squared analysis (p = 0.09), it was found to be significant when the probability of survival was compared using the log-rank (Mantel-Haensel) test (p = 0.03). One control patient with a surgical mass lesion died after his 12-month follow-up examination; his death is not reflected in Table 3 but was included in the Mantel-Haensel analysis. Morbidity. No statistically significant differences resulted between hyperbaric oxygen-treated and control patients when favorable outcome was analyzed at 12 months (Table 5).

Discussion

Mechanism of Action

Inadequate oxygen supply to the traumatized brain results in the conversion of aerobic glucose metabolism to anaerobic metabolism. Anaerobic metabolism results in acidosis and depletion of cellular energy. As the demands for energy production are no longer met, the brain cells lose their ability to maintain normal ionic homeostasis. Abnormally high intracellular concentrations of calcium result. This abnormal cellular environment causes the formation of highly reactive free radicals that are extremely damaging to cell membranes.

When ischemia is immediate and profound, as from cerebrovascular occlusion, the above events occur rapidly (in minutes to hours); however, there is evidence that ischemia can occur days after the initial head

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**TABLE 4**

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment Group</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperbaric O₂</td>
<td>Control†</td>
</tr>
<tr>
<td>all patients</td>
<td>14/84 (17%)</td>
<td>26/82 (32%)</td>
</tr>
<tr>
<td>GCS score 3</td>
<td>3/4 (75%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>GCS score 4 to 6</td>
<td>7/42 (17%)</td>
<td>16/38 (42%)</td>
</tr>
<tr>
<td>GCS score 7 to 9</td>
<td>4/38 (11%)</td>
<td>7/39 (18%)</td>
</tr>
<tr>
<td>mass lesions</td>
<td>8/33 (24%)</td>
<td>19/41 (46%)</td>
</tr>
<tr>
<td>contusions</td>
<td>6/51 (12%)</td>
<td>7/41 (17%)</td>
</tr>
<tr>
<td>ICP ≤ 20 mm Hg</td>
<td>3/32 (9%)</td>
<td>5/35 (14%)</td>
</tr>
<tr>
<td>ICP &gt; 20 mm Hg</td>
<td>10/47 (21%)</td>
<td>19/40 (48%)</td>
</tr>
<tr>
<td>fixed pupil(s)</td>
<td>9/23 (39%)</td>
<td>13/23 (57%)</td>
</tr>
</tbody>
</table>

* Abbreviations: GCS = Glasgow Coma Scale; ICP = intracranial pressure.
† Two patients lost to follow-up study.
‡ Chi-squared analysis.

**TABLE 5**

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment Group</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hyperbaric O₂</td>
<td>Control†</td>
</tr>
<tr>
<td>all patients</td>
<td>44/84 (52%)</td>
<td>44/82 (54%)</td>
</tr>
<tr>
<td>GCS score 3</td>
<td>1/4 (25%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>GCS score 4 to 6</td>
<td>17/42 (40%)</td>
<td>16/38 (42%)</td>
</tr>
<tr>
<td>GCS score 7 to 9</td>
<td>26/38 (68%)</td>
<td>28/39 (72%)</td>
</tr>
<tr>
<td>mass lesions</td>
<td>15/33 (45%)</td>
<td>14/41 (34%)</td>
</tr>
<tr>
<td>contusions</td>
<td>29/51 (57%)</td>
<td>30/41 (73%)</td>
</tr>
<tr>
<td>ICP ≤ 20 mm Hg</td>
<td>17/32 (53%)</td>
<td>25/35 (71%)</td>
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<tr>
<td>ICP &gt; 20 mm Hg</td>
<td>23/47 (49%)</td>
<td>16/40 (40%)</td>
</tr>
<tr>
<td>fixed pupil(s)</td>
<td>4/23 (17%)</td>
<td>4/23 (17%)</td>
</tr>
</tbody>
</table>

* Favorable outcome defined as a Glasgow Outcome Scale score of 1 (good recovery) or 2 (moderately disabled). Abbreviations: GCS = Glasgow Coma Scale; ICP = intracranial pressure.
† Two patients lost to follow-up study.
‡ Chi-squared analysis.
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injury.26 Robertson, et al.,26 documented the onset of ischemia/infarction-type cerebral blood flow (CBF) patterns from 1 to 3 days after closed head injury in patients with initially normal CBF. This raises the theoretical possibility that the chain of biochemical events described above may occur at variable times following head injury. Thus, it appears rational to investigate a treatment that can improve the availability of oxygen to the injured brain in order to maintain the aerobic metabolism of cerebral glucose. Still viable but non-functioning tissue could possibly be preserved by supporting the aerobic processes of the threatened cells.

The potential benefits of hyperbaric oxygen in the treatment of severe head injury are several. Hyperbaric oxygen increases the amount of oxygen dissolved in the plasma, depending on the absolute pressure used. At 2 ATA, arterial oxygen tension is increased to between 1000 and 1250 mm Hg and decreases CBF by approximately 22%.13,14,17,18,24 The reduction in CBF is due to cerebral vasconstriction, and several investigators have demonstrated that it is not dependent on hypocarbia.8,30,31 When cerebral autoregulation is lost, CBF no longer decreases with the administration of hyperbaric oxygen.16,23

Corresponding to the reduction in CBF secondary to cerebral vasconstriction, there is also a reduction in ICP, as shown in both experimental and clinical studies.9,19,20,30 In addition, hyperbaric oxygen has been shown to improve glucose metabolism in the injured brain.16 Contreras, et al.,1 documented that, in lesioned rats, improved glucose utilization persisted for at least 24 hours after the last hyperbaric oxygen treatment.

Prior Research

There is clinical and experimental evidence suggesting that hyperbaric oxygen may be beneficial in the treatment of severe head injury.4,9-11,19,30 These investigations demonstrated improved survival data and a decrease in elevated ICP. A clinical trial conducted by Holbach, et al.,21 suggested that hyperbaric oxygen, applied systematically, could improve outcome in severe brain injuries. Forty-nine of 99 patients with a traumatic midbrain syndrome were treated with hyperbaric oxygen. The overall mortality rate for the treated patients was 33% in contrast to 74% for the 50 control patients (chi-squared analysis, p = 0.01). Patients under 30 years old who had cerebral contusions particularly benefitted. Functional outcome was also improved: 33% of the hyperbaric oxygen-treated patients made a good recovery, as compared to 6% of the control patients (one-tailed Fisher's exact test, p = 0.01). However, injury severity in that study was not assessed well and the randomization process was not adequate.

Current Findings

Hyperbaric oxygen treatment dramatically reduced the mortality rate among the severely head-injured patients assigned to receive it. The mortality rate for the 84 hyperbaric oxygen-treated patients was 17%, as compared to 32% for the 82 control patients. In particular, hyperbaric oxygen therapy resulted in an approximately 50% reduction in the mortality rate of patients with GCS scores of 4 to 6, those with mass lesions, and those with increased ICP. These three factors are interrelated and, without this treatment, the mortality rate would be highest in these groups of patients since all three findings are indicative of severe brain injury. Thus, through reducing ICP and probably allowing more aerobic glucose metabolism to occur, hyperbaric oxygen therapy allowed these very severely brain-injured patients to survive.

The functional recovery of the salvaged patients was not satisfactory, however. We cannot say whether this was because the severely damaged brain lacked the potential for further recovery or because a secondary harmful effect was induced by the hyperbaric oxygen, such as increased free-radical production and peroxidation. Throughout the history of the use of oxygen as a therapeutic modality, its potential benefit has had to be balanced against its potential toxicity. The use of oxygen in the treatment of severe brain injury is no exception. We think hyperbaric oxygen therapy needs further evaluation to determine optimum treatment frequency and duration. It is possible that less hyperbaric oxygen delivered earlier would have been more effective. We are investigating combining hyperbaric oxygen therapy with a potent antiperoxidation agent, the 21-aminosteroid U74006F, which may reduce the harmful effects of hyperbaric oxygen, with the goal of maintaining the improved mortality rates but improving the functional levels of survivors.

References

Neurol Neurosurg Psychiatry 34:580–586, 1971


