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Mechanism and application of hyperbaric oxygen therapy in neurosurgery

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Abstract

Hyperbaric oxygen therapy, as a unique non-drug treatment method, is gradually gaining wide recognition by clinicians. In the field of neurosurgery, there is conclusive evidence that hyperbaric oxygen has significant positive effects on the treatment of craniocerebral trauma, cerebrovascular diseases, intracranial infections and intracranial tumors. This review focuses on the mechanism and application of hyperbaric oxygen therapy in neurosurgery.

Key Words: cerebrovascular disease; craniocerebral trauma; HBO; high-pressure oxygen; hyperbaric oxygen; intracranial infection; intracranial malignant tumor; neurosurgery

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Introduction

Hyperbaric oxygen therapy (HBOT), as the name suggests, involves treating the disease by allowing patients to inhale pure oxygen with higher than normal atmospheric pressure.[1-3] This therapy increases the content of dissolved oxygen in the body and promotes the diffusion of oxygen in the blood and tissues, thereby improving the hypoxic state of cells and accelerating the repair and regeneration of damaged tissues.[4] Its clinical application scope has further expanded. HBOT is a well-established practice in the field of neurosurgery, with remarkable curative effects. This review aims to explore the application mechanism of hyperbaric oxygen in neurosurgery and its application in clinical practice.

Mechanism of Hyperbaric Oxygen Application in Neurosurgery

Increasing blood oxygen pressure and enhancing the dispersion of oxygen

According to the results of this study, HBOT expands the effective diffusion range of oxygen, increases the pressure of oxygen at the capillary terminal, and then increases the pressure of oxygen in brain tissue and cerebrospinal fluid. When the pressure of oxygen reaches a specific concentration, the amount of oxygen dissolved in the blood is sufficient to meet the oxygen needs of tissue cells. Therefore, HBOT clearly has a protective effect on brain hypoxia, which has been confirmed in several studies.[5,6]

Under conventional atmospheric pressure, oxygen is mainly transported by hemoglobin in red blood cells, whereas in a hyperbaric oxygen environment, due to the increased pressure, oxygen is able to dissolve more in the plasma, forming what is called "physically dissolved oxygen." When the concentration of this physical dissolved oxygen reaches a certain level, even if it does not rely on hemoglobin transport, it meets the urgent demand for oxygen in tissue cells. This mechanism opens entirely new possibilities for brain tissue to recover from hypoxia.[4]

The metabolic activity of brain tissue is vigorous, and the demand for oxygen is high. In the hypoxic state of the brain, nerve cells are often the first to suffer damage.[5] HBOT provides a sufficient oxygen supply to nerve cells by increasing the oxygen partial pressure of brain tissue and cerebrospinal fluid and effectively alleviates the cell damage caused by hypoxia.[4] This process helps restore the normal function of nerve cells and promotes the repair and regeneration of damaged nerve cells. Hajhosseini et al.[7] found that HBOT affects perfusion in chronic wounds of patients with diabetic foot ulcers by ameliorating hypoxia and improving angiogenesis and proposed a potential role for indocyanine green angiography in the early identification of those who would benefit the most from HBOT. Cannellotto et al.[8] found that HBOT increased blood oxygen content and oxygen dispersion in coronavirus disease 2019 (COVID-19) patients.

Promoting the contraction of cerebral vessels, thereby reducing cerebral blood flow, effectively reducing intracranial pressure and alleviating cerebral edema

At normal pressure, the oxygen concentration in the air is approximately 21%, but HBOT, a technique through which 100% oxygen is provided at a pressure higher than 1 atmosphere absolute (101.325 kPa), has become a well-established treatment modality for multiple conditions. In this high-pressure environment, oxygen molecules are more efficiently dissolved in the blood, forming more physically dissolved oxygen, which greatly increases the oxygen content in the blood.

First, with increasing blood oxygen content, the cerebrovascular system adapts accordingly.[2,9,10] Studies have shown that in a hyperbaric oxygen environment, cerebrovascular reactive contraction occurs. This contraction is not pathological but rather a self-protective mechanism through which the body maintains the balance between cerebral blood perfusion and the oxygen supply. By constricting the blood vessels, unnecessary blood shunts are reduced, allowing more blood to concentrate on areas of the brain tissue that need oxygen.[2] In this process, although cerebral

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blood flow is decreased (according to literature reports, it is reduced by approximately 21% at 0.2 MPa oxygen pressure), the oxygen content per unit blood flow is increased, thus ensuring adequate oxygenation of brain tissue. Second, the contraction of cerebral vessels not only affects the cerebral blood flow, but also indirectly leads to a reduction in brain volume.[11] Under hyperbaric oxygen, the intercellular spaces of brain tissue may become tighter due to reduced water, further reducing the total volume of brain tissue. This reduction in brain volume is important for reducing intracranial pressure. Intracranial pressure, that is, the pressure generated by the contents of the cranial cavity against the wall of the cranial cavity, is one of the important indicators to evaluate the severity of craniocerebral diseases. HBOT effectively reduces intracranial pressure by reducing brain volume and significantly relieves patients with craniocerebral trauma and brain edema.

Improving the efficiency of white blood cell therapy

White blood cells, as the "guards" of the immune system, destroy the cell structure via the phagocytosis of pathogens and release oxygen free radicals, thus achieving bactericidal effects. The hyperbaric oxygen environment increases the amount of oxygen free radical production in the body. Oxygen free radicals, as a class of highly reactive molecules or ions, may cause damage to cells in excess, but under appropriate conditions, they are indispensable "messengers" of the immune system. The participation of oxygen free radicals is crucial, especially in the process of phagocytosis and sterilization of leukocytes.[12,13] Therefore, the increase in the production of oxygen free radicals in a hyperbaric oxygen environment undoubtedly provides a more powerful "arsenal" for white blood cells and enhances their ability to fight pathogens.

In addition, HBOT has been found to regulate the behavior of neutrophils. Neutrophils, another important type of immune cells, play a key role in the inflammatory response and pathogen clearance. However, in some cases, neutrophils may lose their mobility due to excessive adherence to blood vessel walls or other tissues and thus cannot effectively perform their bactericidal role.[12] Kraus et al.[14] found that HBOT and normobaric oxygen therapy influence neutrophil functionality and surface epitopes in a measurable way, which may have an impact on disorders with neutrophil involvement. HBOT inhibits the expression of adhesion factors on the surface of neutrophils, so that neutrophils change from an adhesive state to a free state and re-enter the blood circulation. In this way, neutrophils give full play to their inherent bactericidal ability in a high-oxygen environment, further improving their immune defense capacity.[15,16]

Improving tissue microcirculation and blood perfusion

HBOT reduces the adhesion between blood cells and endothelial cells, reduces blood viscosity and blood cell aggregation, eliminates and slows thrombosis, thereby improving the microcirculation and blood perfusion at the injury site, and is conducive to the recovery of brain tissue in the lesion area. HBOT also promotes the transformation of fibroblasts, allows capillaries to regenerate rapidly, establishes collateral circulation, reduces tissue bleeding and exudation, alleviates local edema, and improves microcirculation.[17,18] In addition, HBOT relieves vasospasm, increases the frequency of microvascular autonomous movement, speeds up blood flow, increases the number of effective circulating arteries, and improves microcirculation.[1,10]

Under normal circumstances, proper adhesion of blood cells helps maintain the integrity of blood vessel walls and the steady flow of blood. However, in pathological conditions, such as stroke and myocardial infarction, excessive adhesion of blood cells to endothelial cells leads to increased blood viscosity, and blood cells easily aggregate, thus causing thrombosis and obstructing the normal flow of blood. HBOT reduces this adhesion phenomenon by increasing the pressure of blood oxygen and increasing the content of dissolved oxygen in the blood. A study has shown that HBOT reduces the red blood cell aggregation index and plasma viscosity, thus effectively preventing and improving thrombosis.[2] This effect not only helps to restore microcirculation at the injury site but also improves blood perfusion, provides more oxygen and nutrients to the lesion area, and accelerates the tissue repair process.

In addition to improving hemorheology, HBOT has also shown a strong ability to promote vascular regeneration. Under hyperbaric oxygen, fibroblasts are activated and transformed into cells with angiogenic potential that secrete growth factors, such as vascular endothelial growth factor, which in turn stimulates rapid regeneration of capillaries. Moreover, HBOT also promotes the establishment of collateral circulation, provides additional blood supply to the ischemic area, and reduces the degree of tissue hypoxia. This process is important for reducing tissue bleeding and exudation and alleviating local edema. Clinical studies have shown that HBOT reduces the volume of edema in stroke patients, improves the oxygenation ability of brain tissue, and improves the recovery of nerve function.[4] In addition, HBOT further improves microcirculation by relieving vasospasm and increasing the frequency of microvascular autonomous movement. Vasospasm is a common symptom of many vascular diseases, which causes narrowing of the vascular lumen and increases blood flow resistance, thereby affecting the blood supply to the tissue. HBOT relieves vasospasm through its unique physiological effects so that blood vessels maintain a proper dilated state, which is conducive to the smooth flow of blood. Moreover, HBOT also improves the self-regulating motor ability of microvessels, accelerates the blood flow speed, increases the number of effective circulating arteries, and thus improves the microcirculation status. This effect not only helps alleviate the symptoms of ischemia and hypoxia but also enhances tissue resistance to injury and repair ability. Doenyas-Barak et al.[19] found that HBOT improves changes in the intracranial injury microenvironment and the condition of patients with craniocerebral trauma.

Antibacterial activity and enhancing the efficacy of antibiotics

The survival conditions of anaerobic bacteria, a unique group of microorganisms, are very specific; they tend to thrive in an environment without oxygen or very low oxygen partial pressure, and once exposed to a high-oxygen environment, these microorganisms often face a survival crisis and even quickly die. HBOT increases the pressure of oxygen in the patient's body so that the dissolved oxygen in the blood increases to achieve a method of treatment. In the treatment of anaerobic bacterial infection, HBOT has shown unique advantages.[20]

According to previous studies, HBOT not only has a direct bactericidal effect but also enhances the efficacy of some antibiotics, such as aminoglycoside and sulfonamide antibiotics. These findings suggest that HBOT may have a broad spectrum of bactericidal effects and may be effective against a variety of anaerobic bacteria. However, this does not mean that HBOT replaces traditional antibiotic therapy. In practical applications, doctors need to formulate personalized treatment plans according to the specific situation and infection type of patients to achieve the best treatment effect.

In a study involving 120 trauma patients, Millar et al.[21] found that early HBOT reduced the likelihood of tissue necrosis and long-term complications and improved functional outcomes in patients with severe lower limb trauma. Sarabhai et al.[22] also reported that HBOT rapidly improves tissue-specific insulin sensitivity and mitochondrial capacity in humans with type 2 diabetes. In a study of 242 patients with necrotic soft tissue infection treated with HBOT, Hedetoft et al.[23] found that HBOT may induce immunomodulatory effects by decreasing plasma granulocyte colony-stimulating factor and interleukin[6]. High levels of inflammatory markers were associated with disease severity, whereas high baseline granulocyte colony-stimulating factor was associated with increased 30-day mortality.

Reducing tumor volume and improving tumor sensitivity to radiation therapy and chemotherapy

HBOT regulates macrophages and induces them to release tumor necrosis factor and other inflammatory factors to directly attack and inhibit the growth of tumor cells. This process has been verified in a number of studies, such as the literature on the significant reduction in tumor volume caused by this mechanism.[15,24,25]

Furthermore, HBOT improved the oxygenation environment of tumor tissue in a unique way. In the conventional state, the internal tumor is in a long-term hypoxic state due to the distortion of blood vessels and poor blood flow, which not only provides a hotbed for the malignant proliferation of tumor cells but also increases resistance to radiotherapy and chemotherapy. However, HBOT allows more oxygen to penetrate, transforming oxygen-poor cells into oxygen-containing cells, which greatly increases the sensitivity of tumors to radiation therapy. This process not only improves the therapeutic effect but also reduces the possible side effects of radiotherapy.[26,27]

In addition, HBOT has shown its potential to enhance the effectiveness of chemotherapy. By increasing the permeability of tumor cell

membranes, HBOT enables chemotherapy drugs to cross the cell membrane more easily and enter the cell interior, thus achieving higher drug concentrations in the cytoplasm. This physical change directly improves the killing efficiency of chemotherapy drugs, making it difficult for tumor cells to gain a foothold under the double blow.28 Forner et al.[29] found that, compared with standard care, HBOT has a protective effect on radiation (70% *vs.* 51%).

Application of Hyperbaric Oxygen Therapy in Neurosurgical Diseases

Craniocerebral trauma

Craniocerebral injury is a common neurosurgical disease, and its treatment process is often long and complicated.[30,31] HBOT plays a crucial role in the rehabilitation of traumatic brain injury patients.[1] HBOT has shown remarkable efficacy in the acute phase of trauma, brain trauma syndrome and prolonged coma caused by trauma.[32,33] A study has shown that HBOT increases the oxygen supply to brain tissue and reduces brain edema and intracranial pressure, thus effectively relieving headache, vomiting and other symptoms in patients.[32] Moreover, HBOT promotes the repair and regeneration of damaged neurons, accelerates the recovery of nerve function, and provides a solid guarantee for patients to return to social life.[1,6] HBOT alleviated the decrease in the anti-apoptotic gene Bcl-2 and promoted the expression of neurotrophic factors, such as nerve growth factor, brain-derived neurotrophic factor, glial cell-derived neurotrophic factor and neurotrophin-3, *in vivo*. Therefore, it protects injured brain cells.[15]

Ablin et al.[34] found that HBOT improves pain symptoms, quality of life, and emotional and social function in patients suffering from fibromyalgia syndrome triggered by traumatic brain injury. The beneficial clinical effect is correlated with increased brain activity in frontal and parietal regions, which is associated with executive function and emotional processing. Boussi-Gross et al.[35] found that HBOT exhibited superior benefits over medications in terms of physical, functional, and emotional improvements among fibromyalgia syndrome patients with a history of childhood sexual abuse. This finding was associated with increased activity in prefrontal and temporal brain areas, highlighting the neuroplasticity effect of HBOT. Liu et al.[36] treated 120 patients with craniocerebral injury and coma by HBOT and median nerve stimulation. They reported that HBOT combined with right median nerve stimulation improves the state of consciousness and promotes the recovery of consciousness for patients with consciousness disorders caused by brain injury, and the effect of right median-nerve stimulation combined with HBOT in the chamber on improving the recovery of consciousness is better than that after HBOT outside the chamber.

Cerebrovascular diseases

Cerebrovascular diseases, such as cerebral infarction and cerebral hemorrhage, seriously threaten human life and health.[37] HBOT also plays an irreplaceable role in the prevention and treatment of cerebrovascular diseases. For patients with cerebral infarction, HBOT increases the oxygen supply to brain tissue, improves the microcirculation of the ischemic penumbra, and reduces the apoptosis of neurons, thus preserving the nerve function of patients to the maximum extent.[38,39] For patients with cerebral hemorrhage, HBOT promotes the absorption and dissipation of hematoma, reduces the compression and injury of brain tissue, and accelerates the rehabilitation process.[6] A number of studies have shown that the combination of HBOT and conventional drug therapy improves the cure rate and recovery rate of cerebrovascular diseases.[18,40,41]

Intracranial infection

Intracranial infection is a major challenge in neurosurgery. Once it occurs, the mortality and disability rates increase, which increases the serious adverse events for the prognosis of patients. HBOT has also shown unique advantages in the treatment of this disease. First, HBOT enhances the body's immunity and resistance. In the hyperbaric oxygen environment, the activity of immune cells such as macrophages and lymphocytes in the body is increased, and these cells recognize and remove pathogens in the body more effectively, thus inhibiting the spread and deterioration of infection.[12,42] In addition, HBOT promotes the production of more antioxidant enzymes, reduces the generation of free radicals, and protects nerve cells from oxidative stress damage. Many free radicals are present in the infection process.[43] Second, HBOT is also excellent in promoting the absorption and dissipation of inflammation. After intracranial infection, local tissues often exhibit an obvious inflammatory response accompanied by pathological changes such as edema and exudation. HBOT increases the oxygen supply to local tissues, promotes the phagocytosis and digestion of inflammatory cells, accelerates the metabolism and excretion of inflammatory mediators, and effectively reduces the damage caused by the inflammatory response in brain tissue.[16] More importantly, HBOT also speeds up the control process of intracranial infection. Through multiple mechanisms, such as enhancing the body's immunity and promoting the dissipation of inflammation, HBOT rapidly reduces the number of pathogens in the infection focus, alleviates the symptoms of infection, and provides valuable treatment time for patients. Moreover, HBOT promotes the regeneration and repair of nerve cells, reduces the sequelae of nerve injury, and lays a solid foundation for the rehabilitation of patients.

Intracranial malignant tumors

For patients with intracranial tumors, HBOT increases the sensitivity to radiotherapy and chemotherapy by increasing the oxygen supply to tumor tissues, enhances the therapeutic effect, and reduces the side effects and complications during treatment. In recent years, with the continuous progress and improvement of HBOT technology, its role in the comprehensive treatment of intracranial tumors has become increasingly prominent.[24]

First, intracranial tumors often lead to insufficient blood supply within tumor tissues due to their occupying effect, resulting in an anoxic environment.[44] This lack of oxygen not only limits the growth of tumor cells but also reduces the effectiveness of traditional treatments such as radiation and chemotherapy. HBOT effectively alleviates hypoxia by increasing the partial pressure of oxygen in the body of patients, prompting more oxygen molecules to penetrate the blood–brain barrier and penetrate deep into the tumor tissue. This process creates favorable conditions for the deep penetration of radiotherapy and chemotherapy drugs.

Second, with the aid of HBOT, the sensitivity to radiotherapy and chemotherapy has improved. Radiation destroys the DNA structure of tumor cells through high-energy radiation, while chemical drugs interfere with the division and proliferation of tumor cells. HBOT enhances the lethality of these two means to tumor cells so that the therapeutic effect is more significant.

However, HBOT also has other potential anti-tumor mechanisms. It promotes the production of free radicals, which in turn stimulates macrophages to release tumor necrosis factor. This process not only improves the permeability of the cell membrane but also increases the concentration of chemotherapy drugs in the cytoplasm to kill tumor cells more effectively and promote cell apoptosis.[28]

Finally, during the treatment of intracranial tumors, patients often experience side effects and complications caused by radiotherapy and chemotherapy, such as nausea, vomiting, hair loss, and decreased immunity. Owing to its unique physiological effects, HBOT effectively reduces these adverse reactions. On the one hand, HBOT promotes blood circulation and accelerates the excretion of toxins and metabolites in the body; on the other hand, it also enhances the immune function of the body and improves the disease resistance of patients. These effects work together to provide patients with a more comfortable and safe treatment environment.

Other diseases

HBOT also plays a protective and therapeutic role in other diseases during neurosurgery. El-Tellawy et al.[45] studied 146 children with autism and found that the combination of Tomatis sound therapy with HBOT has a superior effect on improving autism symptoms compared with each intervention alone. HBOT also has a therapeutic effect on pain and reduces the use of pain medications.[46,47]

Risks of Hyperbaric Oxygen Therapy

HBOT is a type of oxygen therapy that involves inhaling pure oxygen or in an environment above normal pressure. It is widely used to improve tissue hypoxia, promote wound healing and treat some toxic diseases. However, the potential risks cannot be ignored, especially as problems such as oxygen poisoning and barotrauma pose serious threats to patients' health.[48-51] Manning[48] reported the mechanism of central nervous system poisoning caused by HBOT and suggested related complications resulting in dizziness.

Oxygen poisoning is one of the most typical

complications of HBOT and is mainly caused by excessive accumulation of oxygen free radicals in the body for a long time or high concentrations of inhaled oxygen, leading to oxidative damage to cells.[52,53] According to its pathogenesis and site of involvement, oxygen poisoning can be divided into central nervous system type and pulmonary type. Central nervous system oxygen poisoning usually occurs in the high-pressure stage of HBOT (usually when the pressure is higher than 2 atmosphere absolute), and patients may experience convulsions, vertigo, tinnitus, nausea and other symptoms, which can lead to epileptiform seizures in severe cases and can even be life-threatening.[48,51] Pulmonary oxygen poisoning is associated with prolonged (usually more than 6 hours) exposure to high levels of oxygen and is characterized by pain, cough, and dyspnea behind the sternal bone, which may lead to lung inflammation or fibrosis.[52,54] Arieli50 proposed related factors for the occurrence of pulmonary oxygen poisoning. The occurrence of oxygen poisoning is closely related to the oxygen partial pressure, exposure time and individual sensitivity, which should be prevented by strict control of the treatment pressure, duration and oxygen concentration.[55,56]

Barotrauma is associated with changes in pressure inside and outside the hyperbaric oxygen chamber and is most common in the middle ear, sinuses, and lungs.[55] Middle ear barotrauma is the most common type of trauma. Due to the imbalance of eustachian tube adjustment during pressure rise and fall during treatment, the pressure difference between the inside and outside of the tympanic membrane increases, leading to earache, tinnitus and even tympanic membrane perforation.[55] Barotrauma of the sinuses is more common in patients with sinusitis, and pressure changes may aggravate mucosal damage, resulting in bleeding or severe headache. The most dangerous type of pneumobaric injury is a sudden increase in the internal and external pressure of the alveoli due to breath-holding or airway obstruction in the patient, which may lead to alveolar rupture, resulting in pneumothorax, mediastinal emphysema, or arterial gas thrombus, which can lead to sudden death in severe cases. In addition, the high-oxygen environment in the hyperbaric oxygen chamber also has a fire hazard; if there is a spark or static electricity in the chamber, deflagellation accidents may occur.

In addition to the above risks, HBOT may also cause side effects such as temporary myopia,[57] claustrophobia, or neurological dysfunction after oxygen poisoning. McMonnies[57] reported on ocular diseases caused by HBOT. Wang et al.[58] reported that HBOT increased the risk of tuberculosis. Therefore, patient indications and contraindications should be strictly evaluated before treatment, vital signs should be closely monitored during treatment, and risk should be minimized through standardized procedures (such as controlling the rate of pressure increase/decompression and guiding the patient to breathe correctly). In general, HBOT should be carried out under the guidance of a professional medical team, weighing the efficacy and potential harm to ensure patient safety.[56,59]

Conclusion

HBOT, an important treatment in the field of neurosurgery, has remarkable curative effects, a wide application range and broad application prospects. With the further definition of the mechanism of HBOT and the continuous innovation and development of treatment technology, we believe that, in the future, HBOT will play a more important role in the field of neurosurgery and bring the prospect of rehabilitation to more patients.

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