HYPERBARIC OXYGEN THERAPY FOR TRAUMATIC BRAIN INJURY: A REVIEW OF HISTORY, DEVELOPMENT, CURRENT TECHNIQUES, AND FUTURE DIRECTIONS

Yudi Yuwono Wiwoho[1*], Abdul Halim Sadikin[2,3], Ahmad Aulia Jusuf[4], Wawan Mulyawan[5], Ninik Mudjihartini[2,3], Nurhadi Ibrahim[6], Sri Widia A. Jusman[2,3], Mohamad Sadikin[2,3]

[1]Doctoral Programme in Biomedical Sciences, Faculty of Medicine University of Indonesia; [2]Department of Biochemistry and Molecular Biology, Faculty of Medicine University of Indonesia; [3]Center of Hypoxia and Oxidative Stress Studies (CHOSS); [4]Departement of Histology, Faculty of Medicine University of Indonesia [5]Master Programme in Flight Medicine, Faculty of Medicine University of Indonesia; [6]Department of Medical Physiology and Biophysics, Faculty of Medicine University of Indonesia

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Corresponding Author
Name : Yudi Yuwono Wiwoho
Email : yudiyuwonowiwoho@yahoo.com

ABSTRACT

Hyperbaric oxygen therapy (HBOT) has gained increasing attention as a potential adjunctive treatment for traumatic brain injury (TBI) patients. This narrative review discusses the historical background, current preclinical and clinical studies, and explores its underlying mechanisms from biomolecular, histological, and clinical perspectives. HBOT promotes neural recovery by improving oxygenation, preserving mitochondrial integrity, enhancing neurotrophic support and synaptic connectivity, mitigating secondary injury pathways (including oxidative stress, inflammation, and apoptosis), and promoting angiogenesis and vascular stability. These mechanisms have demonstrated improvements of motor, cognitive, and memory functions both in preclinical and clinical studies, although outcomes and treatment protocols vary. However, challenges remain regarding optimal protocols, patient selection, and adverse effects. Further high-quality clinical trials are required to define the optimal HBOT regimen are required.

Keywords: Hyperbaric oxygen therapy, traumatic brain injury, hypoxia.

Introduction

Traumatic brain injury (TBI) is one of the leading global problems, contributing to significant mortality and morbidity. Around 27.16 million new cases of TBI with high morbidity and significant disability occurred in 2019.[1] In 2021 alone, roughly 20 million new cases of TBI occurred worldwide. In addition to physical and physiological issues that may follow, TBI often results in non-medical catastrophic events caused by loss of productivity among the younger generation and the high cost of treatment.

TBI pathogenesis encompasses a spectrum, starting from direct mechanical force causing primary injury, to secondary injury which may develop immediately or even years after injury, such as ischemia, inflammation, and oxidative stress.[2] These injuries might worsen neuronal damage, alter neuroplasticity, and impair functional recovery.[2] Treatments for TBI mainly focus on mitigating the acute phase causes by primary injury, such as hematoma evacuation, administration of anti-edema agents administration, and seizure prophylaxis. Treatment targeting other pathways of brain injury, such as addressing hypoxia is needed to prevent further damage from secondary injuries.

Hyperbaric Oxygen Therapy (HBOT), defined as delivering 100% oxygen at elevated atmospheric pressures has been proposed as one of the strategies to improve neurological outcome in TBI patients.[3] HBOT may enhance oxygen availability to hypoxic tissue, mitigating hypoxia, reducing ischemia and edema, and producing an anti-inflammatory effect.[4] Several preclinical studies have demonstrated HBOT's potential to reduce cell apoptosis, modulate oxidative stress, and improve neuroplasticity.[3] HBOT was observed to improve cognitive and memory functions and cerebral metabolism when conducted in multiple sessions.[3,5] At present, HBOT has been used in the management of chronic post-concussive symptoms.[6]

However, to date, there is no established standard for HBOT administration, including its general protocol, timing of delivery, and patient characteristics for a certain HBOT dose and time. Evidence from existing studies still varies. This review was aimed to explore the historical background of HBOT, its possible mechanism and impact on TBI, and its efficacy and safety profiles.

Method

In this narrative review, we summarize the data on the history, biochemical mechanisms, histological findings, and functional outcomes following HBOT, with emphasis on the TBI population in both preclinical and clinical studies. A literature search was conducted in PubMed, ScienceDirect, Scopus, and Google Scholar for English-language articles published up to November 2025. Search terms included "hyperbaric oxygen therapy," "biomolecular mechanisms," "oxidative stress," "inflammatory response," "HIF-1α," "hypoxia," "BDNF," "neurogenesis," "synaptic plasticity," "mitochondrial function," "angiogenesis," "histological findings," "functional outcomes" (motor, cognitive, memory, consciousness), and reported adverse effects. Included studies consisted of preclinical and clinical studies, systematic reviews, descriptive narrative reviews, and current guidelines on HBOT use. Exclusion criteria included non-English language articles and studies unrelated to the topic.

Discussion

Definition and Basic Principles of HBOT

HBOT comprises the delivery of 100% oxygen concentration at supra-atmospheric pressure, typically ranging from 1.2 to 3.0 atmospheres absolute (ATA).[6,7] Administration of HBOT can be done in a monoplace chamber, or a multiplace chamber, where oxygen is delivered through endotracheal tube, a head hood, or a mask.[8] The key principle is the inhalation of hyperbaric pressure by the patient, intended to increased alveolar oxygen pressure, resulting in increased dissolved oxygen in the blood and cerebrospinal fluid, thereby enhancing oxygen diffusion into hypoxic tissues.[4]

Currently, HBOT is approved by the Undersea and Hyperbaric Medical Society (UHMS) as a treatment for air or gas embolism, arterial insufficiencies, carbon monoxide poisoning, gas gangrene, decompression sickness, radiation injuries (necrosis), sudden sensorineural hearing loss, intracranial abscess, necrotizing soft tissue infection, refractory osteomyelitis, severe anemia, and adjunctive therapy in thermal burns.[6] However, there are several contraindications to HBOT, such as patients with or at risk of pneumothorax and middle ear rupture. The relative contraindications include patients with uncontrolled seizure disorder, pulmonary disease (i.e. COPD), congestive heart failure, hyperthyroidism, pregnancy and claustrophobia.[9] In patients with cardiovascular disease, optimal pretreatment and monitoring should be aggressive, as HBOT might induce reflex bradycardia and increase systemic vascular resistance.[10]

Historical Evaluation

The history of HBOT traces back to 1662 when Henshaw, an English physician, used compressed air to treat pulmonary and gastric disease using domicilium (a spherical wooden chamber with one-way valve to change the air pressure).[7,11] The discovery of oxygen in 1775 further enhanced the fundamental understanding of gases, their pressure, and toxicity.[9] The discovery of oxygen toxicity caused reluctance of the use of hyperbaric oxygen, thus further research was conducted. The utilization of HBOT to treat decompressive sickness was carried out for the first time in the 1930s by Behnke and Shaw.[7] Literature regarding the study further carried out especially during World War II, which increased the demand for this treatment.[6] The implementation of hyperbaric oxygen was notable in 1980s to treat carbon monoxide poisoning, kidney failure, and gas gangrene.[9] The potential use in TBI has been studied since the 1990s and showed several promising outcomes with the understanding of neurobiological mechanisms. The use of HBOT in Indonesia was first traced back in 1967 to treat Caisson disease and Tetanus.[12,13]

Biochemical and Biomolecular Mechanisms Oxidative Stress Modulation

TBI causes a surge in oxidative stress, as a stress response and due to hypoxia resulting from the injury. This is marked by overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to cell death through oxidative stress pathways. HBOT increases oxygen supply, decreases ROS/RNS production and also increases antioxidant enzymes. Increased level of superoxide dismutase (SOD) was found after HBOT administration in craniocerebral injury patients. Upregulation of SOD2 was also observed in rat models after HBOT. This is followed by a decreased level of malondialdehyde (MDA), a lipid peroxidation biomarker indicating the severity of oxidative stress. Other studies also showed the same result along with an increase in catalase level.[14–17]

Inflammatory Response

After the primary insult, inflammatory cascade is initiated as a response to increase neuronal survival. Over time, the secondary brain injury may start, causing further damage due to prolonged inflammation. Microglia as the primary immune cells in the brain and undergo phenotypical changes during this response. The M1 phenotype secretes pro-inflammatory cytokines, such as TNF-α and IL-1β, meanwhile, the M2 phenotype induces an anti-inflammatory response. After administration of HBOT, studies on rat models showed fewer M1 phenotype microglia. While some also showed decreased levels of M2, others observed no significant change in this phenotype. The levels of TNF-α, IL-1β, and IL-6 were found to decrease while the TGF-1β, an anti-inflammatory cytokine, increased.[4,15,18–20]

The anti-inflammatory effect of HBOT has also been associated with the inhibition of NF-kB, a transcription factor for pro-inflammatory genes. Concurrently, increased levels of its inhibitor, IkBa, were observed—an effect contrary to its usual degradation seen during hypoxic conditions. This suggests the anti-inflammatory effect of HBOT was led through down or upregulation of cytokines.[15,17,21]

Biomolecular Pathways: HIF-1α, BDNF, and Mitochondrial function Hypoxia-inducible factor-1α (HIF-1α) pathway

HIF1 is a transcription factor that acts as the key mediator in oxygen homeostasis. In hypoxic conditions, increased expression of HIF1 enables cells to shift into anaerobic metabolism and promotes angiogenesis through VEGF and EPO activation, allowing transcription of various target genes to maintain cell adaptation to hypoxic environment. However, severe hypoxia induced inflammation and mitochondrial dysfunction, causing apoptosis, pyroptosis, and ferroptosis. Optimal level of HIF-1a in the context of injury should be obtained to ensure maximal benefit.[22]

A decrease in HIF-1α levels was observed after the administration of HBOT. Hyperoxic environment thought to promote degradation of HIF-1α, the oxygen sensitive subunit that will be degraded by proteasome in the prescence of oxygen. This reduction is particularly seen in the perilesional site of the injury on rat models. This in turn could downregulates its downstream genes, such as p53, as seen in lung cancer models.[5,23,24]

Brain-Derived Neurotrophic Factor (BDNF) and Neurogenesis

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotropin in the brain, acting to ensure neuronal survival, its differentiation, synaptic plasticity and axonal growth. Activation through its tyrosine kinase receptor (TrKB) stimulates neural regeneration and supports cognitive and memory function. Following traumatic brain or spinal injury, levels of TrkB was increased, CSF BDNF was decreased and serum BDNF was increased. Elevation of BDNF in CSF at the first week after injury were associated with higher mortality in the chronic phase.[25–28]

Several preclinical studies have demonstrated that HBOT enhances BDNF level. In animal model, neurotropic factors, including BDNF expression, were elevated following HBOT after TBI. In SCI rat model, both BDNF and TrkB expression were increased. Following this finding, dendritic degeneration pathways were also found to be inhibited. Concentration of its downstream protein was also increased. [27,29]

Furthermore, experimental studies have also demonstrated that HBOT can stimulate the proliferation of neural progenitor cells and support neurogenesis within the subventricular zone and hippocampus. Neuron staining showed significantly more new neurons in the perilesional cortex of TBI animals after HBOT. [30,31]

Changes in cerebral microstructure was also observed following HBOT, which was assessed by diffusion tensor imaging (DTI) on MRI. Overall improvement in microstructure integrity was observed, particularly in regions related to motor functions. Significant rise in number of fibers was also seen in left cingulum, right ILF, and right uncinate fasciculus, indicating enhanced connectivity and neural reorganization after HBOT.[32]

Mitochondrial Function

The high oxygen tension generated from HBOT increases the oxygen availability for the already compromised mitochondrial oxygen transport chain in the context of TBI. This alleviates the oxidative phosphorylation process, resulting in ATP generation. Hu et al (2017) found the increased ATP expression after HBOT, along with increased NAD+ expression, NAMPT activity, and upregulation of Sirt1. This in turn will decrease NF-kB and

p53, potentially reducing inflammation and the apoptotic pathway the ischemic rats models.[15,21]

Some studies also showed a decrease in Bcl-2, caspase 2, caspase 3, cytoplasmic cytochrome C level, and modulation of Bax level after HBOT administration. This could inhibit the intrinsic apoptotic pathway in mitochondria. Measurement of mitochondrial transmembrane potential showed similar results between sham and HBOT administered groups. Hence, HBOT restores mitochondrial function, improving ATP production and neuronal survival.[33]

Angiogenesis, Vascular Remodeling, and Cerebral perfusion

Enhanced cerebral perfusion is a critical factor in facilitating neural recovery. Multiple studies reported elevated levels of vascular growth factors, such as vascular endothelial growth factor (VEGF), VEGF receptor-2 (VEGFR-2), and hematopoietic growth factors, following HBO treatment. In some cases, these increases were observed as early after initial HBOT session, with no significant changes noted in subsequent treatment. A study on animal model showed an increase in BrdU-endothelial staining, which presents endothelial cells, and VEGF-positive cells, both in HBO and Normobaric treatment at 4 days after TBI, but more predominant in the HBOT group. Further study reported an improvement in blood-brain barrier integrity after 2.5 ATA HBOT evaluated at 48 and 72 hours after an ischemic insult. These findings suggest an improvement in angiogenesis and vascular stabilization during acute phase following hypoxic insult with HBOT.[17,34]

Additionally, evidence supports the efficacy of HBOT in the chronic phase of TBI. A study showed improved cerebral perfusion, which can be detected with an MRI perfusion test, using dynamic susceptibility contrast (DSC). Tal et al (2017) observed the brain perfusion in post-concussive syndrome patients from mild to severe TBI 6 months to 27 years prior to HBOT. Post-HBOT imaging revealed an increase in cerebral blood flow (CBF), cerebral blood volume (CBV), and a decrease in MTT (mean transit time; low MTT indicates faster blood flow) compared to the level before the treatment. This increment was more prominent in the injured brain regions and positively correlated with improved cognitive functions.[32]

Histological Findings: Tissue Remodeling and Cellular Protection

Besides biomarkers, the impact of HBOT can be seen in histological examination. Apoptosis, improvement of blood-brain barrier integrity, attenuation of neuroinflammation, and neurogenesis can be assessed. TUNEL staining (Terminal deoxynucleotidyl Transferase dUTP Nick End) has been used to detect apoptotic cells by labelling the free 3'-hydroxyl ends of DNA fragments. Significant reduction of TUNEL-positive cells was seen in HBO groups compared to untreated TBI groups. Myelin injury was also preserved in the HBO treatment groups which can be seen histologically by Luxol

Fast Blue and MBP immunochemistry (IHC) staining. Another staining such as anti-NeuN and caspase-3 expression can also be used to evaluate neuronal injury with IHC. Both of those expression indicates healthy neurons which was found to be increased in HBOT treated groups compared to the untreated groups. This indicates reduction of apoptotic cells after HBOT. Decreased astrocytosis (through GFAP staining) and reduced microglial activation (Iba1 staining) were also seen to demonstrate attenuated gliosis and neuroinflammation. Increased VEGF-positive cells and improvement of blood-brain barrier were also observed following treatment with HBO. [20,27,33,34]

Functional outcome

Clinical and preclinical studies support the beneficial effects of HBOT on cognitive and motor function following TBI. However, studies on animal and human subjects were performed in different patient backgrounds, protocols, and its outcome measurements, resulting in conflicting results.

In rat models, Morris water and Y maze test are usually used to assess spatial learning and memory ability. Motoric function is tested with Rotarod to assess its strength. Several animal studies have demonstrated improvement in these functions following the application of HBOT after hypoxic insult. In between the pressures tested, 2.5 ATA revealed more promising results compared to 1.5 ATA HBOT. Particularly, administration in the acute phase of injury showed better results.[20,33]

In human studies, HBOT administration after TBI showed varying outcomes. Generally, in TBI patients, the Coma Recovery Scale-Revised (CRS-R) and Rancho Los Amigos Revised Scale (RLAS-R) scores were found to be higher in the HBO groups compared to the control group, which indicates better conciousness and cognitive function. At six month, they had higher Functional Independence Measure (FIM) and Glasgow Outcome Scale Extended (GOSE) score, indicating improvement in their functional outcome. The Stockholm CT score was also found to be lower in the HBO groups, predicting their lower severity and better prognosis. Chen Y et al (2022) found these findings particularly to be statistically significant and in line with the increased expression of biomarkers that act on neurogenesis and neuroplasticity, such as BDNF, NGF, and VEGF. Improvement of GCS, GOS, and overall lower mortality were found in TBI patients receiving HBOT compared to control groups. Improvement of cerebral blood perfusion and volume after HBOT, through perfusion MRI was positively correlated with improved cognitive function. However, most of these studies performed HBOT in mild TBI and chronic phase. The method of assessing motoric, cognitive, and memory function still varies. Some studies showed no significant difference between the groups. Hence, the optimal timing and HBOT protocol in human subjects need to be further studied. [3,32,35–37]

Limitations and Controversies

Despite encouraging evidence, role of HBOT in TBI management remains controversial. Heterogeneity in study designs, inconsistent treatment protocols (e.g., variations in pressure, duration, and timing), and small sample sizes make it challenging to draw conclusion. Regulatory bodies, including the U.S. Food and Drug Administration (FDA), have yet to approve HBOT as a standard treatment for TBI, highlighting the need for further high-quality, multicentred trials to establish efficacy and safety.

There are also concerns regarding oxygen toxicity and effect of pressure in HBOT. Administration of hyperbaric oxygen at 1.5 ATA and 2.5 ATA for 60 minutes produced 130 and 296 unit pulmonary toxicity doses (UPTD,) respectively. These doses remained below the established threshold of oxygen toxicity, defined as ≤ 615 UPTD. Intermittent administration were associated with lower UPTD while maintaining similar benefit. These findings could help contribute to refine HBOT protocols to maximize efficacy while minimizing oxygen toxicity. Pressure related-complications of HBOT include barotrauma, affecting the lungs, middle ear, and sinus, and risk of air embolism. Pulmonary barotrauma can be life-threatening, particularly if it leads to tension pneumothorax. Since the lungs are a part of an open respiratory system, barotrauma typically does not occur unless there is reduced lung compliance, bronchoconstriction, or a closed glottis, all of which can result in increased intrapulmonary pressure. These conditions are more likely to occur in patients with chronic obstructive pulmonary disease, especially during acute exacerbation, bullous lung disease, or in the presence mucous plug. Arterial gas embolism may occur if there are vascular injuries or leaks within the pulmonary system that allow air to enter the bloodstream, leading to emboli. This can result in serious complications such as myocardial infarction, stroke, or even cardiac arrest. Therefore, thorough screening to identify risk factors is essential prior to HBOT. However, these adverse event rates remain low when proper protocols are followed. Monge et al (2023) observed the overall adverse effects associated with HBOT was around 7.1% and 4.1% for any barotrauma per session.[3,22,38,39]

Future Perspectives and Challenges

Variability in patients condition, such as its TBI severity, comorbidities, and genetic predisposition might necessitate individualized approach to HBOT regimens. Measurement of biomarkers such as BDNF, HIF-1a, and imaging indicators (e.g., cerebral perfusion) may guide the selection and predict treatment responsiveness.

Current HBOT research used different protocols and is still exploring the optimal pressure, duration, frequency and timing of HBOT. Most protocols used 1.5–2.5 ATA for 60–90 minutes per session. Some studies showed higher pressure might improve benefit but also raises the risk of side effects. Lowest optimal pressure with most benefit and minimal risk is still being explored. Regarding timing, initiation in early post injury generally showed

better outcomes. Adverse effects of HBOT should also be carefully monitored to ensure patient safety. Monitoring tools includes transcranial Doppler, cerebral oximetry, and biomarker panels can enhance safety profiles.[3,22,40]

Translating the HBOT research outcome into a real clinical setting may require challenges and adjustments. Consequently, further studies on human subjects are required, especially to ensure safety. Future direction may involve investigating the efficacy of combination strategies, integrating HBOT with pharmacological agents and rehabilitative intervention. Integration of treatment modalities may act synergistically to improve patient outcomes.

Conclusion

HBOT offers a multifaceted approach to TBI management. Combined biochemical and histological evidence supports the conclusion that HBOT promotes a microenvironment facilitating neural recovery by improving oxygenation and mitochondrial integrity, enhancing neurotrophic support and synaptic connectivity, mitigating secondary injury pathways (oxidative stress, inflammation, apoptosis), and promoting angiogenesis and vascular stability. Despite promising preclinical and clinical data, variability in HBOT protocol has led some controversy, regarding its efficacy in human subjects. Further research is needed to establish the optimal HBOT protocol and its considerations in various patients conditions. This narrative review provides foundational information to guide further studies in this field.

Competing Interests

There is no conflict of interest between authors.

Generative AI Declaration

The authors acknowledge the use of OpenAI's ChatGPT (GPT-4.0, October 2025) to assist with language refinement. As English is not the author's first language, the tool was used to improve clarity and grammar. The model did not contribute to the interpretation of data, analysis, or final conclusions. All outputs were carefully reviewed, revised, and refined by the authors. All intellectual content remains entirely the authors' original work.

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