REVIEW

A review on the neuroprotective effects of hyperbaric oxygen therapy

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Abstract

Hyperbaric oxygen therapy, intermittent breathing of 100% oxygen at a pressure upper than sea level, has been shown to be some of the neuroprotective effects and used therapeutically in a wide range of neurological disorders. This review summarizes current knowledge about the neuroprotective effects of hyperbaric oxygen therapy with their molecular mechanisms in different models of neurological disorders.

Key words: apoptosis; clinical trial; hyperbaric oxygen; inflammation; *in vitro*; *in vivo*; neuroprotection; oxidative stress

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Introduction

Nervous system diseases are one of the leading causes of death and disability worldwide due to the limitation of effective treatment strategies. Although some promising strategies have been reported in the animal models of nerves system disorders, they often fail to work in clinical practice. Therefore, new treatment strategies need to be developed and exploited. Within the previous decades, various pharmaceutical compounds as well as various therapeutic methods with neuroprotective effects have been described, including high pressure oxygen therapy as a nondrug and noninvasive therapy. Hyperbaric oxygen (HBO) therapy (HBOT) is defined as the intermittent breathing of pure oxygen inside a hyperbaric chamber at a pressure above sea level. During HBOT, the amount of dissolved oxygen in the plasma as well as saturated hemoglobin with oxygen increases, leading to greater oxygen availability to the organs.[1,2] It is well documented that HBOT has neuroprotective effects against experimental spinal cord injury (SCI),[3] brain injury,[4,5] neurodegenerative disease,[6,7] peripheral nerve injury,[8,9] and neurotoxicity models of rodents.[10] On the other hand, clinical evidence to support the neuroprotective properties of HBOT is limited.[11] In regard to the neuroprotective effects of HBOT, accumulating evidence indicates an association between the beneficial effects to a variety of biological properties mainly anti-oxidative,[12] anti-inflammatory,[13] and anti-apoptotic properties,[14] in addition to improvement of oxygen supply and neural metabolism.[15,16] This paper presents an up-to-date review of the neuroprotective effects of HBOT with its molecular mechanisms in different models of neurological disorders in three parts.

In Vivo Studies

A lot of *in vivo* experimental studies have been conducted on the HBOT neuroprotection and its underlying molecular mechanisms, summarized in **Additional Tables 1–5**.

SCI

SCI is a complex process that is first caused by primary mechanical trauma or ischemia and then continues by secondary damage caused by various mechanisms.[17] SCI outcome is related to the amount of secondary damage caused by a series of biochemical, molecular, and cellular cascades including, apoptosis, inflammatory reaction, and lipid peroxidation.[18-21] In this regard, despite the report of Balentine[22] which indicates spinal cord gray matter necrosis and subsequent motor deficit following exposure to HBO (413.68 kPa on consecutive days) in rats, Higgins et al.[23] documented for the first time that HBOT during the early phases of SCI preserves the marginal spinal cord long tracts due to reduction of edema or reversal of focal hypoxia. HBOT shortly after spinal cord ischemia in rabbits (30 minutes after reperfusion) had protective effects through attenuation of the selective motor neuron death; however, delayed therapy (6 hours after reperfusion) with HBO did not change the prognosis.[24] Subsequent studies demonstrated that multiple HBOT (once daily for 1 week starting at 6 hours following injury) produced significantly more neurological improvements than the control group.[25,26] Biochemical analysis of HBOT on the oxidative status after SCI revealed that HBO prevents oxidative damage to the spinal cord.[27] Another study to determine other mechanisms of neuroprotective effects of HBOT on experimental SCI showed that HBOT significantly attenuated SCI-induced interleukin (IL)-1β and tumor necrosis factor-α (TNF-α) overproduction, and in turn significantly increased the number of both glial cell line-derived neurotrophic factor- and vascular endothelial growth factor (VEGF)-positive cells and spinal cord IL-10 production.[28] In regard to spinal cord tissue enzyme levels following HBOT, it was found that postoperative HBOT was useful in terms of biochemical parameters such as nitric oxide, glutathione peroxidase, superoxide dismutase (SOD), and nitric oxide synthase (NOS) activity rate in the damaged part of the spinal cord tissue following SCI.[29] HBOT decreases spinal cord edema, improves neuronal function, and stabilizes the blood-spinal cord barrier

through downregulation of matrix metalloproteinase (MMP)-2, IL-6, and MMP-9 and upregulation of VEGF.[30] Another study documented that HBOT through inducible NOS (iNOS) mRNA-iNOS-nitric oxide signaling pathway can promote the neuroprotection following SCI.3 The inflammatory process is one of the major causes of secondary SCI. In this regard, Yang et al.[31] documented that HBO intervention reduced secondary SCI via nuclear factor-κB (NF-κB) and high-mobility group protein B1 (HMGB1) downregulation in rats with acute SCI. In regard to the other neuroprotective mechanism of HBO on SCI, it was documented that hypoxia-inducible factor-1α (HIF-1α) reduction and VEGF elevation by HBO intervention may be inversely associated with spinal cord repair.[32] Another study documented that HBOT via Toll-like receptor (TLR)2/NF-κB signaling induced protective effects against rat SCI.[33] The researchers believe that HBOT reduces secondary SCI and promotes neurological outcome through TLR2/NF-κB signaling pathway. A research has shown that early HBOT (at the 1st hour after trauma) contributed to the biochemical and histopathological improvement of the rats after SCI.[34] To determine the mechanisms of HBOT in SCI, a study measured the expression levels of connexin 43 and VEGF in the damaged part of the spinal cord.[35] The results showed that VEGF significantly increased, while the level of connexin 43 significantly decreased after HBOT. Immunoreactive responses are like a double-edged sword in which the macrophages were considered as predominant inflammatory cells. In this regard, results of a study showed that HBOT by altering the macrophage M1 phenotype to the M2 phenotype modified the inflammatory environment, which promotes functional recovery and axonal extension.[36] Liang et al.[37] demonstrated that HBOT compromised NACHT domain leucine rich repeat and pyrin domain containing protein 3 (NALP-3) inflammasome, caspase 1 and adaptor molecule apoptosis-associated speck-like protein, in addition to mitigating IL-1β release in the damaged spinal tissue. HBOT has a protective effect on SCI by reducing neuronal cell apoptosis and *MMP-9/2* gene expression in rats, so that improved motor function scores and increased myelinated nerve fibers.[38] Studies emphasize the key role of endoplasmic reticulum stress in the induction of neuronal apoptosis following SCI. In this regard, it was documented that HBOT by inhibiting endoplasmic reticulum stress-induced apoptosis alleviated secondary SCI and thereby improved the neurological function.[39] Another study tested the hypothesis that HBOT via regulation of c-Jun N-terminal kinase (JNK) and glucose-regulated protein 78 expression ameliorates secondary SCI.[40] The results showed that HBOT increased glucose-regulated protein 78 level and decreased that of JNK which leads to tissue and motor recovery. In regard to the HBOT effects on inflammatory process after SCI, Kang et al.[41] documented that HBO intervention by regulation of NF-κB, TLR4, and HMGB1 signaling pathways reduces secondary SCI in rats. Autophagy, a lysosome mediated metabolic pathway, plays a key role in cell survival, differentiation, development, and homeostasis. It has been reported that regulation of autophagy improves neurological function after SCI.[42] In this regard, it was documented that enhancement of autophagy expression and acceleration of cell repair rate after SCI may be another mechanism of action of HBOT.[43] HBOT potentially by inhibiting receptor expression for monocyte chemoattractant protein 1 and advanced glycation end products recovers locomotor function.[44] Results of another study which was investigated the mechanisms of HBOT following SCI, suggested that reducing lipid oxidation and oxygen free radicals is one of the mechanisms.[45] Sun et al.[46] documented that HBO significantly improved the recovery of neuronal function and fractional anisotropy compared to SCI group on days 7, 14, and 21 after SCI. Recently, it was documented that HBOT improves neurological disorders by amelioration of apoptosis and suppressing dendritic/synaptic degeneration through upregulating the brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B signaling pathways in the anterior horn of spinal cord after SCI.[47] Also, another study revealed that HBO via stromal cell-derived factor-1/CXC chemokine receptor 4 axis activation and promotion of BDNF expression improves neurological function after SCI in rats.[48] HBO improves functional recovery through inhibiting iNOS, cyclooxygenase-2, glial fibrillary acidic protein, and neuron-glial antigen 2; meanwhile this process may be due to inhibition of NF-κB and Akt pathways.[49] Assessment of HBOT in rat model of SCI using diffusion tensor imaging showed that HBOT for 4 weeks is the more appropriate course.[50]

Brain injury

Studies have shown that brain damages after stroke or trauma are due to a variety of pathophysiological processes such as nitrative and oxidative stress, disruption of the blood-brain barrier (BBB), excitotoxicity, neural cell death, inflammatory reactions, and deficits in angiogenesis.[51-53] In this regard, Weinstein et al.[54] showed that HBOT conferred significant protection against death from untreated cerebral ischemia in anaesthetized gerbils, while histological examination showed that the extent of patchy bilateral ischemic neuronal damage was much less in surviving gerbils that received HBOT. After that, a study was conducted to determine the effects of HBOT on free radical generation and lipid peroxidation following global cerebral ischemia.[55] Results of this study showed that HBOT elevated the level of oxygen free radicals after ischemia in the brain, but, this elevation was not accompanied with increased lipid peroxidation or decreased neurophysiological recovery. In fact, despite the initial increase in free radical generation, the amount of peroxidation was similar to control group, while the cortical somatosensory evoked potential recovery was more than 50-fold in the HBO-treated animals relative to the control group. Another study documented that HBO reduces blood flow and brain vascular permeability after global cerebral ischemia in rabbits, however, recovery of the somatosensory evoked potential was the same as control and HBO groups.[56] While, HBOT in another study had no beneficial effects on neurologic outcome after acute focal cerebral ischemia.[57] It was reported that adult rats with middle cerebral artery occlusion which are exposed to HBO immediately or after a 60-minute delay showed improvement in motor impairment, as well as a reduced cerebral infarction compared to normal atmospheric pressure.[58] Assessment of the role of neutrophils and prophylactic HBO on cerebral injury revealed that HBOT before ischemia at 2.8 atmosphere absolute (ATA; 1 ATA = 101.325 kPa) for 45 minutes reduces myeloperoxidase

concentration, functional neurologic deficits, and cerebral infarct volume through inhibiting neutrophil sequestration.[59] Results of an investigation revealed that altered excitatory amino acids and brain energy metabolites which occurred during brain ischemia were regulated with HBOT at different times after ischemia.[60] Neurotrophin-3 plays a protective role against neuronal cell death in response to brain ischemia. In this regard, it was documented that HBOT decreases down-regulation of the post-ischemic neurotrophin-3 mRNA in the rat hippocampus.[61] HBOT has dual effect on cerebral infarction, and using HBO within 6 hours of ischemia-reperfusion injury can be beneficial but using HBO 12 hours or more after injury can be harmful, while tissue damage was not reduced by HBO during 4 hours of permanent focal cerebral ischemia.[62] Yin et al.[63] revealed that HBOT can lead to an inhibition of cyclooxygenase-2 over-expression in cerebral cortex after cerebral ischemia. Hyperbaric oxygenation reduces focal brain damage and reduces striatal dopamine secretion after occlusion of middle cerebral artery.[64] One of the molecular mechanisms of protection by HBO is the prevention of apoptosis which might preserve more tissue in the brain and improve neurological function. In this regard, Yin et al.[65] documented that HBOT (7 days after reperfusion) reduced brain infarction and improved neurologic scores by preventing apoptotic death (abolished DNA fragmentation and reduced terminal deoxynucleotidyl transferase dUTP nick end labeling-positive cell number) in rat ischemic cortex. It is well known that cerebral ischemia causes significant changes in the Na^+,K^+-ATPase and SOD activities. In this regard, it was documented that preservation of Na^+,K^+-ATPase and reinforcement of SOD activity are the possible mechanisms of HBOT in severe brain ischemia.[66] Assessment of the apoptotic cell number revealed that HBOT attenuated secondary brain damage in an experimental transient brain injury (TBI).[67] To elucidate the timing and mechanisms of HBO protection following cerebral ischemia, Veltkamp et al.[68,69] examined the early *in vivo* effects of HBO by repetitive magnetic resonance imaging and BBB permeability for sodium fluorescein 2 hours after transient focal ischemia. The results showed that HBO significantly decreased abnormal diffusion weighted imaging signal volume, lesion size on T2-weighted images, BBB permeability on T1-weighted images, and vasogenic edema assessed on T2-weighted images and histologic sections after 24 hours. Another study suggested that delayed, but multiple HBOT (2.5 ATA, 2 hours per dayfor 6 consecutive days) can improve neurological function and reduce cerebral infarction after transient focal ischemia.[70] Recent data emphasize the key role of apoptosis in the spread of lesion after TBI. In this regard, Bcl-xL, Bcl-2 and Bax proteins immunostaining in the brain tissue showed a significant increase in Bcl-2 and Bcl-xL anti-apoptotic proteins after HBOT, while staining for pro-apoptotic protein Bax did not significant.[71] A study was conducted to assess HBOT effects on intracranial pressure dynamics and survival in rat severe fluid percussion brain injury, concluding HBOT during the early phase of injury significantly diminished intracranial pressure elevation rate and reduced mortality rate.[72] In regard to BBB integrity preservation with HBOT after cerebral ischemia, Veltkamp et al.[73] documented that HBO decreases ischemic degradation of cerebral microvascular laminin-5 and blocks upregulation of postischemic plasma MMP. Calvert et al.[74] tested the hypothesis that HBO alternates the expression of HIF-1α in neonatal hypoxia-ischemia. The results showed that HBOT increased glucose transporter-1, glucose transporter-3, aldolase, and lactate dehydrogenase expression, while decreased p53 expression and HIF-1α-p53 interaction. Therefore, HIF-1α phenotype alternation is one of the underlying mechanisms of HBO neuroprotection following neonatal hypoxic-ischemic injury. Effectiveness of HBO is controversial in permanent ischemia models, so that in extensive focal ischemia HBOT is only effect in early recanalization.[75] HBOT can reduce neuronal apoptosis after TBI by reducing cytochrome c secretion and Bax dimers and over-regulation of Bcl-2 expression.[76] The effects of HBOT on inflammatory infiltration and expression of MMPs in rat dynamic cortical deformation have been evaluated.[77] HBOT showed that a significant reduction in the number of terminal deoxynucleotidyl transferase dUTP nick end labeling positive cells, neutrophilic inflammatory infiltration, and MMP-9 expression. The potential neuroprotective effects of HBOT in a focal cerebral ischemia model proved with significant neuroprotection (reduction of infarct volume) at 5 hours after ischemia that lasted for 168 hours.[78] A study revealed that early intra-ischemic HBOT could reduce hemorrhagic transformation (hemoglobin content) in a rat model of focal transient cerebral ischemia.[79] A 40-day series of 80 low-pressure HBOTs following TBI increases vascular density in the damaged hippocampus and improves cognitive function.[80] Zhou et al.[81] tested the effects of HBOT on mitochondrial function, as measured by cognitive improvement and cellular adenosine triphosphate after lateral fluid-percussion injury in rat. The results showed that HBO-treated animals had significantly higher levels of cerebral ATP and cognitive recovery and lower neuronal loss in the CA2/3 and hilar regions. In another study, cerebral partial pressure of oxygen was measured using electron paramagnetic resonance oximetry before and after occlusion of the middle cerebral artery and HBO exposure in rats.[82] The results of the study revealed that measurements of the partial pressure of oxygen showed no increase in ischemic or normal hemispheres minutes after HBO exposure, despite decreasing the infarct size. Another study suggested that hyperoxia protection is due to a negative regulation of the proapoptotic function of mitochondrial translocator protein such as mitochondrial membrane potential conservation after cerebral contusion.[83] Study on optimal dosing and timing of HBOT in a rat model of transient ischemia/reperfusion revealed that oxygen is a highly neuroprotective molecule when used early and in high doses.[84] Results of a study suggested that single HBOT has a time limitation of 12 hours after TBI; meanwhile multiple HBOTs have the ability to extend the delivery time window after TBI.[85] Sun et al.[86] found that HBO decreases infarct size and reduces post-thrombolytic intracerebral hemorrhage after thromboembolic occlusion of the middle cerebral artery in rats. Also, it was documented that hyperbaric oxygenation has neuroprotective effects in middle cerebral artery occlusion-induced brain injury through reducing hydroxyl free radical formation and glutamate release.[12] Zhao et al.[87] documented that HBOT increases claudin-5 and claudin-1 expression, and decreases permeability of the BBB

via the suppression of MMP-2 and MMP-9 after cerebral ischemia–reperfusion in rats, respectively. HBOT stimulates IL-10 overproduction, neurogenesis, and angiogenesis, while reduces gliosis following TBI in rat.[13] Also, HBOT reduced TBI-induced TNF-α expression and microglial activation during the acute phase of TBI resulting in a neuroprotective effect.[88] Data of another study showed that HBOT through promoting axonal sprouting and synapse remodeling can intensify neuroplastic responses, which contributes to the improvement of locomotor function following cortical ablation in rat.[89] Study on the effects of hyperbaric oxygenation on oxidative stress in acute transient focal cerebral ischemia in rats revealed significant reduction in infarct volume, activation of astrocyte, and increasing glutathione level.[90] Neonatal hypoxia-ischemia encephalopathy causes brain damage and neurodegeneration leading to cognitive and behavioral impairment. Liu et al.[91] suggested that HBOT is effective in promotion of histological and long-term functional recovery after neonatal hypoxia-ischemia brain damage due to caspase-3 inhibition and apoptosis inducing factor-mediated pathways. In regard to the effects of delayed HBOT on cerebral ischemia and its potential mechanisms, it was documented that delayed HBOT promotes neurogenesis and improves neurofunctional recovery in the late-chronic phase of stroke probably due to reactive oxygen species/HIF-1α/β-catenin pathway.[92] Despite the mentioned beneficial effects of HBOT in experimental models of stroke, Lu et al.[93] documented that HBOT increases brain damage area by activation of extracellular signal-regulated kinase (ERK) 1/2, which interrupts autophagy flux in a transient cerebral ischemic rat model. IL-10 plays an important role in the neuroprotection of HBOT against TBI, so that IL-10 deficiency aggravates the brain damage and abrogates the beneficial effects of HBOT on apoptosis, inflammation, and edema after injury.[94] A study was conducted to investigate the effect of the different hyperbaric oxygenation manipulations based on morphological, molecular-biological, and behavioral tests at 4 hours, 15 days and 75 days after TBI in rats.[95] The results showed that hyperbaric oxygenation inhibits cell apoptosis in the rat hippocampus and improves their physiological functions in the HBO-early group better than the HBO-delayed group. Another study demonstrated that HBO could enhance neuroprotection and improve prognosis through inhibiting cerebral edema, intensifying the metabolism of local neurons, reducing apoptosis, inhibiting the inflammatory reaction, and protecting BBB integrity in a blast-induced TBI model in rabbits.[96] Kraitsy et al.[97] showed that the long-term protective effects of HBOT are provided by the cortex remyelination, which is demonstrated by the recovery of sensorimotor function. Also, using diffusion-weighted imaging and DCE-magnetic resonance imaging revealed that HBO improves cytotoxic edema and impaired BBB and promotes the recovery of neurofunction after experimental TBI.[98] HBOT during the acute phase of TBI can attenuate TNF-α and transforming growth-interacting factor, and increase transforming growth factor β-1 which leads to decreased apoptosis in the affected cortex.[14] Liu et al.[99] found that daily HBOT significantly improved Morris water maze performance and attenuated edema in the ipsilateral hippocampus after TBI, suggesting that the therapeutic effect of HBO is at least partially mediated through reducing brain edema. The effects of HBO on cognitive dysfunction showed that HBOT, provided 5–7 days after craniocerebral trauma, improves cognitive function and neuroplasticity in a controlled cortical impact rat model.[100] Study of the relative neuroprotective effects HBOT and TLR4 knockout following temporary middle cerebral artery occlusion in mouse revealed that a single HBOT immediately after occlusion and after 24 hours reperfusion significantly reduces edema and improves perfusion, while, TLR4 knockout protects mice against ischemia but to a lesser extent than HBOT.[101] It was documented that HBOT due to inhibition of the TLR4/NF-κB signaling pathway protects the neurons after traumatic injury in rat, so that significantly inhibits the activation of the TLR4/NF-κB signaling pathway, reduces TNF-α, caspase-3, IL-1β and IL-6 expression, and reduces neural apoptosis and improves the neurological function.[102] HBOT increased expression of the heme oxygenase, nuclear factor erythroid 2-related factor 2 (Nrf2), and quinine oxidoreductase 1 in the brain tissue around the lesion and also improved neurological function after TBI.[103] A study revealed that HBO reduces IL-1β and IL-18 and suppresses protein expression of inflammasome components, along with high-mobility group box 1 reduction after TBI in the brain and serum.[104] In regard to repetitive mild TBI, it was found that HBOT significantly decreased the magnetic resonance imaging-identified abnormalities and tissue histopathology.[105] HBOT ameliorates TBI-induced depression-like behavior by reducing neuroinflammation if early intervention is possible, suggesting a possible mechanism by which depression-like behavior recovery might occur.[106] Results of a study showed that immediate and delayed HBOT for moderate TBI in mice have similar effects, so that displayed significant improvement in learning abilities, decreased neuronal loss and reactive astrocytes, and increased myelin basic protein.[107] Recently, it was found that HBO promotes neural stem cell proliferation and migration to the lesion area by activating VEGF/ERK signaling on day 7 after TBI.[108] It is well known that the nucleotide binding oligomerization domain like receptor family pyrin domain containing 3 (NLRP 3) inflammasome has been implicated in the secondary injury of TBI. In this regard, Qian et al.[109] documented that HBO improves motor score and reduces brain edema following TBI, along with IL 1β, IL 18, and NLRP 3 inflammasome components reduction. The results revealed that HBO decreases inflammation via modulation of microglial NLRP-3-inflammasome signaling. HBOT following hyperglycemic middle cerebral artery occlusion in rat reduces hemorrhagic transformation and infarction volume via ATP/NAD^+/Sirt1 pathway which may be a promising approach for diabetic patients with acute ischemic stroke.[110] Multiple HBOT significantly decrease the expression of c-jun, c-fos, and Bax, while increase the expression of Bcl-2, neurotrophin-3, glial cell line-derived neurotrophic factor, BDNF, and nerve growth factor.[111] Also, HBO exposure through increasing tight junction protein zonula occludens-1 and caveolin-1 improved BBB permeability following global cerebral ischemia/reperfusion injury in rat.[112] He et al.[113] found that HBOT attenuates neuronal apoptosis via Akt/GSK3β/β-catenin pathway after TBI.

Nerve injury

Muscle paralysis and neuropathic pain due to the destruction of motor and sensory neurons are among the most common symptoms of nerve injuries.[114,115] Meanwhile, neuroinflammation, oxidative stress, excitotoxicity, apoptosis, and neurotrophic support deficit are some of the mechanisms involved in neural degeneration after nerve injury.[116-118] In this regard, using the rat sciatic nerve model, the effect of HBO on peripheral nerve healing after destruction was evaluated.[119] Results of this study suggested that HBOT for 1 week following microsurgical repair promotes functional recovery in transected peripheral nerves. Also, another study concluded that HBO effectively saves fibers from ischemia.[120] Although, regard to rat peroneal nerve crush and transection injury there were no HBO-related changes in nerve/muscle force measurements and edema.[121,122] Whereas, a study on the regenerative effects of HBO on crushed sciatic nerve injury suggested that therapies consisting of 100% oxygen under pressure can improve the healing of peripheral nerve in rabbits.[123] HBOT (first at 0, 4, and 8 hours postoperatively and then every 8 hours) stimulates axonal outgrowth following a sciatic nerve crush lesion in rat, evaluated using the pinch-reflex test and with neurofilament staining.[124] Whereas, another study concluded that HBOT (twice daily for 3 consecutive days), had no influence on functional recovery after standard nerve crush injuries on sciatic nerves of rats using walking-track analysis.[125] After that, some investigators studied the effect of HBOT on axonal outgrowth in cellular and acellular nerve grafts of sciatic nerves in rat. The axonal outgrowth was significantly longer in animals treated with HBO after cellular nerve grafting,[126] in contrast to acellular nerve grafts with no beneficial effects on axonal outgrowth.[127] Another study confirmed that HBOT could not restore the gait or the strength of muscle after 90 days with nerve transection and repair or with nerve crush injury in rats.[128] Mrsić-Pelcić et al.[129] found that HBOT prevented ischemia-induced changes in the Na^+,K^+-ATPase activity after HBO administration in the optic nerves of global cerebral ischemia-exposed rats, while the level of the SOD activity in the ischemic animals was not changed. Evaluation of long-lasting effects of hyperbaric oxygenation on transected sciatic nerve and repaired with microsurgery showed functional recovery after 7 weeks.[130] Evaluation of the effects of HBOT on the histological pattern of damaged facial nerve in rabbits indicated an increase in the mean axon diameter 2 weeks after injury.[131] In spite of protective effects of HBOT in peripheral nerve injury, some evidence revealed that the ERK1/2 and p38 have been differently activated in the dorsal root ganglion by prolonged HBO exposure.[132] A study showed that HBOT reduces neuropathic pain and inhibits intraneuronal TNF-α production after chronic constrictive injury.[133] Analysis of the thermal hyperalgesia, mechanical allodynia, and neurochemical changes of neuropathic pain in rat sciatic nerve injury showed that repetitive HBOT greatly inhibited behavioral signs of neuropathic pain and nerve injury-induced induction of c-Fos and activation of astrocytes, and increased phosphorylation of N-methyl D-aspartate receptor subtype 2B receptor and the subsequent Ca^{2+}-dependent signals in rats.[134] Pre- and post-HBOT inhibits neuropathic pain following chronic constriction injury in rats through the regulation of neuronal and inducible NOS expression in the spinal cord, demonstrating that HBO has therapeutic effects on neuropathic pain.[8] The role of brain opioid receptors in the anti-allodynic properties of HBO following crush-induced neuropathic pain in rats was investigated in another study.[135] Data analysis of this study revealed that HBOT significantly decreased the nerve crush-induced allodynia, whereas, this anti-allodynic effect by the opioid antagonist naltrexone was reversed. Another study conducted to specify the effect of different times of HBOT application on transected-sciatic nerve regeneration using standard microsurgical techniques.[136] The results showed the best gait analysis and less fibrosis with HBOT started at postoperative first hour compared to postoperative first and second week. In regard to the neuroprotective mechanism of HBOT on chronic constriction-induced neuropathic pain, it was revealed the microglial mitophagy involvement.[137] Results of our laboratory revealed that pre- and post- HBOT had neuroprotective properties following sciatic nerve degeneration through decreasing lipid peroxidation, increasing SOD and catalase activities, attenuating caspase-3 and cyclooxygenase-2 expression, and increasing S100β expression.[9] Recently, it was found that iNOS and neuronal NOS levels were significantly decreased with HBOT following chronic construction injury in rats.[138]

Neurodegenerative disease

Neurodegenerative diseases are associated with progressive nerve cell damage and neuronal loss that impair motor or cognitive function.[139] On the other hand, oxidative stress and inflammatory response play an important role in the pathogenesis of neurodegenerative diseases.[140-142] Dave et al.[143] found that HBOT in an experimental motor neuron disease significantly ameliorates mitochondrial dysfunction in the spinal cord and motor cortex, meanwhile greatly delays the disease onset. Chen et al.[144] documented that HBO prevents cognitive impairments in D-galactose induced aging model in mice due to reducing oxidative stress and blocking NF-κB pathway. Attenuation of neuroinflammatory processes is another possible mechanism underlying the effect of HBO on Alzheimer's disease through decreasing microgliosis, astrogliosis, TNF-α, and IL-1β and increasing scavenger receptor A, arginase1, IL-4, and IL-10 expression.[145] Research on Parkinson's disease has shown that 11-week exposure to mild HBO inhibits the decrease of dopaminergic neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease.[146]

Neurotoxic injury

For the first time, the effect of HBOT on the peripheral nerve disorder produced by administration of clioquinol, an antifungal and antiprotozoal drug which is neurotoxic in large doses, to rabbits was studied.[147] The damage of myelin and axons, which was apparent after administration of clioquinol, decreased in grade with HBO. In another study, the effect of HBO on streptozotocin-induced diabetic neuropathy was investigated.[148] The findings indicated that HBOT will partially reverse induced neuropathy in chronic diabetes. In contrast, Aydin et al.[149] did not document any beneficial effects of HBOT on nerve regeneration in early diabetes. In regard to

the protective effects of HBOT following severe carbon monoxide neurotoxicity, it was found that HBO is not effective in preventing neurologic sequelae in mice following severe carbon monoxide neurotoxicity.[150]

In Vitro Studies

A few numbers of *in vitro* studies regarding HBO neuroprotection and its basic molecular mechanisms began to accumulate (**Additional Table 6**). In spite of the results suggested that activation of N-methyl-D-aspartate receptors and nitric oxide production are involved in the neurotoxicity produced by prolonged HBO exposure (6 ATA for 30, 60, and 90 minutes) in primary rat cortical cultures,[151] Günther et al.[152] found that HBO had neither favorable nor unfavorable effects on the early morphological and functional restitution of ischemically damaged primary corticoencephalic cell cultures of rats under Hypoxia and glucose-deprivation (*in vitro* ischemia). β-Catenin, a protein involved in Wnt signaling and cell adhesion, plays an important role in the development of nervous system. In this regard, it was documented that HBOT intensifies the neural stem cell proliferation and neurogenesis by β-catenin-induced activated Neurogenin 1 gene and suppresses astrocytogenesis by β-catenin-induced down-regulated bone morphogenetic protein 4 gene.[153] An *in vitro* study revealed that HBO via the induction of heat shock protein 32 protected cultured spinal neurons from oxidative and oxygen glucose deprivation injury, while HBO through reactive oxygen species/p38 mitogen-activated protein kinase/Nrf2 pathway induced the expression of heat shock protein 32.[154] Another study documented that *in vitro* HBO after cell injury significantly accelerated neural stem cell proliferation and the VEGF/phospho-ERK pathway.[108] Examination of the effect of HBOT on the neuroprotective factor secretion, proliferation, and BDNF-release in fibroblasts and mesenchymal stem cells showed a significant increased proliferation of fibroblasts and altered the protein expression pattern in mesenchymal stem cells after 5 days of HBOT.[155] Also, it was found that HBOT promotes differentiation of neural stem cells into oligodendrocytes and neurons and reduces the number of astrocytes via regulation of Wnt3/β-catenin and BMP-2 signaling pathways.[156]

Clinical Trials

Despite the growing body of preclinical evidence confirming HBOT neuroprotection, few clinical studies have been performed and therefore limited information is currently available, which are summarized in **Additional Table 7**. In regard to the neuroprotective effects of HBOT against spinal cord injuries, results of a clinical trial study indicated that 8 weeks of HBOT can significantly improve nerve function and consequently promote daily life activities in the patients with incomplete SCI.[157] Another randomized clinical trial studied the effect of HBO in 79 patients with acute SCI.[158] Results of this study showed that plasma HMGB1 and NF-κB expression down-regulated with HBOT in patients on days 3, 7, 10 and 30, and meanwhile F-wave chronodispersion decreased with HBOT on days 10 and 30. Also, American Spinal Injury Association and Frankel Grade motor/pain scores on day 30 were significantly improved in the treatment group.

In regard to brain injuries, results of a prospective randomized trial showed that HBOT did not increase the number of patients in the favorable outcome categories following severely brain injury.[172] A double-blind pilot study suggested that HBO improves outcome after acute ischemic stroke.[159] Rockswold et al.[160] for the first time demonstrated a prolonged effect of HBOT on cerebral blood flow and cerebral metabolism in severely brain injured patients, while, the increased cerebral metabolic rate of oxygen and decreased ventricular cerebrospinal fluid lactate levels after therapy indicated that HBO may improve aerobic metabolism in these patients. Another study documented that HBOT could improve obviously brain electric activity mapping, Glasgow coma and outcome scales in patients with severe brain injury, and decrease the morbidity and mortality.[161] A study was designed to investigate the efficacy, safety, and feasibility of HBO (60 minutes with 100% oxygen to 2.5 ATA) in 33 ischemic stroke patients.[173] Compared to medication treatment alone, HBOT was more effective in controlling epilepsy, improving clinical symptoms, and relieving hydrocephalus in patients with post-brain injury neural status.[162] Treatment of chronic brain injury with HBOT significantly improved motor skills, daily living, communication, and socialization.[163] Results of a study on the metabolism and cerebral circulation of patients in the subacute phase of head injury showed that HBOT significantly decreased both pulsatility index and jugular venous lactate after HBOT.[164] To assess the beneficial effects of HBOT on the prognosis of patients with subacute TBI , the clinical status of the patients were assessed before and 3 to 6 months after HBOT with the Glasgow outcome and Glasgow coma scales.[11] The Glasgow coma and outcome scales of the HBOT group were improved 6 months after HBOT, with minimal adverse side effects. Meanwhile, another study revealed that HBOT (2.4 ATA) following mild TBI had no effect on post-concussive symptoms.[174] Evaluation of the whether elevated dissolved oxygen by HBOT could activate neuroplasticity after stroke, revealed that HBOT significantly improves neurological outcome even in the late chronic stage.[165] A prospective, randomized phase II clinical trial revealed that combined hyperbaric hyperoxia/normobaric hyperoxia therapies after severe TBI significantly improved oxidative metabolism markers, decreased intracranial hypertension, and improved markers of cerebral toxicity, while the mortality significantly reduced.[166] Boussi-Gross et al.[167] tested the effect of HBOT on brain function and quality of life in patients with mild TBI. Results of this study revealed that HBOT induces neuroplasticity and improves quality of life with prolonged post-concussion syndrome. However, another studies demonstrated that HBO at either 1.5, 2.0 or 2.4 ATA equivalent had no effect on postconcussion symptoms after TBI.[175-178] A study conducted to evaluate the safety and potential long-term neurological consequences of HBOT on intracerebral hemorrhage in diabetic patients.[168] Results of this study showed that early HBOT is safe and effective in terms of long-term neurological outcome in diabetic patients suffering from intracerebral hemorrhage. Recently, a retrospective analysis was performed on 62 consecutive patients prescribed for HBOT after stroke.[169] Results of this study showed that some patients ($n = 24$) significantly benefitted from HBOT by

improving their clinical neurological status and quality of life.

In regard to nerve injuries, a clinical trial conducted in patients with idiopathic trigeminal neuralgia supported that one course of HBOT (10 consecutive days) is an effective approach for treating neuropathic pain in human with produced a long-lasting, rapid-onset, and dose-dependent analgesic effects.8

In regard to neurodegenerative disease, a phase I safety study and a phase II efficacy study of HBOT in patients with ALS did not recommended HBOT in ALS patients.[179,180] Some studies conducted on hyperbaric-oxygen therapy of multiple sclerosis. Results of a randomized, placebo-controlled, double-blind study suggested a positive effect of HBO on advanced multiple sclerosis.[170] In contrast, short-term results of a placebo-controlled, double-blind trial did not support the claims made for HBO in the management of multiple sclerosis,[181] similar to some other studies.[182-187]

In regard to neurotoxic injury, results of a study suggested that repetition of HBOT prevents the delayed neuropsychiatric sequelae of carbon monoxide poisoning when applied individually with monitoring of quantitative electroencephalography as an indicator of efficacy.[171]

Conclusion

In recent years, HBOT has attracted considerable attention because of its biological properties. Neuroprotection benefits of HBOT, as a therapeutic option, confirmed with a lot of preclinical *in vivo* and *in vitro* studies. These beneficial effects have been mainly attributed to anti-oxidative, anti-inflammatory, and anti-apoptotic properties, in addition to improvement of oxygen supply and neural metabolism and stimulating autophagy. The evidence presented in this review indicates the potential of HBOT in treatment and prevention of a variety of injuries to the nervous system. Meanwhile, because limited data is available to demonstrate the neuroprotective effects of HBOT in humans, newly designed clinical trials are needed on HBOT's neuroprotection and its possible mechanisms as well as the course and dose of HBOT.

Author contributions
FA and ARK designed and wrote the manuscript. Both authors read and approved the final manuscript.
Conflicts of interest
The authors have no conflicts of interests to declare.
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Additional files:
Additional Table 1: Summary of studies regarding the effects of HBOT against spinal cord injury.
Additional Table 2: Summary of studies regarding the effects of HBOT against brain injury.
Additional Table 3: Summary of studies of the effects of HBOT against nerve injury.
Additional Table 4: Summary of studies of the effects of HBOT against neurodegenerative diseases.
Additional Table 5: Summary of studies of the effects of HBOT against neurotoxic injury.
Additional Table 6: Summary of in vitro studies on neuroprotective effects of HBOT.
Additional Table 7: Summary of clinical trials on neuroprotective effects of HBOT.

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