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Hyperbaric Oxygen Therapy (HBOT) in Moderate Traumatic Brain Injury (TBI): A Randomized Controlled Trial

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Abstract

Introduction Hyperbaric oxygen therapy (HBOT) is a novel technique recently under investigation with intention to improve outcomes in traumatic brain injury (TBI). It increases the partial pressure of oxygen in the blood and tissues by inhaling pure oxygen in an environment pressurized to at least 1.4 times normal atmospheric pressure (ATM) at sea level. The rationale behind the use of HBOT in TBI is its potential to mitigate the secondary brain injury cascade initiated by the primary mechanical trauma. Tissue damage and neuroinflammation secondary to intricate and complex cellular biochemical processes are expected to be counteracted by increased oxygen availability during HBOT, which reduces oxidative stress and improves neuroplasticity.

Materials and Methods All patients, except whose legal guardians denied informed consent, with moderate TBI presenting to the neurotrauma center, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India, were included within the study period of June 2022 to July 2023. Patient allocation was randomized into two arms: namely, treatment and control arm. Simple randomization was done using randomization mobile app, RRApp. Each patient received standard of care per the Brain Trauma Foundation guidelines. Patients randomized under the treatment arm additionally received adjuvant HBOT sessions. One session daily for 10 consecutive days. Session duration was for 60 minutes each at 1.4 ATM. The primary objective of the study was to compare the Glasgow Coma Score (GCS) at discharge and 3-month post-TBI Glasgow Outcome Scale-Extended (GOS-E) among patients in the treatment arm (those who received adjuvant HBOT) with those in the control arm (those who received only standard of care).

Keywords
- traumatic brain injury
- moderate
- hyperbaric oxygen therapy
- HBOT
- TBI

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Results The mean GCS (±standard deviation [SD]) at discharge in the treatment arm was 14.37 (±00.51) with a median of 14 and a range of 14 to 15. Comparatively, the mean GCS (±SD) at discharge in the control arm was 13.40 (±00.84) with a median of 13 and a range of 12 to 15. The difference between the two arms was statistically significant ($p < 0.001$). GOS-E at 3 months postinjury for the treatment arm was 7.62 ± 00.51 (mean ± SD) with a median of 8 (range: 7–8). For the control arm, GOS-E at 3 months postinjury was 6.40 ± 1.50 (mean ± SD) with a median of 7 (range: 4–8). The difference between the two arms was statistically significant ($p < 0.001$).

Conclusion The current study concludes that early adjuvant HBOT using 1.4 ATM with one session of one-hour daily for 10 days among adults sustaining moderate TBI significantly improves GCS at 10 days. Early adjuvant HBOT is also associated with significantly improved GOS-E at 3 months postinjury compared to standard of care alone.

Introduction

Traumatic brain injury (TBI) has a substantial effect on the quality of life (QOL) of victims. Unfortunately, its ever-expanding incidence has become an epidemic in the current era. In the last half century, many therapies, treatment algorithms, intensive care unit protocols, and surgical procedures[1] (decompressive craniectomy, hinge craniectomy, and basal cisternostomy) have been tried and tested to improve survival rates and functional outcomes after TBI. Yet, there has been no significant change in the outcome after TBI, notably severe TBI, in the previous four to five decades. Hyperbaric oxygen therapy (HBOT) is one such novel technique investigated in TBI. It increases the partial pressure of oxygen in the blood and tissues by inhaling pure oxygen in an environment pressurized to at least 1.4 times normal atmospheric pressure (ATM) at sea level. Most centers prefer to use the protocols of 2.0 to 2.8 ATM. The increase in arterial oxygen partial pressure has widespread effects.

Various approved indications for use of HBOT as per the Undersea and Hyperbaric Medical Society clearances[2] are; air or gas embolism, carbon monoxide poisoning or carbon monoxide poisoning complicated by cyanide poisoning, clostridial myositis and myonecrosis (gas gangrene), crush injury, compartment syndrome, and other acute traumatic ischemias, decompression sickness, enhancement of healing in selected problem wounds, exceptional blood loss (anemia), intracranial abscess, necrotizing soft tissue infections, osteomyelitis (refractory), delayed radiation injury (soft tissue and bony necrosis), skin grafts and flaps (compromised), thermal burns, and idiopathic sudden sensorineural hearing loss.

The rationale behind the use of HBOT in TBI is its potential to mitigate the secondary brain injury cascade initiated by the primary mechanical trauma.[3] Tissue damage and neuroinflammation secondary to intricate and complex cellular biochemical processes are expected to be counteracted by increased oxygen availability during HBOT, which reduces oxidative stress and improves neuroplasticity.[3] It offers to boost the oxygen supply to the injured brain[4] and help reduce the final volume of the brain lost to function due to secondary brain injury. It includes reversing hypoxia in injured tissues, changes in connective and immune cell function, inhibition of inflammation, and reduced cell/tissue swelling. Even the release of stem cells[1] has been postulated secondary to the use of HBOT.

Therefore, it is proposed that an adjuvant HBOT, in addition to a standard care regimen, may reduce patient death and disability secondary to TBI.[4,5] Authors of the current study investigated the role of HBOT in management of patients with moderate TBI.

Materials and Methods

Authors followed the Consolidated Standards of Reporting Trials guidelines in screening and recruiting the patients for the trial. After the enrolment of subjects based on inclusion and exclusion criteria, patients were allocated to either of the two arms, that is, the treatment arm or the control arm. Authors followed a simple randomization process using a randomization mobile app,[6] RRApp. The inclusion criteria included patients older than 18 with a diagnosis of moderate TBI, that is, Glasgow Coma Score (GCS) 9 to 12, and caretakers consenting to participate in the study. The investigators excluded patients aged < 18 years, pregnant females, and those with preexisting ear disease, chronic obstructive pulmonary disease, or bronchial asthma. The research submitted here is a pilot project before the HBOT trial in severe TBI shortly at our institute. Patients who were on ventilatory or inhalational O2 support and those with fever or uncontrolled seizures were excluded. We also excluded patients who had concomitant orthopaedic or blunt abdominal trauma.

Patients allocated to the control arm received "standard of care" for moderate TBI. "Standard of care" is a well-established recommendation for managing moderate TBI per the Brain Trauma Foundation guidelines.[7] Patients allocated to the treatment arm received additional adjuvant HBOT. The HBOT protocol provided ten 1-hour sessions (one session per day) each at 1.4 ATM. The authors followed all patients at 3 months for assessing Glasgow

Outcome Scale-Extended (GOS-E), including GCS at discharge.

The primary objective of the study was to compare the GCS at discharge and 3-month post-TBI GOS-E among patients in the treatment arm (those who received adjuvant HBOT) with those in the control arm (those who received only standard of care).

Institutional Ethics Committee Approval

The study received an Institutional Ethics Committee (IEC) approval, letter AIIMS/IEC/22/202/22.04.2022.

Statistical Analysis

Data collection and statistical analysis were performed using the Statistical Package for the Social Sciences, version 22 (SPSS v22.0; IBM). Descriptive statistics such as percentages were calculated for the categorical variables such as gender; while mean, median, range, and standard deviation (SD) will be calculated for continuous data such as age. The statistical tests used was Pearson's chi-square test and the Mann–Whitney *U* test (for assessment of the nonparametric data) for univariate analysis. Comparison of the two groups was done using the Mann–Whitney *U* test. After applying the Pearson's chi-square and Fisher's exact test for outcome with each single variable of interest, a multivariate binary logistic regression analysis with backward elimination method was performed for all interested variables. Significance was established at the 95% level.

Results

Demographic Data

Demographic data are shown in ►**Table 1**. A total of 18 ($n = 18$) patients were recruited in the study, 8 ($n = 8$) in the treatment arm and 10 ($n = 10$) in the control arm. Among the treatment group, the mean age (±SD) at presentation was 30.87 (±15.02) years with a median of 26 years (range: 19–55 years). Among the control group, the mean age (±SD) at presentation was 31.20 (±9.11) years with a median of 28 years (range: 22–52 years). The differences of these values among the two groups were not statistically significant ($p < 0.25$). Seventy-five percent ($n = 6$) of patients in the treatment arm and 70% ($n = 7$) of patients in the control arm were males ($p < 0.96$). All these patients ($n = 18$) sustained head injury secondary to road traffic accidents after a fall from a motorized two wheeler.

GCS at Admission and Marshall Computed Tomography Score

The median GCS at presentation was 10 with a range of 9 to 12 in both the groups. The mean GCS (±SD) in the treatment and control groups was 10.37 (±00.91) and 10.10 (±00.99),

Table 1 Comparison of Demography, GCS, Marshall CT score, and GOS-E between treatment and control arm

Variable	Treatment arm ($n = 8$)	Control arm ($n = 10$)	*p*-Value
Age (y)			0.25
Mean ± SD Median Range	30.87 ± 15.02 26.00 19.00–55.00	31.20 ± 9.11 28.00 22.00–52.00	
Gender			0.96
Male Female	6 (75.00%) 2 (25.00%)	7 (70%) 3 (30%)	
GCS (at presentation)			0.96
Mean ± SD Median Range	10.37 ± 00.91 10.00 9.00–12.00	10.10 ± 00.99 10.00 9.00–12.00	
Marshall CT			0.48
Mean ± SD Median Range Class 2 Class 3 Class 4	3.12 ± 0.64 3 2–4 1 (12.5%) 5 (62.50%) 2 (25.00%)	3.50 ± 0.52 3.5 3–4 0 (nil) 5 (50.00%) 5 (50.00%)	
GCS (at discharge)			< 0.001
Mean ± SD Median Range	14.37 ± 00.51 14.00 14.00–15.00	13.40 ± 00.84 13.00 12.00–15.00	
GOS-E (3 months)			< 0.001
Mean ± SD Median Range	7.62 ± 00.51 8.00 7.00–8.00	6.40 ± 1.50 7.00 4.00–8.00	

Abbreviations: CT, computed tomography; GCS, Glasgow Coma Score; GOS-E, Glasgow Outcome Scale-Extended; SD, standard deviation.

respectively, with no difference ($p < 0.96$) between the two groups. After the randomized allocation of patients and protocol completion of each arm for 10 days, the patients were discharged home or general hospital near their residence according to their need for care.

The mean (±SD) value of the Marshall computed tomography (CT) score for the treatment arm was 3.12 (±00.64) with a median of 3 (range: 2–4). The mean (±SD) value of the Marshall CT score for the control arm was 3.50 (±00.52) with a median of 3.5 (range: 3–4). Thus, like GCS and demographics, both these groups had comparable findings in presenting CT ($p < 0.48$).

GCS at Discharge and GOS-E at 3 Months

The mean GCS (±SD) at discharge in the treatment group was 14.37 (±00.51) with a median of 14 and a range of 14 to 15. Comparatively, the mean GCS (±SD) at discharge in the control group was 13.40 (±00.84) with a median of 13 and a range of 12 to 15. The difference between the two groups was statistically significant ($p < 0.001$).

GOS-E at 3 months postinjury for the treatment group was 7.62 ± 00.51 (mean ± SD) with a median of 8 (range: 7–8). For the control group, GOS-E at 3 months postinjury was 6.40 ± 1.50 (mean ± SD) with a median of 7 (range: 4–8). The difference between the two groups was statistically significant ($p < 0.001$).

Discussion

Ranging from mild concussion to deep coma, TBI encloses a wide range of clinical spectrum at presentation. HBOT chambers administer 100% oxygen at higher than ATM, enhancing oxygen delivery to tissues, including the injured brain in case of TBI. The role of HBOT on outcomes of severe TBI, mild TBI, and cognitive improvement in the long term, postconcussion, and posttraumatic stress disorder (PTSD) has been studied by various authors. Among the different treatment modalities intended to improve outcomes in TBI, HBOT needs further research.

Studies have demonstrated better long-term cognitive function and improved QOL in TBI treated with HBOT. Proponents of HBOT highlight improved cerebral blood flow, reduced cerebral edema, and enhanced mitochondrial function, leading to better neuroprotection and repair. HBOT achieves these neuroprotective effects by modulating neuroinflammatory responses by regulating the nuclear factor-κB/mitogen-activated protein kinases (c-Jun N-terminal kinase and extracellular signal-regulated kinase)-CXCL1 inflammatory pathways following TBI, which provide the basis of HBOT use in the treatment of TBI.[3]

The hyperbaric oxygen brain injury treatment review summarizes 40 years of clinical ($n = 8$) and preclinical ($n = 22$) research on treating acute TBI with HBOT within 30 days of sustaining TBI. This comprehensive review[4] demonstrated that HBOT is potentially a first significant treatment for acute phase of severe TBI. The current study explored similar grounds in the context of moderate TBI.

A study[8] attempted to determine whether 40 sessions of 150 kPa (~1.5 ATM) HBOT can improve symptoms and cognitive function in subjects with persistent postconcussion syndrome (PPCS) of mild TBI, using a randomized controlled crossover design with a 2-month follow-up. These authors studied 63 civilian and military subjects with mild TBI-PPCS. Randomization was done for either 40 sessions at 1.5 ATM for 1 hour, 5 days a week in 8 weeks, or no treatment control period. Those who received these 40 sessions had significant improvement in postconcussion and PTSD symptoms, memory, cognitive functions, depression, anxiety, sleep, and QOL, compared with controls, with the improvement persisting for at least 2 months after the 40th session.[8]

There are seven randomized control trials (RCTs)[5,9–15] published that examined the efficacy of HBOT (1.5, 2.0, or 2.5 ATM) in acute setting for moderate and severe TBI. Two of these studies[14,15] (of the four trials reporting patient mortality following HBOT or standard neurosurgical care and HBOT), led to significantly reduced patient mortality at 3 months to 1 year. In three trials[9,11,12] comparing HBOT to standard care or medication therapy, improvement in GCS significantly favored HBOT (follow-up periods ranged from posttreatment to 6 months after treatment or were not reported). Four trials assessed changes in functional outcomes; GOS after HBOT or standard care, and two[12,15] reported that improvement in functionality significantly favored HBOT at 6 to 12 months from baseline. One trial[11] reported improvement over standard care only among those with the highest functional rating at baseline (GOS 4), while another trial[14] found that functional outcomes did not differ between groups.

In stroke and TBI, preconditioning for treating inflammation, HBOT has been shown to be able to transfer mitochondria from astrocytes to primary rat neuronal cells.[16] In 2009, a case of a 25-year-old male military veteran was reported[17] to have his 3-year long postconcussion syndrome and PTSD getting cured with HBOT after a block of 39 sessions of 1.5 ATM of absolute hyperbaric oxygen treatments.

HBOT holds a promising hand in the future of management of TBI, especially moderate and severe TBI, and long-term improvement in QOL.

Limitations

In most instances, HBOT comes with no serious adverse effects. If any, mild barotrauma (ear, sinus, or tooth pain or injury) and headache are the only adverse effects, secondary to chamber pressurization. Seizures, oxygen toxicity, pneumothorax, and tympanic membrane rupture are also to be regarded for careful patient selection before a session of HBOT can be started.

In two studies,[18,19] participants reported withdrawal from the intervention due to minor adverse events (ear problems, claustrophobia, or headache). Only one trial[8] reported a serious event (psychiatric deterioration and hospitalization of a single patient). The current study did not encounter any adverse event that caused the session to be discontinued. Only a single patient (Marshall CT score, 3)

complained of worsening headache and irritability on the first day of his session. Protocol with lower pressure and shorter duration might have played a protective effect in the current study.

Like many other interventions in managing TBI, poor study designs, mixed HBOT protocols, and inhomogeneous patient populations are quoted for poor strength of evidence. In addition to variation in HBOT pressure, available trials differed in treatment frequency (single or multiple daily sessions), session duration (30–120 minutes), and length of treatment course (3 days to 4 weeks). A large-scale multicentric RCT inclusive of all representative groups of TBI is needed to clarify the long-term role of HBOT in the clinical practice for TBI. Till then, the currently used heterogeneous and individualized HBOT protocols will keep raising queries about the optimal duration of therapy, postinjury timing to start the HBOT, and the O2 pressure used at various centers. A multidisciplinary team involving neurosurgeons and hyperbaric medicine specialists is expected to enhance our understanding and application of HBOT in all categories of TBI, whether immediately after injury or in a delayed fashion.

A small sample size of the study is an evident and significant weakness of the current trial. Also, the authors kept the chamber's pressure and session duration at the lower end of the recommended spectrum. Being the first HBOT intervention study for neurological indication at their center, authors attempted to keep the variables at this range.

The authors believed that the adverse effects would have increased with increasing pressure and duration, with uncertainty of expected improvements in beneficial effects. Many researchers/clinicians may raise concerns on the risk–benefit analysis or cost-effectiveness of the moderate TBI treatment with HBOT, which is not done in the current study.

At the end of this discussion, all things boil down to ensuring adequate sample sizes capable of detecting anticipated differences between the two groups to increase the power of the study. Future studies need to define and select target patient criteria. Establishing an appropriate range of oxygen doses per treatment session (considering pressure and duration, being the foremost one). Implement effective and explicit blinding methods (e.g., sham therapy) for outcome assessors, neurosurgeons, and intensivists. Future researchers must thoroughly document any adverse effects that may arise and evaluate the cost-effectiveness and utility of the therapy.

In a post hoc analysis, the authors additionally admit that the study could have also investigated a volumetric comparison (of contusion/injured brain) on CT images among the two groups at 0 and 10 days post-injury. The current clinical study is, still, the first to investigate the role of HBOT in acute moderate TBI.

Conclusion

The current study concludes that early adjuvant HBOT at 1.4 ATM with one session of one-hour daily for 10 days among adults sustaining moderate TBI significantly improves GCS at 10th day of therapy. Early adjuvant HBOT is also associated with significantly improved GOS-E at 3 months postinjury compared to standard of care alone.

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Conflict of Interest
None declared.

References

1 Kumar P, Goyal N, Chaturvedi J, et al. Basal cisternostomy in head injury: more questions than answers. Neurol India 2022;70(04): 1384–1390
2 Indications for Hyperbaric Oxygen Therapy. Undersea & Hyperbaric Medical Society. Updated 2020. Accessed December 21, 2020 at: https://www.uhms.org/resources/hbo-indications.html
3 Xia A, Huang H, You W, Liu Y, Wu H, Liu S. The neuroprotection of hyperbaric oxygen therapy against traumatic brain injury via NF-κB/MAPKs-CXCL1 signaling pathways. Exp Brain Res 2022;240 (01):207–220
4 Daly S, Thorpe M, Rockswold S, et al. Hyperbaric oxygen therapy in the treatment of acute severe traumatic brain injury: a systematic review. J Neurotrauma 2018;35(04):623–629
5 Parr NJ, Anderson J, Veazie S. Evidence Brief: Hyperbaric Oxygen Therapy for Traumatic Brain Injury and/or Post-traumatic stress disorder. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09–199; 2021. Accessed October 13, 2024 at: https://www.hsrd.research.va.gov/publications/esp/reports.cfm
6 Clinical Research APPS. RRApp Robust Randomization App (Version 3.0.1). [Website application software]. 2017. Accessed October 13, 2024 at: http://clinicalresearch-apps.com/RRApp.html
7 Hawryluk GWJ, Rubiano AM, Totten AM, et al. Guidelines for the management of severe traumatic brain injury: 2020 update of the decompressive craniectomy recommendations. Neurosurgery 2020;87(03):427–434
8 Harch PG, Andrews SR, Rowe CJ, et al. Hyperbaric oxygen therapy for mild traumatic brain injury persistent postconcussion syndrome: a randomized controlled trial. Med Gas Res 2020;10(01):8–20
9 Xie Z, Zhuang M, Lin L, Xu H, Chen L, Hu L. Changes of plasma C-reactive protein in patients with craniocerebral injury before and after hyperbaric oxygenation. Nerual Regen. 2007;2(05): 314–317
10 Artru F, Chacornac R, Deleuze R. Hyperbaric oxygenation for severe head injuries. Preliminary results of a controlled study. Eur Neurol 1976;14(04):310–318
11 Lin J-W, Tsai J-T, Lee L-M, et al. Effect of hyperbaric oxygen on patients with traumatic brain injury. Acta Neurochir Suppl 2008; 101:145–149
12 Ren H, Wang W, Ge Z. Glasgow Coma Scale, brain electric activity mapping and Glasgow Outcome Scale after hyperbaric oxygen treatment of severe brain injury. Chin J Traumatol 2001;4(04): 239–241
13 Rockswold GL, Ford SE. Preliminary results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. Minn Med 1985;68(07):533–535
14 Rockswold GL, Ford SE, Anderson DC, Bergman TA, Sherman RE. Results of a prospective randomized trial for treatment of severely brain-injured patients with hyperbaric oxygen. J Neurosurg 1992;76(06):929–934
15 Rockswold SB, Rockswold GL, Zaun DA, Liu J. A prospective, randomized Phase II clinical trial to evaluate the effect of

combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. J Neurosurg 2013;118 (06):1317–1328

16 Gonzales-Portillo B, Lippert T, Nguyen H, Lee JY, Borlongan CV. Hyperbaric oxygen therapy: a new look on treating stroke and traumatic brain injury. Brain Circ 2019;5(03):101–105

17 Harch PG, Fogarty EF, Staab PK, Van Meter K. Low pressure hyperbaric oxygen therapy and SPECT brain imaging in the treatment of blast-induced chronic traumatic brain injury (post-concussion syndrome) and post traumatic stress disorder: a case report. Cases J 2009;2:6538

18 Boussi-Gross R, Golan H, Fishlev G, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial. PLoS One 2013;8(11):e79995

19 Churchill S, Deru K, Weaver LK, et al. Adverse events and blinding in two randomized trials of hyperbaric oxygen for persistent post-concussive symptoms. Undersea Hyperb Med 2019;46(03): 331–340

