Use of Hyperbaric Oxygen in Traumatic Brain Injury: Retrospective analysis of data of 20 patients treated at a tertiary care centre

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ABSTRACT

Brain Injury has serious physical, mental and socioeconomic impact. While the degree of neurological impairment may vary depending on the location of the injury and resulting damage. Acute treatment of traumatic brain injury (TBI) patients has essentially not changed for over 40 years and surgical decompression of intracranial haematomas along with supportive care remains the mainstay of management of such cases. Standard treatment consists of removing the cause, restore perfusion, support metabolic requirement and limit inflammatory and oxidative damage. However the outcome of these patients is not satisfactory and many centres worldwide are researching newer modalities for better outcomes. Hyperbaric Oxygen Therapy (HBOT) is one such promising treatment enhancing neurological recovery to some extent.

HBOT is intermittent inhalation of 100% oxygen at greater than normal atmospheric pressure and is internationally accepted for its role in well defined medical/surgical indications. It is hypothesised that HBO has a role in reviving 'idling neurons' also called the ischemic penumbra defined as area of reduced cerebral blood flow, abolished synaptic activity but preserved structural integrity. Routine assessment tools are CT and MRI, though the role of SPECT scans to visualise the presence of the ischemic penumbra is gaining relevance. HBO leads to improvement of oxygenation, reduction in cerebral oedema, reduction in Intra-cranial Pressure and improved metabolic function. For this study we carried out a retrospective analysis of medical records of 20 patients of TBI who had been treated with HBOT in addition to standard management. These were placed in Group A (test group) and were in the age groups of 17 -55 years. They had no other pre existing illness and have received at least 30 sessions of hyperbaric oxygen along with standard treatment. The patients were assessed along the Disability Rating Scale (DRS), Glasgow coma scale and Rancho Los Amigos Scale (RLAS). Another 20 patients of TBI, matched in age and severity of brain injury, who received standard treatment but not HBOT, were selected as the control group (Group B).

Assessment on the DRS scale showed maximum improvement in patients with scores of 22-24 (vegetative state). The percentage of patients in the test group (Group A) fell from 45% to 5% whereas only 20% patients in group B had similar progress. After the treatment, a significantly higher proportion of HBOT treated subjects showed a good response in cognitive functions, as measured by Rancho Los Amigos scale. In group A, 90% patients had a score of ≤ 3 and in Group B 95% had a similar score, which improved to ≥ 3 in 60% patients versus 30% patients respectively. GCS evaluates only three parameters and hence may not provide adequate information to compare the prognosis of patients in the two groups.

KEY WORDS • hyperbaric oxygen therapy • traumatic brain injury • neurorehabilitation

INTRODUCTION

TBI describes a heterogeneous set of injury mechanisms and pathological conditions, but there are common metabolic pathways leading to depressed aerobic metabolism, reduced cellular ATP production and ultimately cell death. Traumatic Brain Injury (TBI) is a significant public health problem worldwide and is predicted to surpass many illnesses as a major cause of death and disability by the year 2020. In India, the annual incidence of TBI is 1,240,436 cases leading to 30,000 deaths. Road traffic injuries are leading cause of TBI's, accounting for up to 60% cases followed by falls (20-25%) and violence (10%).[38] It is reported that 46% of these cases suffer from severe disabilities, 30% from moderate and 24% minor disabilities at the time of discharge from hospital.[38]

Hyperbaric oxygen therapy (HBOT) is intermittent inhalation of 100% oxygen at greater than normal atmospheric pressure and may be beneficial for traumatic brain injury because it improves cerebral blood flow into tissues exhibiting low blood flows. Hyperoxia improves cerebral metabolic consumption of oxygen. It also leads to improvement of oxygenation, reduction in cerebral oedema, reduction in Intra-cranial pressure. The rationale of use of hyperbaric oxygen in neurological conditions is based on the observation in SPECT studies that around the central area of neuronal death is a penumbra or periinfarct zone, which can be revived. SPECT has also shown that areas that appear as gliosis on CT scans may actually be viable tissue for years following the insult and be reactivated with HBO.[34]

While hyperbaric oxygen has been used for neurorehabilitation of TBI cases since 1965, there is still no consensus that addition of HBOT to overall treatment plan leads to reduced morbidity and mortality. The Hyperbaric Oxygen Unit at this tertiary care hospital has been treating patients referred with traumatic brain injury since 2005. However, this study analyses the data of patients treated from 2007-2009.

The objective of this study is to determine whether addition of HBOT to standard treatment plan of patients having TBI improves outcomes and which subgroup of patients will or will not respond to HBOT. The results of this pilot study may form the basis of further, larger, prospective studies on the role of HBOT in Traumatic Brain Injury.

Materials and Methods

We approached this study by reviewing the medical records of 20 patients of Traumatic Brain Injury who had been treated with HBOT in addition to standard treatment during the period 2007-2009 and another 20 patients who received standard care but did not receive HBOT.

The incidence of TBI treated at this hospital is shown in Table I. A total of 705 patients were admitted to the hospital from Jan 2007 to Dec 2009, 562 were males and 143 were females with age ranging from 1 to 91 yrs.

The test group (**Group A)** consisted of patients of TBI referred for HBOT during this period. These patients were in the ages ranging from 17-55 years. They received hyperbaric oxygen as an adjunct to standard surgical, medical management and physiotherapy. An equal number of patients matched with respect to baseline characteristics viz. age, severity of injury, lag period and management protocol, but did not receive HBOT, were identified and labelled **Group B**.

The test group received at least 30 sessions of HBOT at 1.5 ATA for 60 minutes O2 once daily in addition to standard care. HBOT was given in a “Multiplace Chamber” which was pressurized with compressed air and 100% O_2 was administered via specialized mask or T-tube if patient was tracheostomized. The control group did not receive HBOT, however standard treatment was given.

Table II shows the clinical profile of patients included in the study. Most patients were in the age groups of 18-50 years with more males than females and had sustained a TBI within 6 months of having received Hyperbaric Oxygen Therapy. The cause of Injury was motor vehicle accident in most cases and had focal or Diffuse Axonal injury.

The clinical characteristics of patients in group A has been tabulated in table III. On RLA score, 95 %(n= 19) patients had score of ≤3 (poor response) and only 5% (n=1) had >3 score (good response).On DRS scale, maximum patients (45%, n=9) in this group were in vegetative state with DRS of 22-24 and 30% (n=6) patients in extreme vegetative state with DRS of 25-29. 35% (n=7) patients on GCS scale had score between 3-8 indicating severe injury and 15% (n=3) patients were in moderate to mild condition.

The clinical characteristics of patients in group B is tabulated in table IV using the same scales as for group A. On DRS scale, 90 %(n=18) patients had a low RLA score of ≤3 and only 10 %(n=2) subjects had higher RLA score. On the basis of DRS, we see that 45 %(n=9) subjects were in

vegetative state with DRS of 22-24 and 35% (n=7) subjects were grouped in extreme vegetative state.

The low score of DRS was present in only 20% (n=4) subjects. On the basis of severity as shown by GCS, 40% (n=8) subjects had a score from 3-8 and 25% subjects had moderate to mild severity.

Statistical Analysis:

Sample size relevant for statistical calculation was not performed since data was collected and analysed reterospectivly. All values are expressed as percentage and mean (± S.D.) for comparison of data among groups.

Results

This study investigated the hypothesis that the use of hyperbaric oxygen therapy as an adjunctive treatment to standard care can help improve outcomes. Our results show that HBO has significant effects on several neurological as well cognitive variables. In our study 80% patients were in the productive age group of18-50 years and TBI was more common in males, traditionally the bread earners of family. Motor vehicle accidents are the leading cause of TBI accounting for more than 50% cases suffering from focal head injuries and more than one-third population had permanent disability resulting from diffuse brain injuries.

In our retrospective study, forty patients were included: 20 patients received HBOT with standard care (Group A) and 20 patients received only standard care (Group B).

During the period 2007 to 2009 twenty five patients of severe traumatic brain injury were referred for HBOT. The patients who completed at least 30 sessions of HBOT were included in the study, while those who had risk factors to hyperbaric treatment or could not complete the treatment cycle were excluded. One patient developed pneumothorax after 3 HBOT sessions, 2 patients went against medical advice and two patients did not complete the prescribed HBO sessions due to financial constraints.

Of the patients studied (Group A) 13 were males and 7 were females. Age varied from 17 years to 51 years.17 patients sustained head injury due to road Traffic accidents, one patient was the victim of fall and remaining two patients sustained injury due to other causes. Radiological investigations like CT scan/ MRI revealed diffuse axonal injury in 7 cases, subdural haematomas in 3 cases subarachnoid haemorrhages in 5 patients and other contusion injuries in 5 cases. SPECT was not used in any of our patients.The GCS level of the patients at the time of admission ranged from 2-10T ($E_1V_tM_1$ to $E_4V_TM_6$).

In Group B, 16 were males and 4 were females. Age varied from 19 years to 53 years.18 patients sustained head injury due to road Traffic accidents and 1 patient was the victim of fall and one suffered gun shot injury in the head. Radiological investigations like CT scan/ MRI revealed 5 cases of diffuse axonal injury, subdural haematomas in 5 case, subarachnoid haemorrhages in 4 patients and other contusion injuries in 6 cases. The GCS level of the patients at the time of admission ranged from 3- 10T ($E_1V_tM_2$ to $E_4V_TM_6$).

A comparative assessment between the two groups has been tabulated in Table V. The study demonstrated better outcome in the test group compared to the control group.

Assessment using the Disability Rating Scale (DRS) showed a significant improvement in the Test group in the vegetative state. The patients in the Vegetative state (DRS Score 22-24) showed maximum improvement and the percentage dropped from 45% to 5% in Test group compared to a reduction from 45% to only 25% in the control group.

Patients in extreme vegetative state (DRS >24) reduced from 30 to 25% in the test group compared to a reduction from 35 to 30% in the control group. Patients with less severe injuries (scores below 17) increased from 25% to 70% in the test group compared to increase from 20% to 45% after treatment in the control group.

The mean score values of DRS fell from 23.75 to 18.85 in test group compared to reduction from 23.4 to 21.65 in the control group.

The improvement in cognitive functions was assessed using Ranchos Los Amigos Scale (RLA). In group A 90% patients had a score of ≤ 3 before starting treatment with HBO and this reduced to 35% after treatment. In Group B 95% had a similar score before treatment and these reduced to 60 % after treatment.

The number of tracheotomised patients was 50% in the test group and 35% in the control group. This may have been a possible cause that we did not find the GCS assessment a suitable assessment tool in cases of TBI. Additonally, since GCS only assess three parameters it is possibly not sensitive enough when compared to other scales.

However, a greater number of patients in the test group showed improvement compared to the control.

Discussion

In India, the prevalence of traumatic brain injury cases is 2,130,141; the Annual incidence being 1,240,436 cases and 30,000 deaths. Nearly one-third of brain-injured persons have long-term disabilities affecting various spheres of life and the costs are comparable to those in the West.[38]

Traumatic brain injury (TBI) is a nondegenerative, noncongenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness.[38]

The heterogenecity and the complex pathophysiologic phenomenon encountered in these patients can be viewed as the response of brain and its coverings to an external mechanical insult. An understanding of causative mechanical factors that result in multitude of head injuries observed clinically is necessary for establishing both effective prevention strategies and therapeutic treatments to mitigate the short and long term consequences of head injury.

Traumatic brain injury can be classified on basis of indices of injury severity at presentation, location or anatomical features of abnormality, by physiological mechanism of injury or by the pathological mechanism of the injury.[10] From a clinical standpoint, primary head injury can be classified into 3 categories: The first are “Skull Fracture” which can occur with or without concomitant damage to the brain and resultant neurological deficit. The second is “Focal Head Injury” which are one of the major cause of damage to brain accounting for more than 50% deaths associated with head injury. The third is “Diffuse Head Injury” which is associated with widespread brain dysfunction and accounts for 40% patients with severe head injury and is the most important pathology responsible for persistent vegetative state and significant disability. [2]

Several studies have focused on hyperbaric oxygen therapy (HBO) in populations with severe TBI [1,40,44] Severe TBI often results in ischemia and anaerobic metabolism leading to a destructive chemical chain reaction at the cellular and mitochondrial level resulting in secondary brain injury or death [52,48.] HBO involves exposing the individual to pure oxygen in an environment with greater than normal atmospheric pressures. It appears to improve cerebral aerobic metabolism at a mitochondrial level ,although there is some debate as to whether this constitutes a promising area for intervention as concerns have been raised about oxygen toxicity and the lack of class I evidence supporting its efficacy. Some literature suggests that HBO can decrease mortality and improve neuropsychological and functional outcomes after severe TBI but there is still insufficient evidence to recommend its use [14,17,43.] Current research is being focussed on comparing the utility of HBO to that of normobaric hyperoxia, a less expensive and easier to administer alternative, and examining the mechanisms of action of HBO[36]

Acute treatment of traumatic head injury patients has essentially not changed for over 40 years in that the mainstays of supportive care and surgical decompression of intracranial hematomas have been the corner stones of definitive care for these patients. Current research is underway to ameliorate the inflammatory biochemical milieu in the acutely head injured patient by employing 21-amino steroids[11,25,39], iron chelators, superoxide anion scavengers, inhibitors of excitatory amino acids[25], opioid peptide antagonists[52], ACTH hormone analogs ,prostaglandin synthetase inhibitors, and hydroxyl radical scavengers (e.g. mannitol).

In 1969, the first report of the use of hyperbaric oxygen therapy for treating acute cerebral injury occurred in Japan[31]. The authors reported on 66 patients suffering "acute cerebral damage." This was a mix of 66 patients in which 51 of the 66 had sustained an acute head injury. They did conclude that the effects of hyperbaric oxygen therapy on acute cerebral injury were beneficial but needed further study. Data from many studies have indicated that increased CSF lactate production and elevated levels of microdiasylate lactate are markers of anaerobic metabolism caused either by lack of oxygen or damage to mitochondria.[28, 32]

Several authors have evaluated patients with marked cerebral injuries and studied metabolism as measured by cerebral glucose consumption under conditions of normobaric air, 100% normobaric oxygen, 1.5 ATA oxygen, and 2.0 ATA oxygen. Cerebral metabolism was found to be optimal at a pressure of 1.5 atmospheres absolute of oxygen. The author concluded that 1.5 ATA was the optimum treatment pressure for patients suffering marked cerebral injuries because cerebral metabolism was optimum at that pressure and was equal to that of normal brain tissue.[7, 34, 39, 30, 40, 50]

Neubauer et al[34] proposed a theory of "idling neurons" in 1990 with a report of a single patient having suffered a right middle cerebral artery infarction 14 years previously. In 1987, Zhou reported on the use of hyperbaric oxygen therapy for 336 comatose patients[52]. His overall success rate on reversing coma was 74.7%. For patients suffering cardiac arrest, the overall coma reversal rate was 62.5% and for those patients not sustaining a cardiac arrest, the rate of coma reversal was 92.4%. Interestingly, there were three cases of coma sustained as a result of traumatic brain injury. In these three cases, consciousness was regained despite length of coma from between 10, 20, and 30 days respectively. HBO requirements varied between 7 and 20 treatments. In all cases, the authors employed hyperbaric therapy between 2-2.5 ATA for 120 minutes twice daily for the first 2-3 days and thereafter, once daily for variable time lengths.

The authors thus concluded that "idling" neurons exist in an area surrounding dense, gliotic, neuronal scar tissue and that these "idling" neurons are salvageable with 1.5 atmospheres absolute (hyperbaric) oxygen therapy and can be identified and followed sequentially for improvement using SPECT brain imaging[2,,15,18,20,21,36]

Despite abundant experimental evidence showing that neurons surrounding an area of trauma or infarct could survive albeit in an electrically silent or vegetative state, a means to visualize this region remained to be found. With the advent of positron emission tomography (PET) and single photon emission contrast tomography (SPECT), a method was found to visualize the functional areas of the brain. In 1991, a study by Gray et al[15] found that HMPAO-SPECT brain imaging of patients with remote traumatic brain injury was superior to CT scan or MRI in detecting regional cerebral blood flow deficits. The authors thus concluded that HMPAO-SPECT brain scanning is a complement to the anatomic deficits seen on CT or MRI, but is vastly superior in detecting anatomically existent, but non-functioning, brain tissue. They further deduced that SPECT brain imaging provides objective evidence of, and correlates with, the impaired neuropsychiatric performance seen in patients with chronic traumatic brain injury.

To date, the treatment of chronic, traumatic, and chronic focal brain injury with hyperbaric oxygen has been little studied. Anecdotal evidence, however, does exist which shows a beneficial effect. In 1992, Harch et al[16] reported on the use of 1.5 ATA hyperbaric oxygen in the case of a scuba diver who had suffered neurologic deficits as well as physical and cognitive impairment as a result of a remote, diving, decompression accident. They confirmed that the patient had potentially treatable penumbral neuronal tissue as measured by HMPAO-SPECT brain imaging. They achieved normalization of the patient's cognitive, neurological, and physical abilities through the use of a six week course of hyperbaric oxygen therapy

In 1994, Neubauer et al[34] reported on the case of a 40 year old male who sustained a traumatic head injury as a result of a single car accident and compounded by the additional insult of an anoxic injury following an improper intubation at the scene that occurred approximately 18 months prior to receiving hyperbaric oxygen therapy. The patient received a single SPECT brain scan prior to hyperbaric oxygen therapy which showed a marked defect in the right posterior tempero-parietal cortex and a diffusely diminished tracer uptake in the cerebral cortex. After one, single, 1.5 ATA hyperbaric oxygen treatment, a repeat SPECT brain scan showed marked filling in of the defect, as evidenced by increased tracer uptake. The authors thus concluded that SPECT brain imaging could reliably measure the progress of the patient undergoing hyperbaric oxygen therapy. Physiologically, this patient went from an individual with marked spasticity of all extremities and a level 7 Ranchos Los Amigos coma scale, requiring total life support and intensive nursing home care to one where he was able to fully ambulate and required only minimal care. The patient planned to return to work.

Several authors have noted that although HBO therapy has shown beneficial effects in animals and humans, this treatment option remains limited because of expense and very limited availability of HBO chambers.[48,49] Given the staggering prevalence of TBI and its impact on activity and participation, medical science has expanded its search to better assess brain function

and the factors that impact injury severity and outcome. We in our tertiary care hospital have a multi occupancy chamber which is designed to accommodate several patients, attendants and medical personnel offering treatment to many patients at one time.

In view of the modest number of patients, methodological shortcomings and poor reporting, the result of study should be interpreted cautiously, and an appropriately powered trial of high methodological rigour is justified to define these patients who can be expected to derive most benefit from HBOT.

Conclusion

A reasonable summary of the research cited above would establish that there exists a penumbra of viable, neuronal tissue that exists around areas of dead gliotic, cerebral tissue. This penumbral area is recoverable with the use of hyperbaric oxygen. Progress is measurable, not only by SPECT brain imaging, but also by conventional neurologic testing and psychometric testing. Patients with traumatic head injuries treated with hyperbaric oxygen therapy can expect to recover more fully than previously thought possible. The patients in our study have shown significant improvement however this is a retrospective study and the small numbers precludes a statistical conclusion. However this justifies and encourages a larger prospective study at the earliest.

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