Hyperbaric oxygen treatment: functional and neurological recovery, following spinal cord injury

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ABSTRACT

Spinal Cord Injury (SCI) is an urgent condition with a high rate of clinical disability. Therefore, it is mandatory for clinical research to find effective therapies to recover from SCI and improve mobility and sensation. The purpose of this study is to review the use of hyperbaric oxygen in the functional and neurological rehabilitation of SCI patients. This is a narrative literature review. The following keywords were searched in the PUBMED literature: "hyperbaric oxygen" AND "spinal cord injury". Inclusion criteria were clinical trials and animal studies investigating the use of hyperbaric oxygen in spinal cord injury recovery. Non-English language studies, systematic reviews, case reports, in vitro studies and research protocols were excluded from the study. Search results showed 100 posts. After checking titles and abstracts, 28 articles were rejected. Of the 72 publications evaluated, 10 were rejected for various reasons, leaving 62 studies (51 animal studies and 11 human studies) for the present review. Hyperbaric oxygen treatment has been found to have neuroprotective properties when administered after SCI. Animal studies have shown promising results and revealed various mechanisms contributing to these neuroprotective effects, including reduction of neuronal inflammation and apoptosis, reduction of oxidative stress, reduction of spinal cord edema and improvement of angiogenesis and autophagy. However, the number of clinical studies is rather small, with small sample sizes, showing various results. Regarding the use of hyperbaric oxygen treatment after SCI, the optimal timing, duration, frequency and pressure of hyperbaric oxygen treatment after SCI has not been clarified. Further high quality human studies are needed to fully elucidate the role of hyperbaric oxygen therapy in SCI management.

KEYWORDS: hyperbaric oxygen, spinal cord injury

Introduction

Spinal cord injury (SCI) refers to the complete or partial loss of spinal cord function often leading to serious consequences, ranging from partial motor and sensory less, incontinence, tetraplegia and even brain death. Symptoms of SCI depend on the extent of the injury or non-traumatic cause, and may include loss of sensation or motor control of the lower limbs, trunk and upper limbs, as well as loss of control of body functions such as breathing, heart rate, blood pressure, body temperature, bladder and bowel control, and sexual function (1, 2).

SCI is a relatively rare but costly disease that changes patients' lives, with the risk of mortality varying great-

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ly depending on the financial status of the country and largely depending on the availability of qualitative clinical care and rehabilitation services. The number of SCI patients today is unclear, but international data on the incidence indicate that each year more than 250.000 people suffer from SCI. The majority of these cases involve traumatic SCI, with the main causes being traffic accidents, falls and violence. Recent data show that SCI is associated with an increased risk of death. The cost of SCI varies greatly and many of these costs are covered by SCI patients (3).

Hyperbaric oxygen therapy is a safe and non-invasive treatment that involves placing patients in a pressure chamber and inhaling oxygen at higher than atmospheric pressure to increase dissolved oxygen in the blood to relieve symptoms and treat disease with fewer side effects. The benefits of hyperbaric oxygen therapy are plentiful including improvement of blood circulation, promotion of healing, suppression of inflammation, regeneration of blood vessels, nerves and bones. Moreover, it induces the release of stem cells from the bone marrow and their activation for tissue repair (4).

Taking into consideration that ischemia is one of the most important mechanisms responsible for secondary SCI injury, a treatment method that increases oxygen tension of the injured spinal cord should theoretically help patients' recovery (5). When administered at an increased pressure, oxygen can increase the concentration of dissolved oxygen, creating a larger pressure gradient that can drive oxygen into ischemic tissue (6).

Cells surviving the primary SCI are sensitive to secondary damage, particularly through apoptosis (7). Hyperbaric oxygen therapy mainly affects secondary SCI and can prevent further SCI caused by spinal cord ischemia-reperfusion injury. Furthermore, it inhibits cell apoptosis and autophagy, reduces oxidative stress, diminishes inflammation, promotes angiogenesis, reduces spinal cord edema and effectively promotes neuronal regeneration (8,9). Recently, hyperbaric oxygen therapy for SCI has been increasingly studied having shown promising neuroprotective results in several experimental studies; however a limited number of clinical reports have shown mixed findings.

SCI is a condition with a high rate of clinical disability. Therefore, it is urgent for clinical research to find effective ways to recover from SCI and improve mobility and sensation. The purpose of this study is to review the use of hyperbaric oxygen in the functional and neurological rehabilitation of SCI patients.

A literature review was performed in the PUBMED literature with the keywords: "hyperbaric oxygen" AND "spinal cord injury". Inclusion criteria were clinical trials and animal studies investigating the use of hyperbaric oxygen in spinal cord injury recovery. Non-English language studies, systematic reviews, case reports, in vitro studies and research protocols were excluded from the study (Figure 1).

Discussion

Search results showed 100 posts. After checking titles and abstracts, 28 articles were rejected. Of the 72 remained publications, 10 were rejected for various reasons (see flowchart), leaving 62 studies for the present review and including 51 animal studies (5, 10-63), 4 prospective randomized studies (64-67), 3 prospective case series (68-70) and 4 retrospective studies (71-74).

Animal studies

Impact of hyperbaric oxygen treatment on cell apoptosis

Plenty of studies have used the TUNEL staining to show that hyperbaric oxygen treatment significantly diminishes cellular apoptosis in injured spinal cord tissue, with a plethora of proposed mechanisms (5,33,35,37,44,47,57). Lu suggested that hyperbaric oxygen preconditioning may decrease the number of apoptotic cells and enhance the nerve functional recovery in rats after SCI (36,37).

High amounts of nitric oxide (NO) are associated with inflammation, while smaller concentrations have neuroprotective effects (75). iNOS, the enzyme that is responsible for NO production, has been found to induce cell apoptosis by increasing NO after SCI. In 2004, an experimental study by Yu et al observed that hyperbaric oxygen treatment attenuates apoptosis after traumatic SCI through the downregulation of the hypoxia-induced expression of the iNOS gene, implicating that NO regulates apoptosis (57). In 2010, in a rat SCI model, IL-1β and TNF-α were significantly decreased in the hyperbaric oxygen treatment group, a finding accompanied by reduced apoptosis by TUNEL staining (47). In 2013, Huang et al, showed that, in 36

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SCI rats, hyperbaric oxygen treatment affects the iNOS mRNA-iNOS-NO signaling pathway, by decreasing iNOS mRNA and protein expression and NO serum levels (22).

CHOP is a transcription factor that plays a significant role in endoplasmic reticulum stress-induced apoptosis (76). Caspases comprise a family of intracellular enzymes that mediate cellular apoptosis (77). An experimental study by Liu et al found that the upregulation of CHOP, caspase-12, and caspase-3 was mitigated in the SCI rats that received daily hyperbaric oxygen treatment initiated 6 hours after SCI, suggesting that hyperbaric oxygen therapy reduces SCI-induced neuronal apoptosis by downregulating the ER-stress-induced apoptotic pathway (33). Pan et al concluded that hyperbaric oxygen preconditioning protects neuron cells by reducing cell apoptosis and calcium overload, through the inhibition of expression of caspase-3, -7, -8 and -12. Moreover, it reduces neural apoptosis by inhibiting the endoplasmatic reticulum pathway; thus it may reduce the loss of motor function in SCI rats (41).

In 2014, Long et al found that mRNA and protein expression of the pro-apoptotic protein adaptor molecule ASC increased after SCI but significantly decreased when daily hyperbaric oxygen treatment was initiated immediately after SCI (35). An animal study by Chen et al showed that hyperbaric oxygen therapy may inactivate mTOR signaling pathway, leading to suppression of apoptosis and improving motor disability in SCI rats (11). Hou et al observed a protective effect on SCI through reduction of neural cells apoptosis and decreased expression of MMP-2 and MMP-9 in rats with SCI (19). Recently, Ying et al found that hyperbaric oxygen treatment diminished dendritic/synaptic degeneration and lessened apoptosis, increasing BDNF and TrkB expression and improving neurological recovery in SCI rats (56). The combination of hyperbaric oxygen therapy and erythropoietin administration enhanced the recovery of locomotor function in the hind limbs of SCI rats by attenuating neuronal apoptosis (63).

Impact of hyperbaric oxygen treatment on oxidative stress

ROS production occurs at the early stages after SCI and plays an important role in secondary injury. Nerve tissue is sensitive to alterations of the oxidative stress because of its high lipid concentration. Several studies have shown the property of hyperbaric oxygen therapy to reduce oxidative stress, but the precise mechanism by which hyperbaric oxygen therapy influences lipid peroxidation has not yet been clarified (78).

Many animal studies have shown that hyperbaric oxygen treatment leads to upregulation of antioxidant enzyme levels, such as SOD, catalase, and GPx, after SCI (13,21). Two animal studies concluded that hyperbaric oxygen treatment increased ROS and NO levels and induced heat shock protein (HSP) 32 expression through a ROS/p38 MAPK/Nrf2 pathway (20,60). Sun et al found that hyperbaric oxygen treatment in SCI rats reduced SOD and MDA levels after SCI, resulting in better clinical scores and less cystic degeneration of spinal cord (46).

Malondialdehyde (MDA) and TBARS are markers of lipid peroxidation (79). The experimental study by Topuz et al evaluated a 90-minute hyperbaric oxygen regime immediately after SCI in 40 rats. Hyperbaric oxygen treatment increased GPx, SOD and catalase levels, while significantly attenuating MDA levels in comparison to the control group. Hyperbaric oxygen therapy was found to improve neurological outcomes through reduction of oxidative stress (49). In 2007, a comparative animal study by Kahraman et al found that hyperbaric oxygen therapy and not methylprednisolone, led to a significant decrease of TBARS levels and an increase of SOD activity 5 days after SCI, further indicating the ability of hyperbaric oxygen therapy to reduce oxidative stress and thus alleviate secondary SCI (23).

The combination of hyperbaric oxygen treatment with the administration of chondroitinase ABC was found to improve neuromotor function in a rat model of SCI, compared with the hyperbaric oxygen treatment or chondroitinase ABC treatment alone. Hyperbaric oxygen treatment with or without chondroitinase ABC significantly increased SOD and decreased MDA levels, as well as GSK3β expression. The combination of hyperbaric oxygen treatment with the administration of chondroitinase ABC was found to significantly inhibit SCI-induced AQP-4 expression (32).

In animals with mid-cervical SCI, hyperbaric oxygen treatment may preserve diaphragm function and respiratory health, through an increase in antioxidant

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capacity (43). The combination of hyperbaric oxygen treatment with N-acetylcysteine administration was found to have synergistic neuroprotective effects in SCI rats, along with upregulation of IL-10 expression and downregulation of TNF-α, IL-1β and caspase-3 (58). Hyperbaric oxygen therapy combined with the administration of the nitroxide antioxidant tempol had no neuroprotective effect in rats with SCI (18).

Impact of hyperbaric oxygen treatment on inflammation

The effect of hyperbaric oxygen treatment on the inflammatory processes after SCI has been extensively investigated (5, 11, 16, 24, 25, 47, 48, 52, 53, 59). In 2010, Tai et al observed that a single hyperbaric oxygen treatment immediately after SCI, resulted in increased levels of IL-10 and decreased levels of IL-1β, TNF-α and myeloperoxidase, a marker of neutrophil infiltration, in SCI rats (47). MCP-1 is a chemokine with a role in the recruitment of monocytes and lymphocytes to inflammation sites. In 2016, the upregulation of MCP-1 after SCI was significantly decreased by hyperbaric oxygen treatment and was associated with improvement of neurological scores in a rat SCI model (50). Liang et al observed that hyperbaric oxygen therapy resulted in decreased expression of NALP3, ASC, caspase-1, and IL-1β in 120 SCI rats (25). Hyperbaric oxygen treatment has been associated with increased IL-4 and IL-13 levels along with decreased TNF-α and IFN-γ in rats with compressive SCI. This modification of the inflammatory environment led to alterations in macrophage phenotype, which may further enhance the axonal extension and functional recovery (16).

MMP-2 and MMP-9 contribute to secondary SCI, by triggering the production of pro-inflammatory cytokines (80). In 2013, a neuroprotective role of hyperbaric oxygen treatment post-SCI was found, along with significantly decreased MMP-2, MMP-9 and IL-6 levels (53). HMGB1 contributes to inflammatory damage following SCI by stimulating TLRs, RAGE and NF-κB signaling pathways, which in turn activate other cytokines, such as IL-1β and TNF-α (81,82). Hyperbaric oxygen has been found to downregulate HMGB1 and its subsequent signaling pathways, including NF-κB, TLR2, TLR4, RAGE, IL-1β and TNF-α (24,48,53). Hyperbaric oxygen treatment may enhance the recovery of neurologic function in SCI rats through the activation of the SDF-1/CXCR4 axis and the promotion of BDNF expression (38).

According to an experimental study by Zhou et al, hyperbaric oxygen therapy decreased the inflammatory reaction and glial scar formation in SCI rats through the inhibition of inflammatory cytokines iNOS and COX-2 and glial scar-related molecules GFAP and NG2 (61). In 2014, Liu et al observed that daily hyperbaric oxygen treatment after SCI decreased CX43 expression, thereby reducing inflammation by blocking the spread of inflammatory cytokines from injured neurons to healthy cells (34). Combination of hyperbaric oxygen treatment and bone marrow stem cells transplantation has a synergistic effect over the reduction of inflammatory cytokines levels (TNF-α, IL-1β, IL-6, IFN-α), promoting functional recovery after SCI in rats (15). The combination of hyperbaric oxygen therapy with Schwann cell transplantation is more beneficial than either treatment alone in the recovery of spinal cord in rats after SCI (42). In a recent rat study, Ahmadi et al showed that combined therapy with methylprednisolone and hyperbaric oxygen treatment has synergistic effects on SCI treatment (10).

Impact of hyperbaric oxygen treatment on angiogenesis

VEGF is important for angiogenesis in the central nervous system as it stimulates endothelial cell proliferation and migration and promotes neuronal proliferation (83). After SCI, VEGF is increased in order to augment vascular density and restore blood supply to the spinal cord. An animal study by Tai et al reported that a single hyperbaric oxygen treatment started immediately after SCI resulted in increased VEGF (+) cells at 4–7 days after SCI (47). Three other studies involving daily hyperbaric oxygen treatments after SCI have also showed a significant increase in VEGF levels in comparison to control groups (34,53,62). Therefore, the improvement of neurological recovery seen with hyperbaric oxygen treatment of SCI may be partially caused by the increased expression of VEGF (84).

Impact of hyperbaric oxygen treatment on spinal cord edema

Hyperbaric oxygen therapy significantly reduces spinal cord edema after SCI (5,53). MMP-2 and MMP-9 degrade type IV collagen causing increased permeability of the blood-spinal cord barrier and leading to

spinal cord edema (85). In 2013, twice daily hyperbaric oxygen treatment in a rat SCI model was associated with a significant reduction in MMP-2 and MMP-9 levels after SCI. A significant reduction in spinal cord water content was also noticed (53). Higgins et al found a neuroprotective effect of hyperbaric oxygen treatment in cats with SCI. These effects were attributed to the preservation of intact nerve fibers of the spinal cord, the reversal of local hypoxia and the reduction of spinal cord edema (17). In a rat animal model, based on MRI studies, hyperbaric oxygen treatment appeared to stop the spread of hemorrhage and resolve spinal cord edema after SCI (40).

Aquaporins are water channels in cellular membranes. In 2014, SCI rats treated with hyperbaric oxygen initiated at 4 hours following SCI were observed to have a significant reduction of AQP4 and AQP9 expression, leading to reduction of water entrance into the spinal cord and decrease of spinal cord edema (5).

Impact of hyperbaric oxygen treatment on autophagy

Autophagy is a process of intracellular degradation important for the maintainance of cellular homeostasis (86). Beclin-1 and LC3-II are direct mediators of autophagy (87). The experimental study by Sun et al indicated that daily hyperbaric oxygen treatment upregulates autophagy after SCI, through increased levels of beclin-1 and LC3-II, in order to promote repair and protection (45).

Timing of hyperbaric oxygen treatment

A comparative animal study by Cristante et al showed that hyperbaric oxygen treatment improves the functional recovery of SCIs in rats, if it is administered immediately after SCI or within 24 hours (12). Falavigna et al reported that, in SCI rats, the sooner hyperbaric oxygen therapy is initiated after SCI and the larger the number of sessions, the greater and earlier is the motor recovery and smaller is the tissue injury (14). Ultra-early hyperbaric oxygen treatment (within 3 hours from injury) enhances the production of femoral CGPR in the sensory neurons in posterior horn of spinal cord (27). Hyperbaric oxygen treatment given 30 minutes after SCI had protective effects against ischemic spinal cord damage and attenuated selective motor neuron death in rabbits. Delayed hyperbaric oxygen therapy did not alter the prognosis (39). An experimental study by Yaman et al demonstrated that immediate hyperbaric oxygen treatment after SCI significantly improved clinical recovery in SCI rats. The sooner the hyperbaric oxygen treatment was initiated, the greater was the decrease in nitrite levels (51). Two old studies by Yeo et al, suggested that hyperbaric oxygen therapy initiated within two hours post-SCI resulted in improved motor recovery in SCI sheep along with less central cord cystic necrosis and degeneration in the surrounding white matter (54, 55). Hyperbaric oxygen therapy for 4 weeks has been associated with better clinical scores in comparison to 2 weeks of treatment in rats with SCI (26).

Human studies

While the beneficial properties of hyperbaric oxygen therapy in the treatment of SCI have been depicted in many animal studies, the number of the clinical studies is rather small. In 1978, the study by Yeo et al, involving complete and partial spinal cord lesions showed that hyperbaric oxygen treatment administered within 14 hours from SCI resulted in varying degrees of neurological improvement (70). A small study, in 1980, including 5 patients with cervical and thoracic SCI, depicted promising results in terms of clinical improvement after hyperbaric oxygen treatment (74). The study by Gamache et al in 1981 did not observe a significant change in neurological recovery in patients treated with hyperbaric oxygen (68). In 1989, a retrospective study by Lee et al did not find any significant correlation between hyperbaric oxygen treatment and cure rate in SCI patients (72).

A retrospective comparative study published in 2000, involved 34 patients with cervical SCI. The patients that received 1,5 hours of hyperbaric oxygen treatment once daily for 10 days were observed to have significantly higher clinical improvement rates versus the control group (71). Another recent retrospective comparative study included 40 acute SCI patients. Those patients that received hyperbaric oxygen treatment depicted significant motor and neurological improvement at 15 and 30 days after treatment (73). Zhang et al published a retrospective study, in 2021, including 78 patients with incomplete SCI. After laminectomy and posterior fixation, 40 patients received hyperbaric oxy-

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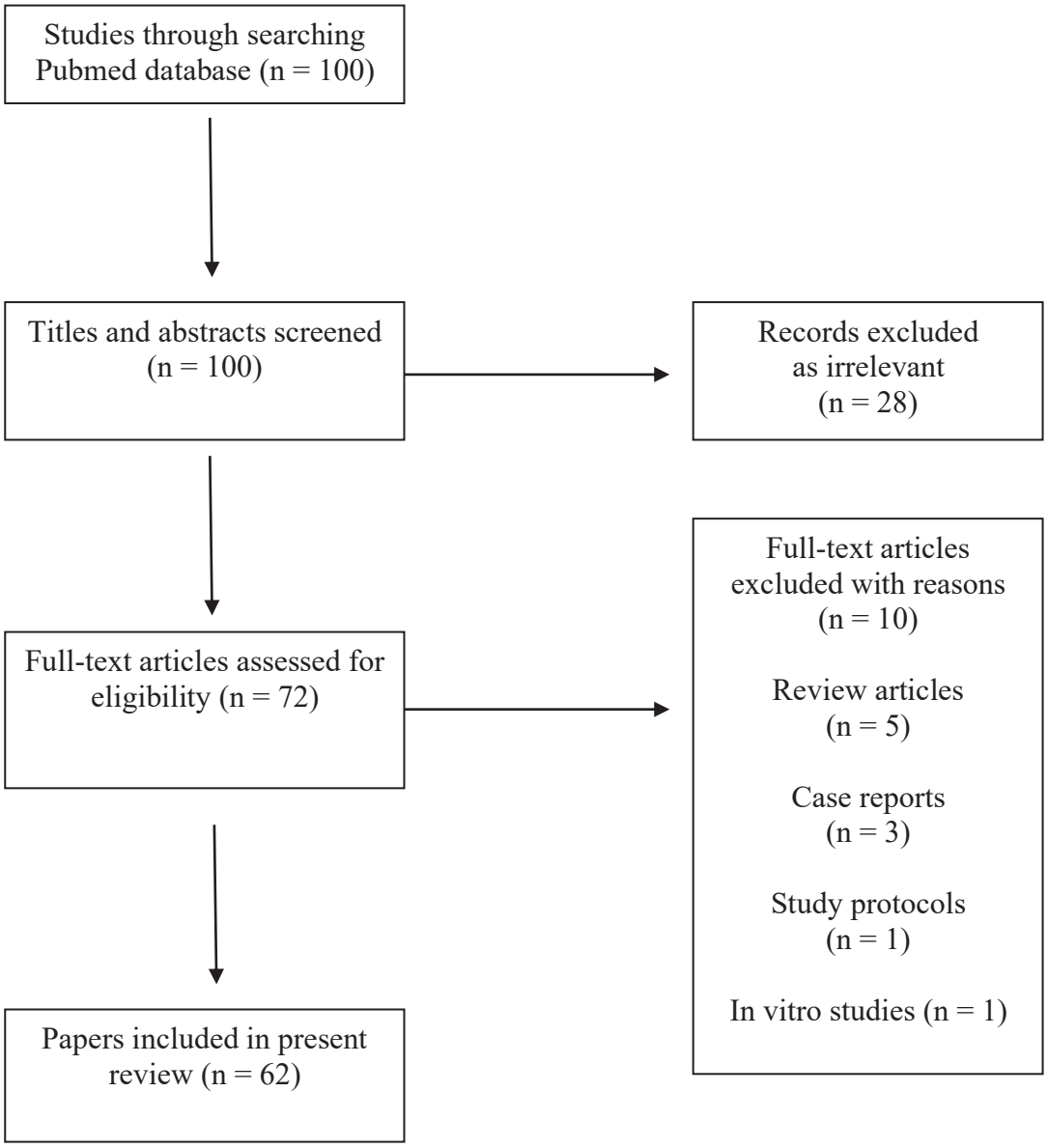
Figure 1



gen treatment while 38 patients received standard care. The study concluded that in all time points, hyperbaric oxygen treatment was associated with better recovery of sensory and motor function. Hyperbaric oxygen treatment was regarded as a safe and effective method for the management of incomplete cervical SCI and the healing effect was corresponding with the duration of therapy. The treatment had a maximum effect in recovery within the first 3 months after surgery (67).

A randomized controlled trial in 2017 compared an 8-week hyperbaric oxygen regime with conventional rehabilitation among 60 SCI patients. Authors found that hyperbaric oxygen treatment significantly improved neurological function and daily activities in SCI patients, but did not have a significant effect on depression and anxiety (64). A cohort study consisting 22 SCI patients found that there was a significant correlation between the hyperbaric oxygen treatment effect and the

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recovery rate of the ASIA motor score (69). A recent randomized controlled trial compared the clinical efficacy of the combination of hyperbaric oxygen treatment with mannitol and riluzole in 80 patients with acute SCI after thoracolumbar fractures treated with posterior laminectomy and fixation. In comparison to the control group, the experimental group showed significant improvement in motor and sensory scores, along with significant decrease of IL-6 and BDNF levels (65). Sun et al, in a recent randomized controlled trial, compared the effect of hyperbaric oxygen treatment, in 79 patients with acute SCI. Authors found that hyperbaric oxygen treatment affected the inflammatory reaction in secondary SCI by reducing serum HMGB1/NF-κB levels thereby enhancing motor and pain scores (66).

Conclusions

Hyperbaric oxygen treatment has been found to have neuroprotective properties when administered after SCI. Animal studies have shown promising results and revealed various mechanisms contributing to these neuroprotective effects, including reduction of neuronal inflammation and apoptosis, reduction of oxidative stress, reduction of spinal cord edema and improvement of angiogenesis and autophagy. However, the number of clinical studies is rather small, with small sample sizes, showing various results. regarding the use of hyperbaric oxygen treatment after SCI. The optimal timing, duration, frequency, and pressure of hyperbaric oxygen treatment after SCI has not been clarified. Further high quality human studies are needed in order to fully elucidate the role of hyperbaric oxygen therapy in SCI management.

Abbreviations List

AQP: Aquaporin
ASC: apoptosis-associated speck-like protein
BDNF: brain-derived neurotrophic factor
CGPR: calcitonin gene-related peptide
CHOP: CCAAT-enhancer-binding protein homologous protein
COX-2: Cyclooxygenase 2
CXCR4: C-X-C Motif Chemokine Receptor 4
IL-1a: Interleukin-1a
IL-1β: Interleukin-1β
IL-4: Interleukin-4
IL-6: Interleukin-6
IL-13: Interleukin-13
iNOS: Inducible Nitric Oxide Synthase
GFAP: Glial fibrillary acidic protein
GPx: Glutathione peroxidase
GSK3β: Glycogen synthase kinase 3 beta
LC3-II: light chain 3 type II
HMGB1: high mobility group box 1
MCP-1: monocyte chemoattractant protein-1
MDA: Malondialdehyde
MMPs: Matrix metalloproteinases
MMP-2: Matrix Metalloproteinase – 2
MMP-9: Matrix Metalloproteinase – 9
mRNA: messenger RNA
MRI: Magnetic resonance imaging
mTOR: mammalian target of rapamycin
NALP3: NAcht Leucine-rich repeat Protein 3
NF-κB: Nuclear factor-κB
NG2: Neuron-glial antigen 2
NO: Nitric oxide
PDGF: Platelet-derived growth factor
PGE2: Prostaglandin E2
RAGE: Receptor for advanced glycation end products
ROS: Reactive oxygen species
SDF-1: stromal cell-derived factor 1
SOD: Superoxide dismutase
TBARS: thiobarbituric acid reactive substances
TGF-β: transforming growth factor – β
TNF-a: Tumor necrosis factor-a
TLR: Toll-like receptor
TrkB: tropomycin receptor kinase B
TUNEL: terminal deoxynucleotidyl transferase (TdT) dUTP nick-end labeling
VEGF: Vascular endothelial growth factor

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REFERENCES

1. Eli I, Lerner DP, Ghogawala Z. Acute Traumatic Spinal Cord Injury. Neurol Clin. 2021 May;39(2):471-88.
2. Chay W, Kirshblum S. Predicting Outcomes After Spinal Cord Injury. Phys Med Rehabil Clin N Am. 2020 Aug;31(3):331-43.
3. Galeiras Vázquez R, Ferreiro Velasco ME, Mourelo Fariña M, Montoto Marqués A, Salvador de la Barrera S. Update on traumatic acute spinal cord injury. Part 1. Med Intensiva. 2017 May;41(4):237-47.
4. Sekhon LH, Fehlings MG. Epidemiology, demographics, and pathophysiology of acute spinal cord injury. Spine (Phila Pa 1976). 2001 Dec 15;26(24 Suppl):S2-12.
5. Wang Y, Zhang S, Luo M, Li Y. Hyperbaric oxygen therapy improves local microenvironment after spinal cord injury. Neural Regen Res. 2014 Dec 15;9(24):2182-8.
6. Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. Plast Reconstr Surg. 2011 Jan;127 Suppl 1(Suppl 1):131S-41S.
7. Emery E, Aldana P, Bunge MB, Puckett W, Srinivasan A, Keane RW, et al. Apoptosis after traumatic human spinal cord injury. J Neurosurg. 1998 Dec;89(6):911-20.
8. Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J Neurosurg. 1991 Jul;75(1):15-26.
9. Patel NP, Huang JH. Hyperbaric oxygen therapy of spinal cord injury. Med Gas Res. 2017 Apr-Jun;7(2):133-43.
10. Ahmadi F, Zargari M, Nasiry D, Khalatbary AR. Synergistic neuroprotective effects of hyperbaric oxygen and methylprednisolone following contusive spinal cord injury in rat. J Spinal Cord Med. 2021 Apr 8:1-10.
11. Chen H, Xu G, Wu Y, Wang X, Wang F, Zhang Y. HBO-PC Promotes Locomotor Recovery by Reducing Apoptosis and Inflammation in SCI Rats: The Role of the mTOR Signaling Pathway. Cell Mol Neurobiol. 2021 Oct;41(7):1537-47.
12. Cristante AF, Damasceno ML, Barros Filho TE, de Oliveira RP, Marcon RM, da Rocha ID. Evaluation of the effects of hyperbaric oxygen therapy for spinal cord lesion in correlation with the moment of intervention. Spinal Cord. 2012 Jul;50(7):502-6.
13. Dayan K, Keser A, Konyalioglu S, Erturk M, Aydin F, Sengul G, et al. The effect of hyperbaric oxygen on neuroregeneration following acute thoracic spinal cord injury. Life Sci. 2012 Feb 27;90(9-10):360-4.
14. Falavigna A, Figueiró MP, Silva PGD, Conzatti LP, Rizkalla EB, Santos SCD, et al. Hyperbaric Oxygen Therapy After Acute Thoracic Spinal Cord Injury: Improvement of Locomotor Recovery in Rats. Spine (Phila Pa 1976). 2018 Apr 15;43(8):E442-E7.
15. Geng CK, Cao HH, Ying X, Yu HL. Effect of mesenchymal stem cells transplantation combining with hyperbaric oxygen therapy on rehabilitation of rat spinal cord injury. Asian Pac J Trop Med. 2015 Jun;8(6):468-73.
16. Geng CK, Cao HH, Ying X, Zhang HT, Yu HL. The effects of hyperbaric oxygen on macrophage polarization after rat spinal cord injury. Brain Res. 2015 May 5;1606:68-76.
17. Higgins AC, Pearlstein RD, Mullen JB, Nashold BS, Jr. Effects of hyperbaric oxygen therapy on long-tract neuronal conduction in the acute phase of spinal cord injury. J Neurosurg. 1981 Oct;55(4):501-10.
18. Hillard VH, Peng H, Das K, Murali R, Moorthy CR, Etlinger JD, et al. Inhibition of x-irradiation-enhanced locomotor recovery after spinal cord injury by hyperbaric oxygen or the antioxidant nitroxide tempol. J Neurosurg Spine. 2007 Apr;6(4):337-43.
19. Hou YN, Ding WY, Shen Y, Yang DL, Wang LF, Zhang P. Effect of hyperbaric oxygen on MMP9/2 expression and motor function in rats with spinal cord injury. Int J Clin Exp Med. 2015;8(9):14926-34.
20. Huang G, Diao J, Yi H, Xu L, Xu J, Xu W. Signaling pathways involved in HSP32 induction by hyperbaric oxygen in rat spinal neurons. Redox Biol. 2016 Dec;10:108-18.
21. Huang G, Xu J, Xu L, Wang S, Li R, Liu K, et al. Hyperbaric oxygen preconditioning induces tolerance against oxidative injury and oxygen-glucose deprivation by up-regulating heat shock protein 32 in rat spinal neurons. PLoS One. 2014;9(1):e85967.
22. Huang H, Xue L, Zhang X, Weng Q, Chen H, Gu J, et al. Hyperbaric oxygen therapy provides neuroprotection following spinal cord injury in a rat model. Int J Clin Exp Pathol. 2013;6(7):1337-42.
23. Kahraman S, Düz B, Kayali H, Korkmaz A, Oter S, Aydin A, et al. Effects of methylprednisolone and hyperbaric oxygen on oxidative status after experimental spinal cord injury: a comparative study in rats. Neurochem Res. 2007 Sep;32(9):1547-51.
24. Kang N, Hai Y, Yang J, Liang F, Gao CJ. Hyperbaric oxygen intervention reduces secondary spinal cord injury in rats

via regulation of HMGB1/TLR4/NF-κB signaling pathway. Int J Clin Exp Pathol. 2015;8(2):1141-53.

25. Liang F, Li C, Gao C, Li Z, Yang J, Liu X, et al. Effects of hyperbaric oxygen therapy on NACHT domain-leucine-rich-repeat- and pyrin domain-containing protein 3 inflammasome expression in rats following spinal cord injury. Mol Med Rep. 2015 Jun;11(6):4650-6.
26. Liu F, Yang L, Liu J, Zhao Y, Xiao Z, Zheng Y, et al. Evaluation of hyperbaric oxygen therapy for spinal cord injury in rats with different treatment course using diffusion tensor imaging. Spinal Cord. 2019 May;57(5):404-11.
27. Liu M, Chen H, Tong M, Zhou J, Wu X. Effects of Ultra-early Hyperbaric Oxygen Therapy on Femoral Calcitonin Gene-Related Peptide and Bone Metabolism of Rats With Complete Spinal Transection. Spine (Phila Pa 1976). 2018 Aug;43(16):E919-E26.
28. Liu M, Wu X, Tong M, Zhou J. Impacts of Ultra-early Hyperbaric Oxygen Therapy on Bone Mass of Rats With Complete Spinal Cord Transection. Spine (Phila Pa 1976). 2016 Jul 15;41(14):E837-E43.
29. Liu X, Li C, Liang F, Wang Y, Li Z, Yang J. Effects of hyperbaric oxygen on glucose-regulated protein 78 and c-Jun N-terminal kinase expression after spinal cord injury in rats. Int J Clin Exp Med. 2015;8(3):3309-17.
30. Liu X, Liang F, Song W, Diao X, Zhu W, Yang J. Effect of Nrf2 signaling pathway on the improvement of intestinal epithelial barrier dysfunction by hyperbaric oxygen treatment after spinal cord injury. Cell Stress Chaperones. 2021 Mar;26(2):433-41.
31. Liu X, Liang F, Zhang J, Li Z, Yang J, Kang N. Hyperbaric Oxygen Treatment Improves Intestinal Barrier Function After Spinal Cord Injury in Rats. Front Neurol. 2020;11:563281.
32. Liu X, Wang J, Li G, Lv H. Effect of combined chondroitinase ABC and hyperbaric oxygen therapy in a rat model of spinal cord injury. Mol Med Rep. 2018 Jul;18(1):25-30.
33. Liu X, Yang J, Li Z, Liang F, Wang Y, Su Q, et al. Hyperbaric Oxygen Treatment Protects Against Spinal Cord Injury by Inhibiting Endoplasmic Reticulum Stress in Rats. Spine (Phila Pa 1976). 2015 Dec;40(24):E1276-83.
34. Liu X, Zhou Y, Wang Z, Yang J, Gao C, Su Q. Effect of VEGF and CX43 on the promotion of neurological recovery by hyperbaric oxygen treatment in spinal cord-injured rats. Spine J. 2014 Jan;14(1):119-27.
35. Long Y, Liang F, Gao C, Li Z, Yang J. Hyperbaric oxygen therapy reduces apoptosis after spinal cord injury in rats. Int J Clin Exp Med. 2014;7(11):4073-81.
36. Lu PG, Feng H, Yuan SJ, Zhang RW, Li M, Hu R, et al. Effect of preconditioning with hyperbaric oxygen on neural cell apoptosis after spinal cord injury in rats. J Neurosurg Sci. 2013 Sep;57(3):253-8.
37. Lu PG, Hu SL, Hu R, Wu N, Chen Z, Meng H, et al. Functional recovery in rat spinal cord injury induced by hyperbaric oxygen preconditioning. Neurol Res. 2012 Dec;34(10):944-51.
38. Meng XL, Hai Y, Zhang XN, Wang YS, Liu XH, Ma LL, et al. Hyperbaric oxygen improves functional recovery of rats after spinal cord injury via activating stromal cell-derived factor-1/CXC chemokine receptor 4 axis and promoting brain-derived neurothrophic factor expression. Chin Med J (Engl). 2019 Mar 20;132(6):699-706.
39. Murakami N, Horinouchi T, Sakurai M, Ejima Y, Matsukawa S, Kato M, et al. Hyperbaric oxygen therapy given 30 minutes after spinal cord ischemia attenuates selective motor neuron death in rabbits. Crit Care Med. 2001 Apr;29(4):814-8.
40. Narayana PA, Kudrle WA, Liu SJ, Charnov JH, Butler BD, Harris JH, Jr. Magnetic resonance imaging of hyperbaric oxygen treated rats with spinal cord injury: preliminary studies. Magn Reson Imaging. 1991;9(3):423-8.
41. Pan JY, Cai RX, Chen Y, Li Y, Lin WW, Wu J, et al. Analysis the effect of hyperbaric oxygen preconditioning on neuronal apoptosis, Ca2+ concentration and caspases expression after spinal cord injury in rats. Eur Rev Med Pharmacol Sci. 2018 Jun;22(11):3467-73.
42. Peng CG, Zhang SQ, Wu MF, Lv Y, Wu DK, Yang Q, et al. Hyperbaric oxygen therapy combined with Schwann cell transplantation promotes spinal cord injury recovery. Neural Regen Res. 2015 Sep;10(9):1477-82.
43. Smuder AJ, Turner SM, Schuster CM, Morton AB, Hinkley JM, Fuller DD. Hyperbaric Oxygen Treatment Following Mid-Cervical Spinal Cord Injury Preserves Diaphragm Muscle Function. Int J Mol Sci. 2020 Sep 30;21(19).
44. Sun W, Tan J, Li Z, Lu S, Li M, Kong C, et al. Evaluation of Hyperbaric Oxygen Treatment in Acute Traumatic Spinal Cord Injury in Rats Using Diffusion Tensor Imaging. Aging Dis. 2018 Jun;9(3):391-400.

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45. Sun Y, Liu D, Su P, Lin F, Tang Q. Changes in autophagy in rats after spinal cord injury and the effect of hyperbaric oxygen on autophagy. Neurosci Lett. 2016 Apr 8;618:139-45.
46. Sun Y, Liu D, Wang Q, Su P, Tang Q. Hyperbaric oxygen treatment of spinal cord injury in rat model. BMC Neurol. 2017 Jul 3;17(1):128.
47. Tai PA, Chang CK, Niu KC, Lin MT, Chiu WT, Lin CM. Attenuating experimental spinal cord injury by hyperbaric oxygen: stimulating production of vasculoendothelial and glial cell line-derived neurotrophic growth factors and interleukin-10. J Neurotrauma. 2010 Jun;27(6):1121-7.
48. Tan J, Zhang F, Liang F, Wang Y, Li Z, Yang J, et al. Protective effects of hyperbaric oxygen treatment against spinal cord injury in rats via toll-like receptor 2/nuclear factor-κB signaling. Int J Clin Exp Pathol. 2014;7(5):1911-9.
49. Topuz K, Colak A, Cemil B, Kutlay M, Demircan MN, Simsek H, et al. Combined hyperbaric oxygen and hypothermia treatment on oxidative stress parameters after spinal cord injury: an experimental study. Arch Med Res. 2010 Oct;41(7):506-12.
50. Wang Y, Li C, Gao C, Li Z, Yang J, Liu X, et al. Effects of hyperbaric oxygen therapy on RAGE and MCP-1 expression in rats with spinal cord injury. Mol Med Rep. 2016 Dec;14(6):5619-25.
51. Yaman O, Yaman B, Aydın F, Var A, Temiz C. Hyperbaric oxygen treatment in the experimental spinal cord injury model. Spine J. 2014 Sep 1;14(9):2184-94.
52. Yang J, Liu X, Zhou Y, Wang G, Gao C, Su Q. Hyperbaric oxygen alleviates experimental (spinal cord) injury by downregulating HMGB1/NF-κB expression. Spine (Phila Pa 1976). 2013 Dec 15;38(26):E1641-8.
53. Yang J, Wang G, Gao C, Shao G, Kang N. Effects of hyperbaric oxygen on MMP-2 and MMP-9 expression and spinal cord edema after spinal cord injury. Life Sci. 2013 Dec 18;93(25-26):1033-8.
54. Yeo JD, McKenzie B, Hindwood B, Kidman A. Treatment of paraplegic sheep with hyperbaric oxygen. Med J Aust. 1976 Apr 10;1(15):538-40.
55. Yeo JD, Stabback S, McKenzie B. A study of the effects of hyperbaric oxygen on the experimental spinal cord injury. Med J Aust. 1977 Jul 30;2(5):145-7.
56. Ying X, Tu W, Li S, Wu Q, Chen X, Zhou Y, et al. Hyperbaric oxygen therapy reduces apoptosis and dendritic/synaptic degeneration via the BDNF/TrkB signaling pathways in SCI rats. Life Sci. 2019 Jul 15;229:187-99.
57. Yu Y, Matsuyama Y, Yanase M, Ito S, Adachi K, Satake K, et al. Effects of hyperbaric oxygen on GDNF expression and apoptosis in spinal cord injury. Neuroreport. 2004 Oct 25;15(15):2369-73.
58. Zhao X, Wang Z. Synergistic neuroprotective effects of hyperbaric oxygen and N-acetylcysteine against traumatic spinal cord injury in rat. J Chem Neuroanat. 2021 Dec;118:102037.
59. Zhao Y, Zheng Y, Xiao Z, Liu J, Yang L, Liu F, et al. Diffusion tensor imaging in the evaluation of the long-term efficacy of HBO2 therapy in rats after traumatic spinal cord injury. Undersea Hyperb Med. 2020 Third-Quarter;47(3):435-43.
60. Zhou Q, Meng X, Huang G, Yi H, Zheng J, Zhang K, et al. MEK1/2 Inhibition Synergistically Enhances the Preventive Effects of Normobaric Oxygen on Spinal Cord Injury in Decompression Sickness Rats. Front Physiol. 2021;12:674430.
61. Zhou Y, Dong Q, Pan Z, Song Y, Su P, Niu Y, et al. Hyperbaric Oxygen Improves Functional Recovery of the Injured Spinal Cord by Inhibiting Inflammation and Glial Scar Formation. Am J Phys Med Rehabil. 2019 Oct;98(10):914-20.
62. Zhou Y, Liu XH, Qu SD, Yang J, Wang ZW, Gao CJ, et al. Hyperbaric oxygen intervention on expression of hypoxia-inducible factor-1α and vascular endothelial growth factor in spinal cord injury models in rats. Chin Med J (Engl). 2013 Oct;126(20):3897-903.
63. Zhou Y, Su P, Pan Z, Liu D, Niu Y, Zhu W, et al. Combination Therapy With Hyperbaric Oxygen and Erythropoietin Inhibits Neuronal Apoptosis and Improves Recovery in Rats With Spinal Cord Injury. Phys Ther. 2019 Dec 16;99(12):1679-89.
64. Feng JJ, Li YH. Effects of hyperbaric oxygen therapy on depression and anxiety in the patients with incomplete spinal cord injury (a STROBE-compliant article). Medicine (Baltimore). 2017 Jul;96(29):e7334.
65. Li HX, Cui J, Fan JS, Tong JZ. An observation of the clinical efficacy of combining Riluzole with mannitol and hyperbaric oxygen in treating acute spinal cord injury. Pak J Med Sci. 2021 Mar-Apr;37(2):320-4.
66. Sun L, Zhao L, Li P, Liu X, Liang F, Jiang Y, et al. Ef-

VOLUME 73 | ISSUE 4 | OCTOBER - DECEMBER 2022

fect of hyperbaric oxygen therapy on HMGB1/NF-κB expression and prognosis of acute spinal cord injury: A randomized clinical trial. Neurosci Lett. 2019 Jan 23;692:47-52.
67. Zhang Z, Li Q, Yang X, Li B, Zhou Y, Hu T, et al. Effects of hyperbaric oxygen therapy on postoperative recovery after incomplete cervical spinal cord injury. Spinal Cord. 2021 Jul 29.
68. Gamache FW, Jr., Myers RA, Ducker TB, Cowley RA. The clinical application of hyperbaric oxygen therapy in spinal cord injury: a preliminary report. Surg Neurol. 1981 Feb;15(2):85-7.
69. Ishihara H, Kanamori M, Kawaguchi Y, Osada R, Ohmori K, Matsui H. Prediction of neurologic outcome in patients with spinal cord injury by using hyperbaric oxygen therapy. J Orthop Sci. 2001;6(5):385-9.
70. Yeo JD, Lowry C, McKenzie B. Preliminary report on ten patients with spinal cord injuries treated with hyperbaric oxygen. Med J Aust. 1978 Dec 2;2(12):572-3.
71. Asamoto S, Sugiyama H, Doi H, Iida M, Nagao T, Matsumoto K. Hyperbaric oxygen (HBO) therapy for acute traumatic cervical spinal cord injury. Spinal Cord. 2000 Sep;38(9):538-40.
72. Lee HC, Niu KC, Chen SH, Chang LP, Lee AJ. Hyperbaric oxygen therapy in clinical application. A report of a 12-year experience. Zhonghua Yi Xue Za Zhi (Taipei). 1989 May;43(5):307-16.
73. Tan JW, Zhang F, Liu HJ, Li Z. Hyperbaric oxygen ameliorated the lesion scope and nerve function in acute spinal cord injury patients: A retrospective study. Clin Biochem. 2018 Mar;53:1-7.
74. De Jesus-Greenberg DA. Acute spinal cord injury and hyperbaric oxygen therapy: a new adjunct in management. J Neurosurg Nurs. 1980 Sep;12(3):155-60.
75. Anggård E. Nitric oxide: mediator, murderer, and medicine. Lancet. 1994 May 14;343(8907):1199-206.
76. Nishitoh H. CHOP is a multifunctional transcription factor in the ER stress response. J Biochem. 2012 Mar;151(3):217-9.
77. Hitomi J, Katayama T, Taniguchi M, Honda A, Imaizumi K, Tohyama M. Apoptosis induced by endoplasmic reticulum stress depends on activation of caspase-3 via caspase-12. Neurosci Lett. 2004 Mar 4;357(2):127-30.
78. Kwon BK, Tetzlaff W, Grauer JN, Beiner J, Vaccaro AR. Pathophysiology and pharmacologic treatment of acute spinal cord injury. Spine J. 2004 Jul-Aug;4(4):451-64.
79. Christie SD, Comeau B, Myers T, Sadi D, Purdy M, Mendez I. Duration of lipid peroxidation after acute spinal cord injury in rats and the effect of methylprednisolone. Neurosurg Focus. 2008;25(5):E5.
80. Jang JW, Lee JK, Kim SH. Activation of matrix metalloproteinases-9 after photothrombotic spinal cord injury model in rats. J Korean Neurosurg Soc. 2011 Oct;50(4):288-92.
81. Yang H, Wang H, Czura CJ, Tracey KJ. The cytokine activity of HMGB1. J Leukoc Biol. 2005 Jul;78(1):1-8.
82. Kwon BK, Stammers AM, Belanger LM, Bernardo A, Chan D, Bishop CM, et al. Cerebrospinal fluid inflammatory cytokines and biomarkers of injury severity in acute human spinal cord injury. J Neurotrauma. 2010 Apr;27(4):669-82.
83. Storkebaum E, Lambrechts D, Carmeliet P. VEGF: once regarded as a specific angiogenic factor, now implicated in neuroprotection. Bioessays. 2004 Sep;26(9):943-54.
84. Widenfalk J, Lipson A, Jubran M, Hofstetter C, Ebendal T, Cao Y, et al. Vascular endothelial growth factor improves functional outcome and decreases secondary degeneration in experimental spinal cord contusion injury. Neuroscience. 2003;120(4):951-60.
85. Agrawal SM, Lau L, Yong VW. MMPs in the central nervous system: where the good guys go bad. Semin Cell Dev Biol. 2008 Feb;19(1):42-51.
86. Mizushima N. Autophagy: process and function. Genes Dev. 2007 Nov 15;21(22):2861-73.
87. Edinger AL, Thompson CB. Defective autophagy leads to cancer. Cancer Cell. 2003 Dec;4(6):422-4.

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