

Hyperbaric oxygen therapy as a possible therapeutic candidate for sepsis-associated encephalopathy: A novel hypothesis

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ABSTRACT

Hyperbaric oxygen therapy (HBOT) is being increasingly recognized as a potential therapeutic modality with favorable mechanisms in various diseases. HBOT has demonstrated anti-inflammatory and antiapoptotic effects as well as increased the oxygenation capacity of oxygen-deprived tissues, thus contributing to tissue homeostasis. Focusing on these mechanisms, HBOT could be applied for sepsis-associated encephalopathy (SAE), which is a serious sepsis-related complication. Two vital mechanisms in the pathogenesis of SAE are: (1) neuroinflammation mainly induced by microglia and (2) cerebral ischemia/hypoperfusion caused by cerebral microcirculatory abnormalities. Herein, we highlight the mechanisms of the neuroprotective effects of HBOT and its potential application as a therapeutic modality for SAE. We also discuss the caveats and limitations of applying HBOT in sepsis.

Introduction

Sepsis, which is life-threatening organ dysfunction caused by a dysregulated immune response to a pathogenic infection, is a fatal inflammatory syndrome [1,2]. In 2017, 11 million sepsis-related mortalities were reported among the 48.9 million cases of sepsis worldwide, accounting for approximately 19.7 % of global deaths [3]. Sepsis-associated encephalopathy (SAE), which is severe disturbance of the central nervous system caused by a systemic inflammatory response, is a frequent and serious complication of sepsis [1,2,4]. SAE is characterized by an altered mental status that may range from delirium to coma [2,5,6], and is a major risk factor that worsens prognosis of patients, increases mortality, and lengthens hospitalization (Fig. 1) [7]. Patients who have experienced SAE are likely to have permanent sequelae, including neurocognitive impairment in memory, concentration, and decision-making, as well as mental health problems such as post-traumatic stress disorder, anxiety, depression, and suicidal ideations [7,8]. Although neuroinflammation, which is mainly caused by microglia, and cerebral ischemia/hypoperfusion, which is caused by cerebral

microcirculatory abnormalities, are vital mechanisms in the pathogenesis of SAE, no established treatment has proven effective in decreasing the incidence of SAE as well as in preventing neurological sequelae [1,6,9–11].

Hyperbaric oxygen therapy (HBOT) is a treatment modality wherein a patient intermittently inhales 100 % oxygen at a pressure higher than that of sea level (i.e., >1 atmospheres absolute [ATA], 1 ATA = 101 kPa) in a sealed chamber. The Undersea and Hyperbaric Medical Society indicates that pressurization should be at least ≥ 1.4 ATA (>141 kPa) for the therapy to be considered as HBOT. Common treatment pressures range 2.0–3.0 ATA, with typical treatment times ranging 90–120 min. Although HBOT is a well-established treatment for decompression sickness and carbon monoxide poisoning [12], it has shown favorable effects on intractable and refractory diseases, such as inflammatory bowel disease and rheumatoid arthritis, as well as progressive neurodegenerative diseases such as Parkinson's disease [10,13–16]. The proposed mechanisms of the benefits of HBOT are as follows: (1) anti-inflammatory effects via the regulation of immune cells and release of cytokines; (2) hypoxia-overcoming potential by providing oxygen-rich

Abbreviations: AIM, absent in melanoma; ATA, atmosphere absolute; ATP, adenosine triphosphate; BBB, blood–brain barrier; CBF, cerebral blood flow; CNS, central nervous system; HBOT, hyperbaric oxygen therapy; ICP, intracranial pressure; IL, interleukin; JNK, c-Jun N-terminal kinase; NAD⁺, nicotinamide adenine dinucleotide; NO, nitric oxide; SAE, sepsis-associated encephalopathy; JAK/STAT, Janus kinase/signal transducer and activator of transcription; TNF, tumor necrosis factor; MAPKs, mitogen-activated protein kinases; NLRPs, nucleotide-binding domains and leucine-rich repeat-containing proteins; Nrf-2, nuclear factor erythroid 2-related factor; ROS, reactive oxygen species.

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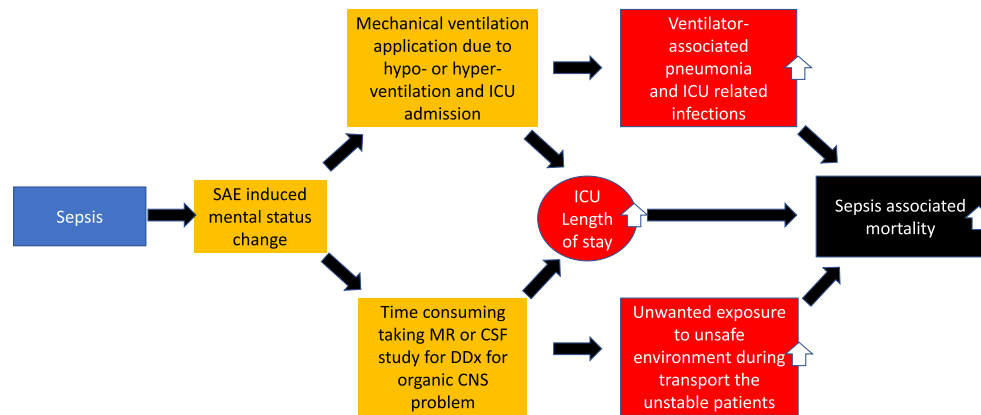


Fig. 1. Clinical consequences of sepsis-associated encephalopathy (SAE) In SAE, changes in mental status are followed by 1) mechanical ventilation and increased risk of intensive care unit (ICU)-related infections. 2) It is time-consuming to conduct neurological examinations to diagnose organic problems of the central nervous system. 3) ICU stay is prolonged.

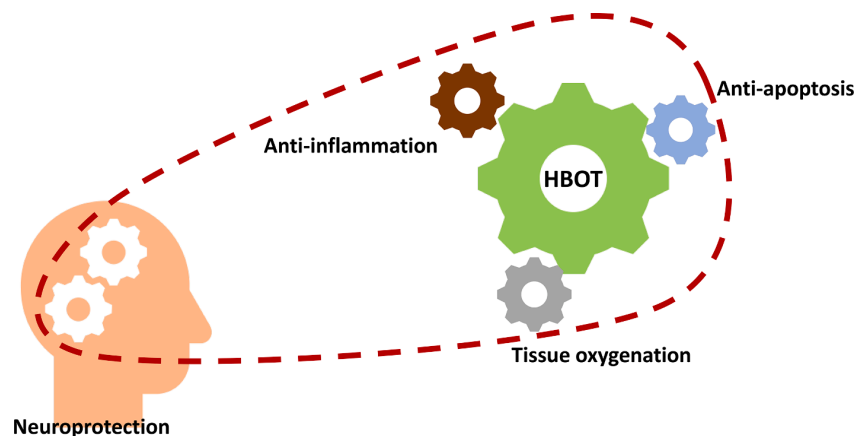


Fig. 2. Schematic diagram of the effects of hyperbaric oxygen therapy (HBOT) on the central nervous system (CNS). HBOT can influence the CNS through (1) its anti-inflammatory effects, (2) tissue oxygenation capacity, and (3) antiapoptotic mechanisms. The favorable effects of HBOT in the CNS may be seen in sepsis-associated encephalopathy.

plasma to tissue-starved oxygen; and (3) antiapoptotic mechanisms through inhibition of the cellular apoptotic pathway in mitochondria (Fig. 2). Notably, proinflammatory mediators, such as interleukin (IL)-1 β , IL-6, and tissue necrosis factor (TNF)- α , are upregulated during the first few days of acclimatization in a high altitude with a hypobaric and hypoxic environment [17,18]. The activity of hypoxia-inducible factor (HIF), which is a transcription factor that regulates gene expression in response to hypoxia, is responsible for this phenomenon [19]. In normal oxygen tension, HIF- α is hydroxylated by oxygen-sensitive prolyl hydroxylase domain proteins (PHD), leading to its degradation; however, decreased PHD activity during hypoxia allows HIF- α to accumulate and bind to HIF- β subunits, causing nuclear translocation and induction of hypoxia-response genes [20]. As one target activated by HIF is the NF- κ B signaling pathway, which is a major proinflammatory regulator, the trend toward proinflammatory conditions at high altitudes may suggest anti-inflammatory reactions in HBOT.

Hypothesis

Cornerstones for SAE treatment are currently based on the early recognition of sepsis using screening tools that estimate serum lactate levels. Meanwhile, its management involves rapid assessment, hemodynamic stabilization by fluid resuscitation, prompt microbiological

cultures for proper diagnosis, and administration of broad-spectrum antibiotics to counter all pathogenic organisms. Therefore, we propose that HBOT may be meaningful as an adjunctive and supportive therapy in the treatment of SAE.

Assessment of hypothesis

1. Regulation of neuroinflammation as a microglia controller

Neuroinflammation is one of main the mechanisms in SAE responsible for the progression of systemic infections to sepsis-related brain injuries [1]. Without any evidence of invasion of pathogenic microbes into the central nervous system (CNS), neuroinflammation could be evoked after systemic inflammation by the leakage of lipopolysaccharides through areas that are not sufficiently protected by the blood–brain–barrier (BBB), such as the choroidal flexus and circumventricular organs (especially the area postrema) [21]. Proinflammatory cytokines released from systemic immune cells in the acute phase of sepsis could also enter the brain through receptor-mediated endocytosis via receptors for IL-1 β , IL-6, and TNF- α , which are expressed on the cerebral endothelium [22,23]. Inflammatory signals from peripheral inflammation may reach medullary autonomic and trigeminal nuclei in the brain through the afferent vagal and trigeminal nerves [9,24–26]. Microglia,

which differentiate from yolk sac-derived primitive macrophages and play a central role as the primary immune cells in brain parenchyma, are activated by these inflammatory mediators and signals in the CNS environment, causing neuroinflammation [27]. Sustained activation of microglia during sepsis promotes not only the release of proinflammatory cytokines but also reactive oxygen species (ROS) and nitric oxide (NO) production, resulting in brain dysfunction through the suppression of neuronal activity and induction of neuronal cell necrosis and apoptosis [5,25,28]. During the neuroinflammatory process, astrocytes, which are a type of glial cell that supports neuronal metabolism, maintain homeostasis in the brain, and collaborate with microglia [29]. Proinflammatory cytokines released by microglia are sensed by astrocytes as potent neuroinflammatory enhancers, resulting in astrogliosis [30]. These abnormal aggregations of activated astrocytes promote the release of even more proinflammatory stimuli, which further activates microglia. This positive feedback loop is possible through autocrine/paracrine proinflammatory mediators [31].

HBOT exerts immunomodulatory actions through attenuation of microgliosis, preventing the release and synthesis of proinflammatory cytokines and upregulating anti-inflammatory cytokine secretion, which is related with microglial differentiation of phenotype polarization [32–35]. HBOT may induce polarization of activated microglia toward the anti-inflammatory M2 phenotype rather than the proinflammatory M1 phenotype [36]. Upon cerebral insults, microglia, which are at rest during normal physiological conditions, are rapidly activated and polarize into M1 and/or M2 phenotypes; these phenotypes have distinct functions in neuroimmunity [4]. M1 microglia, which develop under the influence of proinflammatory factors such as lipopolysaccharides or interferon- γ , produce high levels of proinflammatory cytokines, whereas M2 microglia, which develop under the influence of anti-inflammatory cytokines such as IL-4, IL-13, and IL-10, secrete neurotrophic factors and anti-inflammatory cytokines [37]. In several studies, HBOT attenuated M1 polarization, as demonstrated by decreased expression of mRNA and protein levels of the M1 microglia-specific marker-inducible nitric oxide synthase, after HBOT [36]. HBOT also attenuates microgliosis and decreases TNF- α expression [32]. Western blot analysis has shown that HBOT also downregulates the expression of TNF- α and IL-1 β in animal brains [38]. Moreover, along with enhancement of mRNA expression and levels of the M2 microglia-specific biomarker Arg1, HBOT also upregulated the release of anti-inflammatory cytokines such as IL-10, IL-4, and transforming growth factor- β , in several neuroinflammation-related animal and human experiments [33,34,36].

Other possible mechanisms for the HBOT-mediated anti-inflammatory effect is that HBOT may engage the c-Jun N-terminal kinases (JNK) signaling pathway, which is one of the major signaling cassettes of the mitogen-activated protein kinase signaling cascade that is closely related with the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway [38,39]. As STATs are involved in microglial polarization and HBOT downregulates the expression of phosphorylated STAT1 in activated microglia, HBOT may affect microglial polarization via a reduction in p-JNK expression, which acts as a transcription factor for proinflammatory target genes, through the regulation of STATs, which are downstream regulatory factors of the JNK pathway [38,40].

Another possible mechanism underlying the anti-inflammatory effects of HBOT involves the inhibition of inflammasome-related component expression [41]. Inflammasomes are an assembly of several supramolecular structures in the cytoplasm of activated immune cells that cause proteolytic activation of proinflammatory caspases, which drives subsequent systemic immune responses and inflammation [42]. This multiprotein structure includes a nucleotide-binding domain, leucine-rich repeats containing proteins (also named as NOD-like receptor), and the absence of melanoma 2 (AIM)-like receptors [43]. After immune cells sense specific stimuli, the relevant NLR or AIMS2 can transform into caspase-1-activating scaffold and active caspase-1 to cleave premature IL-1 and pro-IL-18 into the bioactive forms IL-1 β and

IL-18, respectively [42,43]. HBOT downregulates mRNA and protein expression of NLRP1, NLRP2, NLRP3, AIM2, caspase-2-1, and apoptosis-associated speck-like protein containing a CARD, which are components of inflammasomes, after evoking neuroinflammation caused by traumatic brain injury [41]. HBOT could also reduce levels of high mobility group box 1, which is an important damage-associated molecular patterns that mediates activation of innate in the pathophysiology of several neuroinflammatory, and may be considered as an effect of HBOT on inflammasome signaling [41,44].

2. Cerebral oxygenation improvement overcoming microcirculatory dysfunction

Cerebral hypoxia, which causes ischemia in the CNS, is one of the primary mechanisms in the pathogenesis of SAE [1,9,10]. Although the exact pathophysiological mechanisms of the ischemic process have not been elucidated, it may be associated with decreased oxygen delivery and perfusion of cerebral tissue. During sepsis, decreased oxygen delivery occurs due to macrocirculatory dysfunction, such as sepsis-induced hypotension, and microcirculatory impairment such as neurovascular uncoupling with impairment of cerebral autoregulation and micro-thrombosis caused by a hypercoagulable state [1,9,45]. Animal experiments showed a decrease in cerebral perfusion pressure and cerebral blood flow in a septic state [46–48]. Brain imaging, such as computed tomography or magnetic resonance imaging, of patients with sepsis showed similar findings to that in stroke [49]. Impaired cerebral micro- and macrocirculation during sepsis can lead to electrophysiological and neurological changes in the CNS that result in clinical manifestations of SAE.

HBOT is a therapeutic method using 100 % oxygen gas at pressures > 1 ATA [12]. HBOT can increase arterial oxygen tension, which measures the partial pressure of oxygen, to > 2,000 mmHg and 200–400 mmHg in tissues following the Boyle–Mariotte and Henry's Laws [50]. Hence, HBOT may be performed on oxygen-deprived individuals, such as those with carbon monoxide poisoning, air embolism, severe anemia, infections, traumatic brain injury as well as for wound healing as it increases oxygen supply [12,51]. Moreover, in several clinical experiments and case reports, the efficacy of HBOT in vasculature insufficiency-induced ischemic conditions has been reported [52–54]. HBOT used as an adjunctive treatment after surgery results in early wound healing and rehabilitation along with prompt functional recovery following crushing injuries of the extremities [52,53]. In patients with central retinal artery occlusion, which is an ophthalmological emergency, the best corrected visual acuity improves, and fluorescein angiography normalizes, after HBOT [54]. Even in severe COVID-19 pneumonitis with global microvascular injury and thrombosis as well as pauci-inflammatory septal capillary injury and fibrin deposition, HBOT has been proposed as an additional supportive therapy to improve oxygenation [55]. Due to its mechanisms of action, HBOT may increase oxygen content in cerebral tissues affected by SAE. Plasma with sufficiently dissolved oxygen levels following HBOT may be delivered even to hypoxic tissues that hemoglobin has difficulty reaching due to microcirculatory abnormalities.

3. Restoration of mitochondrial dysfunction and inhibition of neuronal apoptosis

Mitochondrial dysfunction in SAE is caused by decreased oxidative phosphorylation, mitochondrial membrane disruption, and ROS, leading to neuronal cell apoptosis [56–58]. Adenosine triphosphate (ATP) is produced through phosphorylation via electron transportation through five complexes in the mitochondrial membrane; oxygen is the final electron acceptor in mitochondrial cellular respiration [57,59]. In SAE, cerebral hypoxia decreases ATP production, and mitochondrial membrane integrity disruption was noted in neural tissues [60]. Disruption of the mitochondrial membrane transition pore, which is a passageway for

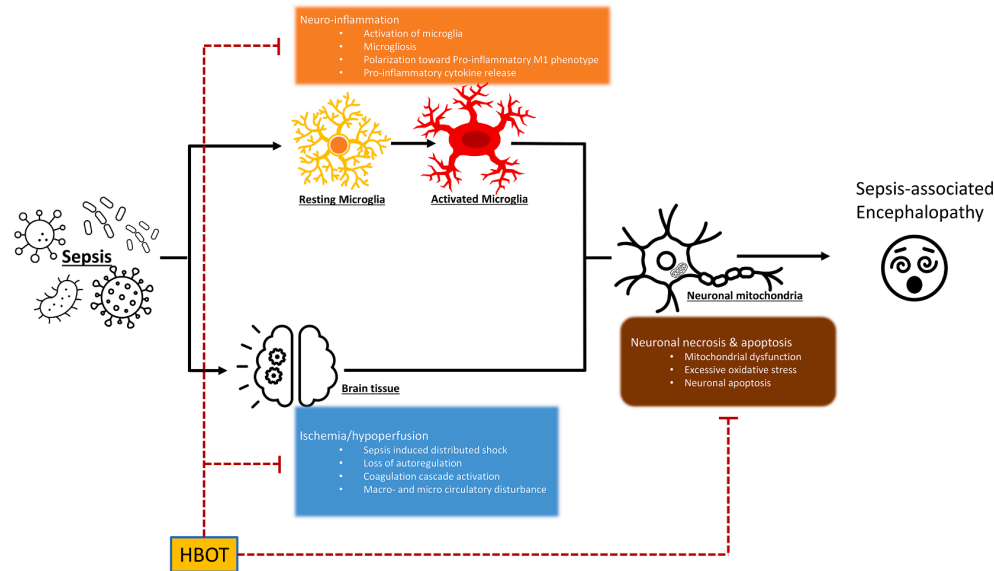


Fig. 3. Mechanisms of the favorable effects of hyperbaric oxygen therapy (HBOT) in sepsis-associated encephalopathy (SAE). HBOT inhibits the initiation and progression of SAE. (1) HBOT suppresses the initiation of dysregulated neuroinflammation by controlling microglial activation. (2) Through excessive elevation of arterial oxygen tension, HBOT could overcome cerebral hypoperfusion and diminish ischemic injury. (3) The restoration function of HBOT in neuronal mitochondria can inhibit the apoptotic pathway.

superoxides, cause accumulation of ROS in the cytosol [58]. Generation of superoxide increases during sepsis due to disrupted oxidative phosphorylation, causing increased ROS production [58]. Tissue hypoxia also increases production of NO, which inactivates mitochondrial phosphorylation [58]. Impaired oxidative phosphorylation and membrane disruption can cause accumulation of ROS and vice versa. These mechanisms of mitochondrial dysfunction in SAE may result in dysfunction of the CNS by suppressing neuronal activity and inducing neuronal cell apoptosis [59,61].

To attenuate SAE-induced apoptosis, treatment should improve mitochondrial function and decrease oxidative stress. HBOT reportedly promotes mitochondrial function and mitigates apoptosis [56,57]. In a rat model of stroke and traumatic brain injury, ATP levels increased along with an improvement in neurological function and levels of nicotinamide adenine dinucleotide (NAD⁺), which play an important role in increasing ATP production via oxidative phosphorylation, following HBOT [62,63]. HBOT upregulates NAD⁺ by activating SIRT1, which is an enzyme involved in neuronal survival that deacetylates transcription factors utilizing NAD⁺ as a substrate in the nucleus, increasing mitochondrial biogenesis of ATP [57]. HBOT also restores mitochondrial membrane integrity with mitochondrial transmembrane potential after injury and prevents apoptosis of injured neurons [56,57,64]. Moreover, although high oxygen levels following HBOT are thought to cause oxidative stress with elevated ROS levels, HBOT could increase antioxidant production depending on the treatment protocol [57]. Short-term and less frequent HBOT treatment may be correlated with reduced ATP production and decreased transmembrane potential resulting from elevated ROS levels [57]. Meanwhile, long-term and frequent HBOT improves mitochondrial activity with ATP production and reduces ROS production in mitochondria, which is related with the activation of the antioxidant pathway [57]. This antioxidant pathway is activated via the nuclear factor erythroid 2-related factor 2 (Nrf-2) pathways [56,57,60]. In HBOT-induced oxidative stress, E3 ligase, which targets Nrf-2 for ubiquitination and proteasome degradation, attaches to free radicals and creates a conformational change [65]. The modified ubiquitin E3 ligase complex stabilizes Nrf-2, which is then transported to the nucleus and activates expression of cytoprotective genes such as the antioxidants heme oxygenase-1, glutathione S-

transferase, and quinone oxidoreductase 1 [66,67]. Additionally, HBOT could also prevent apoptosis due to activation of antiapoptotic factors such as Bcl-2 and Bcl-xL [68]. In injured brain tissues of a rat model, expression of Bcl-2 and Bcl-xL, which directly inhibits the activity of proapoptotic factors Bax and Bak, increased after HBOT treatment, suggesting that the antiapoptotic properties of HBOT could also mitigate apoptosis in SAE [60,68].

Limitations and concerns

This work has some limitations and concerns. The application of HBOT in SAE is limited by the lack of specific and precise protocols for sepsis and sepsis-related conditions. Furthermore, some complications caused by oxygen toxicity may be severe or life-threatening, and there is a lack of understanding regarding the side effects of HBOT for septic conditions.

High oxygen concentrations administered during HBOT could be one of its concerns. Oxygen is essential for cell respiration but is also as a source of ROS [69]. As mitochondria produces ROS during oxidative phosphorylation, increased levels of accessible oxygen from HBOT will also increase oxidative stress and lead to damage of biomolecules such as lipids, DNA, and proteins [70]. However, antioxidant pathways are activated along with increased ROS levels, and the summation of free radical and antioxidant levels and activity determine the resulting degree of oxidative stress [57]. Following HBOT for chronic wounds, levels of oxidative stress biomarkers, which include catalase, extracellular superoxide dismutase, myeloperoxidase, xanthine oxidase, malondialdehyde, and protein carbonyls, decreased [71]. In an experimental animal study that focused on biomolecular damage caused by ROS, levels of free radical peroxides, peroxynitrite production, and lipid peroxidation after HBOT did not increase, suggesting the absence of oxygen toxicity after HBOT [72,73]. Experimental research on intracranial pressure (ICP) changes during HBOT have shown that hyperoxia-induced vasoconstriction could lower ICP by up to 30 % and can also reduce cerebral blood flow (CBF) by up to 19 % [74]. Although HBOT-induced vasoconstriction and reduction in CBF could be a concern in an ischemic/hypoxic cerebral status during SAE, reduction of lactate levels in cerebrospinal fluid following HBOT in severely injured brains

supports the notion that HBOT improves aerobic metabolism despite intracranial vasoconstriction and a reduction in CBF [75]. HBOT may also counteract capillary vasodilation within injured tissues, thereby alleviating retention of interstitial fluids and ultimately reducing brain vasogenic edema [76]. Additionally, as evidenced by experiments that used Evans blue (EB) dye, which forms a large complex with albumin and may determine BBB permeability, HBOT improved BBB permeability as evidenced by decreased extravasation of EB dye following ischemic/hypoxic injury; increased expression of caveolin-1, tight junction protein ZO-1, and HIF-1 is thought to be responsible for this protective effect [77,78]. However, in several experiments using a sepsis-induced model, while EB dye extravasation through BBB was attenuated after HBOT, extravasation of horseradish peroxidase, which has a molecular weight of < 40 kDa, into the brain was not reduced [79,80]. Therefore, considering the characteristics of inflammatory substances permeating through the BBB, which is disrupted in sepsis, the effects of HBOT on BBB integrity during sepsis may also be a concern in its application for patients with SAE.

Based on the evidence presented, future research is needed to verify our hypothesis through in vitro and in vivo experiments. An experimental in vitro cell study will be conducted that will involve microglia to determine differences in mRNA gene expression patterns following HBOT after LPS exposure. For in vivo animal experiments, we plan to use an animal sepsis model (8-week-old rats) to determine differences in gene expression patterns and inflammation-related cytokine production in brain tissues following HBOT.

Conclusions

SAE, which is a critical complication of sepsis, not only worsens the prognosis of patients with sepsis but also results in long-term sequelae, such as cognitive impairment and psychological illness. Additionally, SAE is a burden not only on healthcare systems due to its resource-intensive management but also on families due to its high financial costs. Furthermore, SAE is difficult to differentiate from other neurological diseases, with MR imaging or cerebrospinal fluid analysis often being required. Considering the primary pathogenic mechanisms of SAE, HBOT could be a promising therapeutic alternative for SAE. HBOT for SAE may improve survival and reduce cognitive and psychological sequelae in patients with sepsis (Fig. 3).

Declarations

Ethics approval and consent to participate
Not applicable
Consent for publication
Not applicable
Availability of data and materials
Not applicable

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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