The role of hyperbaric oxygen in idiopathic sudden sensorineural hearing loss

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Abstract

Idiopathic sudden sensorineural hearing loss is an unexplained sudden loss of sensorineural hearing, with no specific pathogenesis, and is difficult to treat. The most common therapeutic strategy for idiopathic sudden sensorineural hearing loss is the use of steroids combined with neurotrophic drugs, as other treatments have shown limited efficacy. However, in recent years, hyperbaric oxygen therapy has emerged as a promising treatment option. Studies have shown that hyperbaric oxygen therapy, in combination with conventional treatments, can effectively alleviate inner ear edema, improve blood circulation, and suppress inflammation. Therefore, hyperbaric oxygen therapy plays an important role in the treatment of idiopathic sudden sensorineural hearing loss. In this review, we aim to assess existing studies and summarize the clinical effects and mechanisms of hyperbaric oxygen therapy in idiopathic sudden sensorineural hearing loss, providing a basis for further research on the clinical treatment of this disorder.

Key words: hyperbaric oxygen therapy; HBOT; idiopathic sudden sensorineural hearing loss; ISSNHL; effect; mechanism; edema; microcirculation; inflammation

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Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is a frightening disorder defined as a sensorineural hearing loss of ≥ 30 dB over three or more frequencies with an onset of ≤ 3 days and no known causes.[1,2] This disorder typically occurs in people over the age of 40 years, with a morbidity rate of 5 to 20 per 100,000 cases per year.[3] The spontaneous recovery rate of ISSNHL ranges from 32% to 68%.[4] Its manifestation is sudden onset of hearing loss accompanied by tinnitus, vertigo, nausea, and vomiting.[5,6] There are also no specific adjuncts for its etiologic diagnosis. Some articles have shown that MRI can indicate minor hemorrhage, increased permeability of peripheral vessels to lymph, and disruption of the blood-labyrinth barrier, in which irreversible damage would lead to a poor prognosis and pre-existing endolymphatic hydrops may be a risk factor for its development.[7] There is no specific pathogenesis for ISSNHL, but several theories have identified possible causes, such as infection, vascular occlusion, immune-mediate, coagulation disorders and disruption of the labyrinthine membranes.[8] The lack of specific causes makes precise treatment of ISSNHL difficult. The most common therapeutic strategy for patients with ISSNHL is the use of steroids combined with neurotrophic drugs or vasodilators. In some cases, anticoagulant drugs may also be used. Steroid treatment is often administered either systemically or intratympanically. The common modalities are oral or intravenous, but the effect of steroid therapy is not greatly affected by either mode of administration, and the effect of steroids is the same independent of the route of administration.[9] Whether higher doses of steroids have higher benefits than standard doses is still debated, and patient outcomes in previous studies have been mixed. There is also no evidence that high-dose treatment is associated with greater risk.[10] And giving adequate steroid therapy as early as possible after the onset of ISSNHL is the main measure to effectively salvage hearing loss, and repetitive systemic steroid therapy may be a promising measure of salvage therapy, but its efficacy remains unclear.[11] The combination of systemic and intratympanic steroids may provide greater benefit than either systemic or intratympanic therapy alone. A previous study has shown that steroid therapy has good efficacy in ISSNHL, but its use is controversial.[9]

Hyperbaric oxygen therapy (HBOT) was first utilized as a treatment for ISSNHL in the late 1970s, but it has only recently been widely used in China. Studies have reported that HBOT can effectively alleviate symptoms and improve curative effects in patients with ISSNHL.[6,12] HBOT is also a kind of important treatment to save hearing loss for patients who have failed steroid therapy.[13] In addition, combining HBOT with traditional steroid therapy was found to be more effective than using steroids alone.[12] Although HBOT has been successfully used as a conventional adjuvant therapy in the treatment of ISSNHL, its exact mechanisms are still unknown. It has been postulated that it works by improving blood circulation, restoring inner ear oxygen tension, and suppressing inflammation, but there is no conclusive evidence for this.[14] This paper reviews the previous literature, summarizes and analyzes the use of hyperbaric oxygen (HBO) in healthcare in recent years and the possible mechanisms of its role in ISSNHL.

Search Strategy

PubMed database was searched up to June 2023. The following search terms were used: idiopathic sudden sensorineural hearing loss, hyperbaric oxygen, effect and mechanism.

Hyperbaric Oxygen

Oxygen is essential for human life as it participates in all physiological activities in the human body. Typically, humans inhale oxygen with a concentration between 19.5% and 23.5% at standard atmospheric pressure. However, HBO is a pressurized environment in which the entire body is placed at an absolute pressure of at least 1.4 atmospheres (usually 2–3 standard atmospheres) and the oxygen concentration is 100%.[15] HBOT aims to increase the level of dissolved oxygen in the tissues. Initially, HBO was primarily used to treat carbon monoxide poisoning and decompression sickness,[16] but in recent years, it has been widely used to treat various disease.[17-20] For examples: In the treatment of ischemic stroke, HBO may increase arterial oxygen partial pressure and oxygen supply by increasing dissolved oxygen in plasma, thereby promoting cellular metabolism and maintaining adenosine-triphosphate synthesis in injured tissues to reduce brain damage, and its role may also involve induction of antioxidant activity, hypoxia-inducible factor-1α, heat shock protein and autophagy, inhibition of apoptosis and inflammation.[21] In treatment of traumatic brain injury, HBO promotes recovery from neurocognitive impairment by inducing neuroplasticity, inducing cerebral angiogenesis and ameliorating cognition-related structural damage, and also reduces intracranial hematoma volume after traumatic brain injury by increasing oxygen concentration and promoting blood circulation. It could also modulate biomarkers associated with neuronal injury, astrocyte injury and neurotrophic effects to alleviate secondary damage from traumatic brain injury.[22] And in ISSNHL, HBO can decrease hematocrit, platelet aggregation, and plasma viscosity, while increasing the amount of oxygen dissolved in the interstitial fluid and cytoplasm to improve the microcirculation in the inner ear, as well as suppressing the inflammatory process.[23] Thus the applications of HBO in medicine seem to be associated with elevated blood oxygen levels, improved circulation, inflammation and others. However HBOT is not suitable for everyone. Studies have shown that patients with eustachian tube dysfunction, asthma, pneumothorax, and exolymphatic fistula should not use HBO, as it may aggravate their existing disease. Meanwhile, due to the high partial pressure of oxygen used in HBOT, it could possibly cause barotrauma and oxidative stress, though this is extremely unlikely.[24] It may also result in air pressure injury to the middle ear, epilepsy, pulmonary edema, progressive myopia, and other diseases. Therefore, adequate assessment of the patient's systemic status and past medical history is required prior to treatment, and the application of HBOT in diseases should be careful (**Table 1**).[12,20,23,25-36]

The Clinical Effect of Hyperbaric Oxygen Therapy in Idiopathic Sudden Sensorineural Hearing loss

ISSNHL is a challenging medical condition characterized by hearing loss, along with tinnitus, ear blockage, vertigo, nausea, and vomiting. The pathogenesis of the disease is not clear, so there has been no targeted treatment. For the last century, steroids have been the gold standard therapy for the initial treatment of ISSNHL. However, it was found that steroids could not cross the blood-labyrinthine barrier effectively and reach sufficient concentrations in the inner ear, making their curative effect difficult to maintain.[32] The development of HBOT seems to offer a new strategy. HBO was first used in the late 1970s to treat ISSNHL, and it was thought to increase the partial pressure of oxygen in the exolymphatic fluid and improve microcirculation in the inner ear.[3] But, the efficacy of single

Table 1: The latest clinical studies on the effects of HBOT in the treatment of ISSNHL

Study	Year	Research findings
Filipo et al.[26]	2012	The intratympanic steroid with HBO therapy was superior in ISSNHL.
Cvorovic et al.[27]	2013	HBO and IT steroid therapy could be successfully used as salvage therapies in patients with ISSNHL.
Psillas et al.[28]	2015	HBO treatment given to patients who fail drug therapy still improves ISSNHL.
Sevil et al.[29]	2016	Intravenous steroid administration and HBO therapy may be benefit for patients with ISSNHL.
Chin et al.[31]	2017	Adjunctive hyperbaric oxygen treatment was efficacious for patients with idiopathic sudden sensorineural hearing loss. The total average hearing gain was recorded to be 17.9 dB.
Hosokawa et al.[30]	2017	Hyperbaric oxygen therapy appears to confer a significant additional therapeutic benefit when used in combination with steroid therapy for idiopathic sudden sensorineural hearing loss
Chi et al.[23]	2018	HBOT plus existing conventional treatment was associated with a better outcome than conventional treatment alone.
Cho et al.[32]	2018	The addition of HBOT to steroid combination therapy does not improve the average PTA values in severe to ISSNHL.
Wang et al.[33]	2019	Combined HBOT can improve the hearing impairment of sudden hearing loss.
Bagli[20]	2020	HBO treatment applied within 14 days effectively improves ISSNHL.
Liu et al.[34]	2020	Hyperbaric oxygen treatment improves hearing level via attenuating TLR4/NF-κB mediated inflammation in sudden sensorineural hearing loss patients.
Ahn et al.[35]	2021	PO + IT + HBOT treatment initially accelerates recovery in patients with a hearing loss below 80 dB.
Tong et al.[12]	2021	HBO combined with pharmacological treatments leads to better hearing recovery than pharmacological treatments alone.
Chin et al.[36]	2022	The improvement of HBOT therapy on ISSHL was obvious after 1−5 sessions. And the earlier HBOT starts, the better the outcome will be.

Note: HBO: Hyperbaric oxygen; HBOT: hyperbaric oxygen therapy; ISSNHL: idiopathic sudden sensorineural hearing loss; IT: intratympanic; PO: oral steroids alone; TLR4/NF-κB: Toll-like receptor 4/nuclear factor kappa-B.

HBOT has not been as effective as expected. Following further research into medical gas, HBOT, alongside the application of steroids, was believed to significantly improve the efficacy of the treatment. And now it was identified as an effective first-line treatment for ISSNHL.[37] Although the pathophysiologic process is still unclear, in recent years, HBOT has been widely used in the treatment of ISSNHL, and its curative effects have been proven in many studies. In a study conducted by Choi et al.,[1] 82 patients with ISSNHL were included and evaluated. The patients were divided into two groups: 45 patients in the control group were treated with steroid therapy only, and 37 patients in the experimental group received steroid therapy and HBOT. The HBOT group underwent mono-place oxygen chamber treatment with 100% oxygen at 1.5 to 3 atmospheres. After 3 months of treatment, the hearing level of the HBOT group increased by 29.7 ± 27.9 dB, while that in the control group improved by 14.4 ± 12.5 dB.[1] Compared with the control group, the HBOT group showed greater relief of symptoms and improved prognostic outcomes. Therefore, HBOT could enhance the clinical effect of steroids in the treatment of ISSNHL.[38] However, effective treatment was observed only in conjunction with fundamental steroid therapy, and the efficacy of HBOT or steroid therapy as a single agent may be inferior.[3] Therefore, HBO is an important strategy for the treatment of ISSNHL, and better results may be obtained when combined with steroid therapy. At the same time, HBOT may be related to the general condition of the patients and individual differences and there may be a time window for its treatment, with an optimal efficacy period beyond which its efficacy may be greatly reduced. In addition, the benefits of patients may also depend on the frequency and severity of their hearing loss and the impact on their quality of life.

Generally, our ears can receive frequencies ranging from 20 Hz to 20,000 Hz. However, in day-to-day life, the most common frequencies we hear are between 500 Hz and 3000 Hz.[39] When patients with ISSNHL experience hearing loss for frequencies below 500 Hz or above 3000 Hz, they can continue with their daily lives, affected slightly or unaffected. However, when the frequency loss falls between 500 Hz and 3000 Hz, their lives can be affected significantly. They might experience insomnia, anxiety, etc. Although HBOT is effective in treating ISSNHL, the response to this therapy may differ based on the severity, degree, and frequencies affected by hearing loss. This is a critical factor to be considered during treatment. In a study by Topuz et al.,[14] five common frequencies of hearing loss were selected: 250, 500, 1000, 2000, and 4000 Hz, and hearing loss was classified into three levels: ≤ 60 dB, 61–80 dB and ≥ 81 dB. Patients with differing frequencies and degrees of hearing loss were treated with HBOT for 2 weeks in comparion with a control group. The results of this experiment showed that except for 2000 Hz, patients with hearing loss at other frequencies showed an obvious improvement in symptoms. Patients younger than 50 years of age had an average hearing gain of 39.1 ± 18.3 dB. Additionally, it was observed that patients who had an initial hearing level greater than 60 dB received a more pronounced hearing gain compared to patients whose initial hearing level was less than 60 dB.[9] This showed that HBOT, when used alongside standard treatment, can be highly effective in treating hearing loss, regardless of whether it is for low, medium or high frequency.[40] Moreover, the higher the initial hearing level, the better the prognosis. Several studies have explored the factors that can influence the efficacy of HBOT in treating ISSNHL. Factors such as earlier onset of HBOT, lower initial hearing threshold, and lower age have all been associated with favorable hearing recovery.[41] Audiogram types have also been shown to impact the prognosis.[42] The therapeutic window is another critical factor, as the cochlear hair cells are not regenerative, and missing the optimal therapeutic window can make recovery difficult. HBOT is most effective within 2 weeks after the onset of ISSNHL, and if treatment is delayed beyond 28 days, poorer outcomes are expected.[30,43,44] In summary, early application of HBOT as an adjunctive treatment, alongside steroid therapy within 2 weeks of the onset of the disease, can achieve significant clinical results. Especially in young patients and those with a low degree of hearing loss before treatment, early detection and treatment may results in maximum benefits.

Mechanisms of Hyperbaric Oxygen in Idiopathic Sudden Sensorineural Hearing Loss

Although HBOT has been widely used as a clinical treatment in recent years, its mechanisms remain unclear. Some researchers have speculated about the process, but there are few inductive research studies. To understand the mechanism, we should start by understanding its etiology. Cochlear hair cells, which are auditory receptors, produce an excitation in response to the mechanical wave motion of lymphatic fluid. When these cells are severely affected, ISSNHL can occur. At the same time, the cochlear labyrinth and its components are also susceptible to ischemia because the inner ear does not have sufficient collateral circulation pathways and consumes a lot of energy in metabolism.[45] Previous research proposed that infections, immunologic diseases, trauma, retrocochlear tumors, vascular deficiencies, abnormal cochlear stress response, toxins, ischemia-hypoxia, and inflammation might be the causes of ISSNHL.[46-48] Cochlear hair cells have a high oxygen consumption rate but poor endurance during hypoxia, and inflammation can give rise to endothelial dysfunction, leading to thrombogenesis that can affect blood supply to the inner ear.[34,49] Therefore, ischemia-hypoxia and inflammation are thought to be the primary causes of ISSNHL.[13] Hypoxia leads to ciliary fusion of cochlear hair cells, edema of synapses and dendrites, and continuous depolarization.[50] HBOT has been reported to improve ischemia and hypoxia of the inner ear by increasing the oxygenation of the inner ear and the partial oxygen pressure of the perilymphatic fluid.[51-53] During this process, oxygen diffuses through various capillary networks in the terminal cochlea to the perilymphatic fluid, providing oxygen to the peripheral nerve structure of the inner ear and stimulating cell repair.[7,53,54] Blood with a higher concentration of oxygen is also transported through the blood to the inner ear, thereby increasing microcirculation and hearing levels. HBOT could not only increase the amount of oxygen dissolved in the interstitial fluid and cytoplasm, but also reduce erythrocyte pressure, platelet aggregation and plasma viscosity.[12] In addition, HBOT can provide enough oxygen

to help maintain normal phosphorylation and alleviate illness by improving ischemic-hypoxic conditions. In ISSNHL, the decrease in blood flow and reduction of oxygen supply causes an inefficient phosphorylation process within the mitochondria, which leads to the production of reactive oxygen species as metabolic by-products. After these reactive oxygen species are produced in the cochlea, interleukin 6 and tumor necrosis factor-α are produced locally in response. These inflammatory cytokines can destroy the cochlear hair cells, while the c-Jun N-terminal kinase signaling pathway is activated by the reactive oxygen species, which could mediate programmed apoptosis of cochlear hair cells. Ultimately, these pathways mediate programmed apoptosis of the cochlear hair cells.[55] Therefore, HBOT can improve symptoms by inducing a state of hyperoxia to improve the hypoxic-ischemic condition of cochlear hair cells. This reduces the production of reactive oxygen species, halting the process that can lead to the damage and programmed apoptosis of cochlear hair cells, allowing them to recover.

HBOT has also been shown to alleviate ISSNHL by influencing the inflammation process. On the one hand, Lam et al.[56] suggested that HBOT could affect three inflammatory cell types (neutrophils, leukocytes, and macrophages) and may combat inflammation by reducing the expression of proinflammatory cytokines in monocytes/macrophages and by reducing neutrophil "2" integrin adhesion. They also postulated that HBOT could enhance the bactericidal activity of leukocytes and induce vasoconstriction to reduce inflammation and local swelling.[56] In contrast, inflammation in ISSNHL may be caused by Toll-like receptor 4, nuclear factor κB, and tumor necrosis factor-α, the levels of which are elevated in the peripheral blood of patients with ISSNHL. Cochlear damage promotes the release of endogenous ligands, which are collectively referred to as damage-associated molecular patterns. It is thought that these ligands can be recognized by Toll-like receptors. Therefore, HBOT may suppress inflammation by reducing the formation of endogenous damage-associated molecular patterns, thus restricting the activation of Toll-like receptor 4 and nuclear factor κB and the release of tumor necrosis factor-α. Additionally, HBOT may repress genetic transcription, reducing Toll-like-receptor 4 mRNA levels, and thereby reducing the activation of nuclear factor κB and release of tumor necrosis factor-α.[40] It has also been shown that serum levels of insulin-like growth factor 1 and heat shock protein 70 levels are elevated after HBOT, that insulin-like growth factor 1 plays a central role in maintaining cochlear homeostasis and regulating inflammation, that heat shock protein 70 is also associated with reduced inflammation, and that upregulation of insulin-like growth factor 1 and heat shock protein 70 inhibits Toll-like receptor 4/nuclear factor kappa-B signaling.[57,58] Moreover, it has been reported that the neutrophil-to-lymphocyte ratio, neutrophil count, and white blood cell count of ISSNHL patients are significantly lower after HBOT treatment than before treatment. The neutrophil-to-lymphocyte ratio has been proposed as a new inflammatory marker to reflect the effect of HBOT.[44,53] In general, the pathogenesis of ISSNHL may be related to hypoxia of cochlear hair cells, impaired microcirculation due to inner ear ischemia, and inflammation mediated by inflammatory mediators such as reactive oxygen species. And HBO seems to act by inhibiting the progression of these pathophysiological processes. Although these mechanisms may be possible, it is still highly controversial and does have enough evidence. Future researches would be still needed to combine clinical trials with basic experiments to explore the specific mechanisms, and better understand how HBOT can effectively treat ISSNHL (**Figure 1**).

Conclusion

HBOT has been widely used as an adjuvant treatment for ISSNHL since the 1970's and has shown great improvement when combined with steroid therapy.[59,60] Patients with varying severity of hearing loss at varying frequencies can benefit from HBOT, and it is considered to be safe. Although some unanticipated complications may occur, fewer related side effects and complications have been reported. However, the optimal

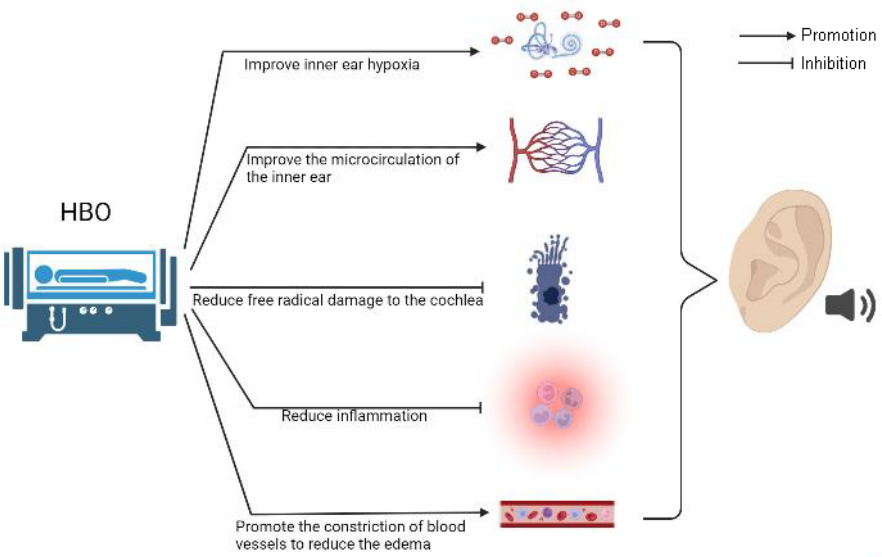

Figure 1: The possible mechanisms of HBO in ISSNHL.
Note: Created with BioRender.com. HBO: Hyperbaric oxygen; ISSNHL: idiopathic sudden sensorineural hearing loss.

time for treatment is within 2 weeks of onset, as delaying treatment can greatly decrease its efficacy. Younger patients and those with less severe hearing loss can effectively save their hearing by receiving HBOT as early as possible. HBOT is thought to work by improving ischemia and hypoxia in the inner ear and reducing inflammation. However, the mechanisms of HBOT in ISSNHL are not entirely clear. Based on recent research, we can summarize the possible mechanisms of HBOT as follows: (i) it can provide sufficient oxygen to increase the oxygenation of the inner ear and rapidly correct the hypoxia of the inner ear; (ii) it can increase the oxygen partial pressure of the perilymphatic fluid, maintain normal phosphorylation and improve the microcirculation of the inner ear; (iii) it can alleviate cochlear damage caused by ischemia-reperfusion and free radicals; (iv) it can reduce the occurrence of inflammation mediated by various inflammatory mediators such as reactive oxygen species; (v) it can promote vasoconstriction to reduce edema. To date, the mechanisms underlying the efficacy of HBOT in the treatment of ISSNHL remain a mystery with no definitive and established pathogenesis.[61] We only retrospectively review previous studies, with no clinical trials conducted and no clinical data obtained to analyze and evaluate the therapeutic efficacy, which is a limitation of this study. Future studies focusing on preclinical medicine and collaborating with clinical scenarios may provide robust evidence to better understand the pathophysiological process.

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YH contributed to drafting the manuscript and preparing figures; YY and XJ contributed to literature collection and preparation of tables; JW contributed to the conception and structure of the manuscript. All authors approved the final version of the manuscript.

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No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

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