Article published online: 2024-06-04

Role of Hyperbaric Oxygen Therapy in Traumatic Brain Injury: A Systematic Review of Randomized Controlled Trials

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Indian J Neurotrauma

Abstract

Background Traumatic brain injury (TBI) is a significant public health concern. Standard care involves conservative management and pharmacological and surgical interventions. Hyperbaric oxygen therapy (HBOT) has emerged as a potential treatment for TBI, with varied findings in the literature. Our systematic review aims to comprehensively assess the efficacy and safety of HBOT in TBI management, addressing existing knowledge gaps and providing insights for clinical practice and future research.

Methods A systematic literature search was performed in PubMed, SCOPUS, Central Cochrane Registry of Controlled Trials (The Cochrane Library), and ScienceDirect databases for the role of HBOT in TBI. We included studies involving randomized controlled trials (RCTs). Quasi-randomized controlled studies, prospective, retrospective observational studies, case series, case reports, letters, editorials, comments, animal studies, and studies from non-English literature were excluded.

Results After identifying 306 articles, we narrowed it to 8 for qualitative synthesis. The studies were categorized into subgroups: those on patients with an acute history of cerebral injury and those with a history of mild TBI. The combined RCTs involved 651 patients (326 in the first subgroup, 325 in the second). Despite a uniform HBOT session duration of 60 minutes, variations in compression, decompression phases, and pressure used (1.5ATA to 2.5ATA) hindered meta-analysis comparability. Outcome measures differed, complicating comparisons. Overall, HBOT appears beneficial in the first group and less so in the second. Complications are primarily pulmonary, which include dyspnea, cyanosis, hyperoxic pneumonia, and increased fraction of inspired oxygen requirement.

Keywords
- hyperbaric oxygen therapy
- traumatic brain injury
- posttraumatic stress disorder

DOI https://doi.org/10.1055/s-0044-1782609.
ISSN 0973-0508.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Conclusion Our study encountered challenges in reaching definitive conclusions due to outcome variability among the included studies. Despite mixed results, HBOT shows potential benefits for acute TBI patients. Conversely, our findings suggest the limited efficacy of HBOT for chronic traumatic brain injury patients. Further research is crucial, particularly exploring diverse HBOT treatment protocols to establish optimal pressure levels and the required number of sessions for effective outcomes

Introduction

Traumatic brain injury (TBI) represents a significant public health concern, characterized by substantial morbidity and mortality, imposing a considerable burden on affected families.[1] Notably, a considerable proportion of TBIs is attributed to road traffic accidents.[2] Current standard care for TBI primarily involves conservative management, encompassing crucial interventions such as intracranial pressure monitoring, maintenance of hemodynamic stability, and pharmacological measures involving antihypertensives and antiepileptics.[3,4] Additionally, efforts to prevent secondary injury by minimizing factors such as hypoxia, hypercapnia, and systemic hypotension are integral components of routine TBI treatment.[5–7] One therapeutic option that gained attention in the context of TBI is hyperbaric oxygen therapy (HBOT). Originally designed to mitigate secondary damage associated with hypoxia, HBOT is believed to enhance oxygen delivery to injured tissues, reduce inflammation, and foster the healing of damaged brain tissue.[2] In animal models, it has been shown that hyperbaric oxygen can prevent the release of plasma endothelins[8] or alter the levels of matrix metalloproteinase-9 [9] or change in cyclooxygenase 2 expression[10] and thus reducing the impact of secondary brain injury. The existing literature on HBOT for TBI presents a spectrum of findings, with both positive outcome studies and those reporting no significant effects.[11–16] Considering the varied evidence and potential gaps in understanding the role of HBOT in TBI treatment, our systematic review aims to comprehensively address this issue. By synthesizing and analyzing the available evidence, our review seeks to provide a more nuanced understanding of the efficacy and potential benefits of HBOT in the management of TBI. This systematic review is undertaken with the goal of bridging existing knowledge gaps and offering valuable insights that may inform clinical practice and guide future research in this critical area.

Methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting the present review.[17]

Patient, Intervention, Comparison/comparator and Outcome (PICO) Question

In this systematic review, we investigated articles focusing on the utilization of HBOT in the management of TBI among adults. Our primary objective was to gather evidence on the effectiveness of HBOT in the treatment of TBI, while also assessing its safety profile and potential complications.

Search Strategy

A systematic literature search was conducted across PubMed, SCOPUS, Central Cochrane Registry of Controlled Trials (The Cochrane Library), and ScienceDirect databases, using the search terms outlined in ►**Table 1**. Additionally, the reference lists of included studies were reviewed for potentially relevant studies. Three investigators independently screened abstracts, with selected articles undergoing full-text evaluation. Conflicts were resolved through consensus, resulting in a final list of studies.

Table 1 Details of the search strategy

Database	Search
PubMed	((“hyperbaric”[All Fields] OR “hyperbarics”[All Fields]) AND (“cell respiration”[MeSH Terms] OR (“cell”[All Fields] AND “respiration”[All Fields]) OR “cell respiration”[All Fields] OR “oxygenation”[All Fields] OR “oxygen”[MeSH Terms] OR “oxygen”[All Fields] OR “oxygen s”[All Fields] OR “oxygenate”[All Fields] OR “oxygenated”[All Fields] OR “oxygenates”[All Fields] OR “oxygenating”[All Fields] OR “oxygenations”[All Fields] OR “oxygenative”[All Fields] OR “oxygenator s”[All Fields] OR “oxygenators”[MeSH Terms] OR “oxygenators”[All Fields] OR “oxygenator”[All Fields] OR “oxygene”[All Fields] OR “oxygenic”[All Fields] OR “oxygenous”[All Fields] OR “oxygens”[All Fields]) AND (“craniocerebral trauma”[MeSH Terms] OR (“craniocerebral”[All Fields] AND “trauma”[All Fields]) OR “craniocerebral trauma”[All Fields] OR (“head”[All Fields] AND “injury”[All Fields]) OR “head injury”[All Fields])) AND ((randomizedcontrolledtrial[Filter]) AND (1000/1/1:2023/12/16[pdat]))
COCHRANE	4 Cochrane Reviews matching hyperbaric oxygen head injury in Title Abstract Keyword
SCOPUS	TITLE-ABS-KEY (hyperbaric AND oxygen AND head AND injury) AND (LIMIT-TO (DOCTYPE, “ar”))
ScienceDirect	Title, abstract, keywords: hyperbaric oxygen head injury

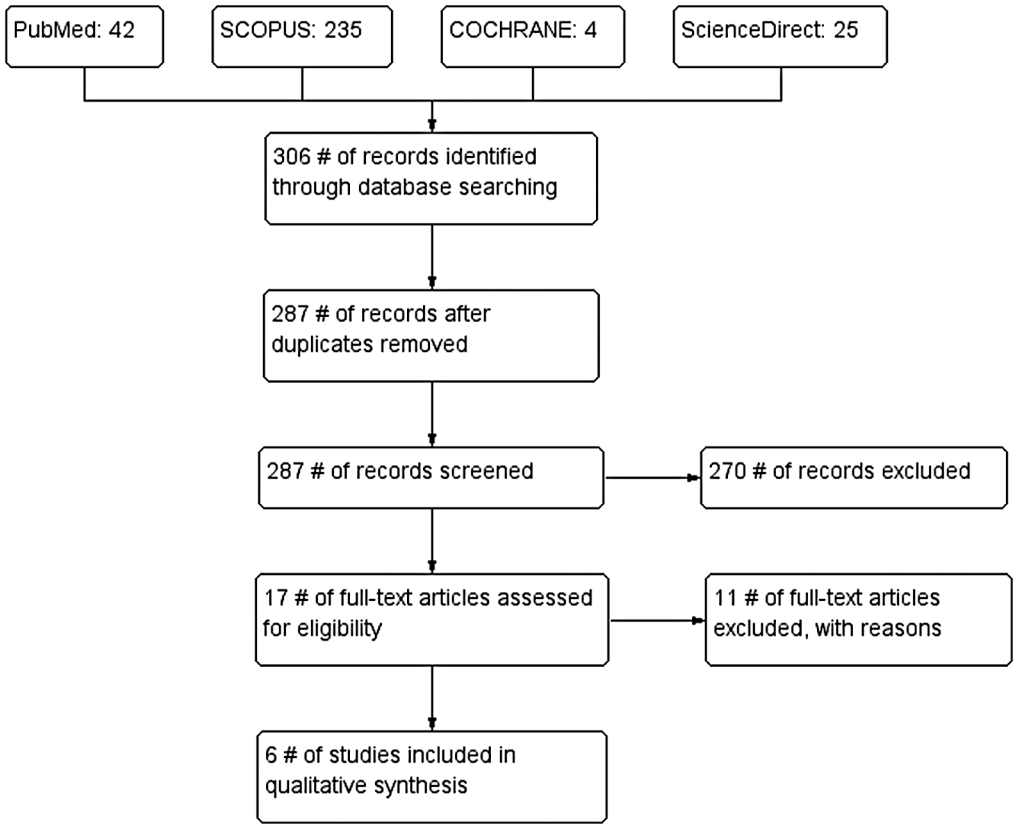

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Eligibility Criteria

Randomized controlled trials (RCTs) meeting the inclusion criteria, which focused on ultrasound-guided procedures for postoperative analgesia in pediatric abdominal surgeries, were included. Quasi-randomized controlled studies, prospective and retrospective observational studies, case series, case reports, letters, editorials, comments, animal studies, and non-English literature studies were excluded.

Data Extraction

Three investigators independently assessed studies and extracted data using a predesigned proforma based on inclusion criteria. Extracted details included study author, publication year, country, sample size, type of block, type of surgery, reported outcomes, and any complications. Authors were contacted for missing data, and discrepancies were resolved through consensus. The PRISMA flowchart illustrating the study selection process is presented in ►**Fig. 1**. We employed the revised Joanna Briggs Institute (JBI) critical appraisal tool to assess the risk of bias in RCTs.[18]

Results

With our search criteria, a total of 306 records were identified. After removing duplicates, 287 articles were screened, leading to 17 articles for full-text review. Out of these, 11 articles were excluded with reasons as mentioned in ►**Table 2**.[2,8–10,19–25] The remaining six articles were included in the qualitative synthesis (►**Table 3**).[11–16] Of these six articles, two studies reported adverse events from three RCTs.[20,25] Out of these studies, four studies were conducted on military personnel with a history of TBI—mild severity, while four studies were conducted on patients with an acute history of cerebral injury. Four studies originated from the United States, two from China, one from South America, and one from France. A total of 651 patients were included in all the combined RCTs. Of these, 325 were military personnel with chronic TBI, and 326 patients had acute cerebral injury. HBOT was administered to 286 patients, with one study not specifying the exact number of patients, and the remaining served as controls. The age of the participants ranged from 26 to 70 years. We categorized our review into two subgroups: one with acute cerebral injury with poor Glasgow Coma Scale (GCS) and the other with chronic TBI.

For patients with acute cerebral injury with poor GCS, the inclusion criteria were TBI with poor GCS, ranging from 3 to 12. Common exclusion criteria across all studies included concomitant trauma to the chest and abdomen, active hemorrhage, lung pathology, open brain wound, skull base fractures, cerebrospinal fluid (CSF) leak, unstable vital signs, arrhythmias, ear diseases, and pregnancy. There was no uniformity in delivering HBOT therapy in all these studies. Therapy was initiated after 24 hours in all the studies, with session durations consisting of compression, maintenance, and decompression phases. The compression phase was

Table 2 Studies excluded with reasons

Study author (Year)	Reason for exclusion
Barrett et al 2004[19]	Pilot study—nonrandomized
Churchill et al 2019 [20]	The authors analyze the data pooled from other two clinical trials[27,28]
Hu et al 2008 [9]	Animal model
Hu et al 2010 [21]	Animal model
Jin et al 2006 [10]	Animal model
Liu and Shang 2023 [2]	Study group and control group both received hyperbaric O2, no nonhyperbaric O2 group
Mao et al 2010 [22]	Article in Chinese
Nelson et al 1994 [23]	Animal model
Rasmussen et al 2015 [24]	Animal model
Wang et al 2004 [8]	Animal model
Wolf et al 2012[25]	Study is only reported adverse events in already performed RCT's. /post hoc analysis. Original study reference is not available.

mentioned in three out of the four RCTs, ranging from 10 to 20 minutes. Rockswold et al[14] did not provide this information. The maintenance phase lasted about 60 to 70 minutes, and the decompression phase lasted about 15 to 20 minutes. Rockswold et al[14] did not mention the decompression phase. The pressure used was reported in atmospheric pressure absolute in two studies and megapascals in two studies. Artru et al[11] and Rockswold et al,[14] 1992, used 2.5 ATA and 1.5 ATA, respectively, while Xie et al[16] and Ren et al[13] used 0.2 MPa, corresponding to approximately 2 ATA. The frequency of sessions per day varied from one to ten sessions per day by Xie et al,[16] to one per day by Artru et al.[11] The total sessions/total duration of therapy varied from 10 sessions,[11,13,16] to sessions till death or awakening,[11,14] restarted sessions after 10 with a 4-day pause until recovery or death.

The outcomes measured were different in all the studies. Xie et al[16] measured C-reactive protein (CRP) concentrations and GCS before and after therapy, showing significant improvement. Ren et al[13] measured levels of superoxide dismutase (SOD), nitric oxide (NO), nerve growth factor, and malondialdehyde, demonstrating a significant decrease with HBOT therapy. Rockswold et al[14] measured mortality, showing significant improvement, but with the Glasgow Outcome Scale, there was not much difference, indicating that functional recovery in salvaged patients was not satisfactory. Artru et al[11] measured mortality and mean duration of coma, which showed no significant difference; however, there was better recovery at 1 month in a subgroup of patients with brain stem contusion without supratentorial mass lesion.

The complications encountered were reported in only two studies.[11,14] The reported complications in these studies can be divided into pulmonary and nonpulmonary. The pulmonary complications reported included dyspnea, cyanosis, hyperoxic pneumonia, and increased fraction of inspired oxygen (FiO2) requirement, totaling 21 patients out of 115. Some patients required termination of treatment due to pulmonary complications. Nonpulmonary complications reported included seizures ($n = 2$) and hemotympanum ($n = 2$).

In the subgroup of patients with chronic TBI, primarily involving military personnel with history of mild TBI, four studies were identified, of which only two reported adverse events.[20,25] Churchill et al[20] reported adverse events from two studies, namely the Hyperbaric Oxygen for Persistent Post-Concussive Symptoms (HOPPS) study and The Brain Injury and Mechanism of Action of Hyperbaric Oxygen for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (mTBI) (BIMA) study, while Wolf et al[25] reported adverse events from the HBO-TBI study. Therefore, a total of five RCTs are included in this subgroup. The total number of patients studied in this subgroup was 325, with only seven being females. Among these patients, 145 received HBOT; however, Cifu et al[12] did not specify the number of subjects who received therapy versus controls. The age of participants ranged from 23 to 33 years. All patients included in these studies had mild TBI, and the exclusion criteria were like the first group mentioned above, excluding those with moderate-to-severe TBI and contraindications for HBOT.

Therapy in all the studies commenced between 8 months and 1 year after the TBI. The duration of the maintenance phase in all studies was 60 minutes, with the compression and decompression phases lasting about 3 to 5 minutes each. Walker et al[15] and Wolf et al[25] did not specify the duration of the compression and decompression phases. A total of 40 sessions were administered in all studies, distributed over 10 to 12 weeks. The pressure used varied from 1.5 to 2.4 ATA. The outcomes measured included sleep, assessed by actigraphy (objective) and self-reports (subjective) in the study by Walker et al,[15] which showed no improvement. The posttraumatic disorder checklist military version and the Rivermead Post Concussion Symptoms Questionnaire were utilized by Cifu et al,[12] revealing no significant differences. Complications reported from the HOPPS study and BIMA study[20] and the HBO-TBI study[25] included common

Table 3 Characteristics of included studies

Study author (Year)	Country	Sample	HBOT/ Control	Age (mean)	Sex (M/F)	Inclusion criteria		Exclusion criteria	HBOT					Outcomes	Complications	Conclusion
						Type of injury	Grade of injury		Started at	Session-C/M/D	Sessions frequency	Total duration	Pressure			
Artru et al 1976[11]	France	60	31/29	30	NA	Trauma	Severity of coma-JOUVET scale all	Severe chest injury, open brain wound	NA	10/60/20	1/day	10 session+ 4 day pause-till recovery or death	2.5 ATA	Mortality no difference, mean duration of coma no difference, brainstem contusion without supratentorial mass, better rate of recovery at 1month	Dyspnea, cyanosis, hyperoxic pneumonia ($n=11$)	Besides the toxic action on normal nervous tissue, HBOT can counteract edema and ischemia in the zones of brain injuries
Cifu et al 2014 [12]	Colombia, South America	61	NA	23	NA	Trauma	TBI mild	Disorders contraindication for HBOT	>8 months	3/60/3	1/day	40 sessions over 10 weeks	2.0 ATA	Posttraumatic disorder checklist military version no significance, Rivermead postconcussion symptoms questionnaire no significance	NA	No effect on postconcussion symptoms after mild traumatic brain injury with sham compression
Ren et al 2023[13]	China	40	20/20	46–70	Not clear	Trauma	GCS 3-12	Active bleeding, unstable vital signs and CSF leak, skull base fracture, thoracic and abdominal injuries	>24 hours	20/60/20	1/day	10 days	0.2 Mpa	Serum levels of superoxide dismutase significant decrease P,0.05, endothelium derived relaxing factor—nitric oxide significantly decreased, nerve growth factor significantly decreased, serum malondialdehyde significantly decreased	NA	HBOT can effectively inhibit the oxidative stress response of the body, enhance the survival of damaged neurons, and accelerate the recovery
Rockswold et al 1992 [14]	Minnesota, USA	166	84/82	32	65/19	Trauma, surgical mass lesions	GCS ≤9	Not clear	26 hours	x/60/x	3/day	2 weeks/ till brain dead/ awake	1.5 ATA	Mortality HBOT (17%) vs. controls (32%) in trauma $p=0.02$, mortality HBOT (17%) vs. controls (32%) in mass lesions $p=0.09$, Glasgow Outcome Scale no difference	Increased FiO2 requirement and chest infiltrates needed termination of treatment ($=10$), seizures ($n=2$), hemotympanum ($n=2$)	50% reduction in the mortality rate of patients with GCS scores of 4 to 6. The functional recovery of the salvaged patients was not satisfactory
Walker et al 2018[15]	USA	71	36/35	33	70/1	Trauma	TBI mild	Moderate-to-severe TBI, disorders contraindication for HBOT	>1 year post-injury	60 minutes	NA	40 sessions-12 weeks	1.5 ATA	Sleep by actigraphy—no improvement, sleep by self-reports—no improvement	NA	HBOT improved some self-report measures of sleep on the PSQI, but overall extremely poor

(*Continued*)

Table 3 (*Continued*)

Study author (Year)	Country	Sample	HBOT/ Control	Age (mean)	Sex (M/F)	Inclusion criteria		Exclusion criteria	HBOT					Outcomes	Complications	Conclusion
						Type of injury	Grade of injury		Started at	Session-C/M/D	Sessions frequency	Total duration	Pressure			
Xie et al 2007[16]	China	60	30/30	26	37/23	h/o craniocerebral injury	GCS 3-12	Trauma to chest and abdomen, active hemorrhage, lung pathology, arrythmias, ear disease, pregnancy	1–10 days	15/70/15	1-10/day	1	0.2–0.25 Mpa	CRP before and after $p < 0.01$, GCS before and after $p < 0.01$	NA	HBOT decrease -plasma CRP in patients with craniocerebral injury

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; FiO2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; HBOT, hyperbaric oxygen therapy; NA, not available; PSQI, Pittsburgh Sleep Quality Index; TBI, traumatic brain injury;

Table 4 JBI critical appraisal checklist for RCT studies[18]

Study ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13
Artru et al 1976[11]	Unclear	Unclear	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Cifu et al 2014[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ren et al 2023[13]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Rockswold et al 1992[14]	Unclear	Unclear	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Walker et al 2018[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Xie et al 2007[16]	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes

Abbreviation: RCT, randomized controlled trial.

occurrences such as ear barotrauma ($n = 33$), sinus pain ($n = 10$), vision changes ($n = 3$), headache ($n = 10$), among 193 patients. The details of risk of bias assessment with JBI tool are shown in ►**Table 4**.

Discussion

TBI can lead to hypoxic injury, which may progress or occur days after the injury. This is in contrast to acute cerebrovascular occlusion, which causes immediate damage.[14] The mechanism of action of HBOT is not fully understood, but possible mechanisms include the correction of hypoxia, as evidenced by an increase in partial pressure of oxygen in CSF,[11] correction of ischemia by decreasing intracranial pressure or by shifting blood from normal to ischemic areas (the reverse steal phenomenon), and correction of acidosis and cerebral edema. HBOT can also act as an antioxidant, preventing oxidative stress in hypoxic-injured cells.[14] However, there are potential negative side effects of HBOT. The oxygen toxicity on the brain is referred to as the Paul Bert effect, while oxygen toxicity on the lungs is known as the Smith effect.[26] Both effects become evident at very high pressures (15–20 ATA) or when the pressure is used for a longer duration. Possible side effects include an increase in cerebral edema, seizures, dyspnea, cyanosis, hyperoxic pneumonia, and an increase in FiO2 requirement. The positive or negative effects will depend on pressure, the duration, and pathophysiological condition of the brain.

HBOT was used for patients with acute cerebral injury with poor GCS in four of the studies included in our review. Xie et al[16] utilized HBOT employing an iced-wheel four-door, two-cabin air compression chamber from 24 hours to 10 days after the injury. A pressure of 0.2 to 0.25 MPa was applied with a compression phase lasting 15 to 20 minutes, maintained for 70 to 80 minutes, and then decompressed over 20 minutes. A total of 10 daily sessions were administered. CRP and GCS were compared between the HBOT group and the control group. They observed a significant difference in the HBOT group ($t = 9.21$, $p < 0.01$), leading to the conclusion that HBOT can remarkably decrease the content of CRP in patients with cerebrovascular injury during stress phases.

Artru et al[11] administered HBOT at 2.5 ATA, involving a compression phase of 10 minutes, a maintenance phase of 60 minutes, and a decompression phase of 20 minutes. The therapy was delivered for 10 daily sessions, followed by a 4-day gap, and then continued with 10 daily sessions until the patient either regained consciousness or succumbed. The average initial treatment delay for starting HBOT was 4.5 days. Treatment was halted in five patients due to severe intolerance, suggesting impending hyperoxic pneumonia, and in six patients with severe pulmonary infections, fearing the exacerbation of lesions. Coma rate at 1 month and mortality rate were the measured outcomes. The study revealed no significant difference between the HBOT and control groups regarding the coma rate at 1 month and the mortality rates at 1 month and 1 year. However, in a subgroup analysis of patients under 30 years old with brain stem contusion who did not undergo surgery, a significant recovery of consciousness was observed. The researchers concluded that there is no significant difference in the overall mortality rate between HBOT and controls, but there were no detrimental effects found concerning the toxic effects of HBOT on the normal brain and lungs. They suggested that early treatment with less frequent interruptions might yield positive results, and any negative effects on the lungs could potentially be mitigated by using premedication with a neuroleptic or a benzodiazepine derivative.

Ren et al[13] employed HBOT daily for 10 days at a pressure of 0.2 MPa, with a pressurization period of 20 minutes, a plateau phase of 60 minutes, and a decompression period of 20 minutes. Oxidative stress indicators such as SOD, endothelium-derived relaxing factor—NO—and nerve growth factor were compared at the end of the therapy. They observed a significant improvement in SOD ($p < 0.05$), NO ($p < 0.01$), and malondialdehyde content ($p < 0.05$) in the HBOT group compared to the controls. The researchers concluded that HBOT can be utilized to reduce systemic oxidative stress response in patients with craniocerebral injury.

Rockswold et al[14] utilized HBOT through a monoplace hyperbaric chamber, maintaining a pressure of 1.5 ATA. The compression rate was set at 1 psi/min, held for 60 minutes, and then decompressed at the same rate. Sessions were conducted three times daily for 2 weeks or until the patient was brain dead or showed improvement in the GCS. Outcomes were assessed using the Glasgow Outcome Scale. The average time from injury to the first HBOT therapy was 26 hours. The most common complication encountered was pulmonary, leading to increased FiO2 requirements. The study revealed that the mortality rate was not significantly decreased compared to the control group ($p = 0.037$), and HBOT did not increase the number of patients in the favorable outcome category (decreased morbidity). However, the researchers suggested that employing a different HBOT protocol or incorporating 21-aminosteroid might have improved the quality of survival.

HBOT was employed for patients with chronic stable TBI in four of the eight studies reviewed. Two of these studies specifically focused on reporting adverse events from three RCTs. Walker et al[15] utilized HBOT, delivering forty 60-minute sessions at 1.5 ATA over 12 weeks. Sleep assessment through self-reports and actigraphy was used as an outcome measure. The study did not identify any statistically significant changes over time attributed to the intervention in most of the Pittsburgh Sleep Quality Index (PSQI) measures. However, an exception was noted for the PSQI component score related to habitual sleep efficiency, where significant changes over time in response to the intervention were observed. Cifu et al[12] employed HBOT through a multiplace chamber, administering a series of 40 once-a-day sessions over 10 weeks at a pressure of 2.0 ATA. The compression phase lasted 3 minutes, with a plateau of 60 minutes and a decompression phase of 3 minutes. They used the Posttraumatic Stress Disorder Checklist–Military Version (PCL-M) for assessing PTSD symptoms and the Rivermead Post Concussion Symptom Questionnaire (RPQ)

for evaluating post-concussion symptoms both pre- and post-therapy. Their findings showed no significant difference between the group testing, leading to the conclusion that HBOT has no significant impact on postconcussion symptoms after mild TBI. Churchill et al[20] and Wolf et al[25] reported adverse effects from the RCTs, and these were detailed in the results section.

Conclusion

Our study faced challenges in drawing definitive conclusions due to the variability in reported outcomes across the included studies. Nonetheless, there appears to be potential benefit from HBOT in patients with acute TBI, despite mixed outcomes, including positive responses in two studies and negative responses in two studies. Conversely, our findings suggest that HBOT may not be beneficial for chronic TBI patients. It is crucial to emphasize the need for further research, specifically testing HBOT with diverse treatment protocols to determine optimal and safe pressure levels, as well as the total number of sessions required for effective outcomes.

Ethical Approval Statement

The study was started after the approval from institutional ethical committee.

Conflict of Interest

None declared.

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