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Hyperbaric Oxygen Therapy: Effect on Wound Healing and Traumatic Brain Injuries

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Abstract

Hyperbaric Oxygen Therapy is a new form of treatment being used to heal and help improve symptoms of traumatic brain injuries, external wounds, and strokes. HBOT helps to completely saturate hemoglobin with oxygen, which then allows for a larger capacity of oxygen to be delivered to the damaged tissues. Tissue wounds benefit from this HBOT because of the increase in oxygen supply to the damaged area, helping to combat hypoxia, which is preventing proper wound healing. The increase in oxygen allows for an increase in myofibroblast differentiation to allow the healing process to continue. HBOT has also proven to increase cognitive function for post-stroke patients by increasing the amount of oxygen and energy being delivered to the brain. This therapy has also been used to treat patients with Alzheimer's disease, helping to improve brain function at the cellular level.

Keywords

HBOT, Oxygen Therapy, TBI

Disciplines

Analytical, Diagnostic and Therapeutic Techniques and Equipment | Medicine and Health Sciences | Neurology

Comments

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Introduction:

Hyperbaric Oxygen Therapy, also known as HBOT, is a form of treatment that allows for people to breath 100% oxygen at a pressure higher than atmospheric pressure (Huang & Obenaus 2011; Al-Waili et al., 2005; Sahni et al., 2012; Wang et al., 2018; Rosario et al., 2018; Ashery, 2018). HBOT occurs in a hyperbaric chamber, either a mono-place chamber which is built for one person, or a multi-place chamber which can fit two or more people at once to receive the treatment in which oxygen is delivered by a hood or mask (Heyboer et al., 2017). The majority of research has been performed in mono-place chambers. In these chambers, the air pressure is increased to above atmospheric pressure (760 hh mg). The increase in air pressure allows the lungs to gather more oxygen than would be possible breathing at normal atmospheric pressure. The delivery of oxygen to the tissues normally occurs through the binding of oxygen to hemoglobin with very little oxygen being dissolved directly into the plasma. With the high pressure from the hyperbaric chamber, the hemoglobin becomes completely saturated with oxygen and the amount of physically dissolved oxygen into the blood plasma increases proportionally to the oxygen partial pressure (Bitterman, 2009; Kessler et al., 2003). The hyperbaric chamber acts as a means to providing a drug, pressurized oxygen, which is dissolved into the blood, raising O_2 pressure allowing it to diffuse deeper into tissues (Kalani et al., 2002).

The body's tissues need an adequate supply of oxygen to continue their daily functions. When a tissue is injured, it causes damage to the body's blood vessels, which then releases fluid that extravasates into the tissues causing swelling. The swelling interrupts the blood supply and oxygen to the damaged cells, leading them to necrosis depending on the duration of interruption (Kalogeris et al. 2014). These tissues then require more oxygen to heal and survive. This is the reason hyperbaric oxygen therapy has become the focus of a new treatment to heal tissue

injuries. It is using a natural drug, oxygen, to heal tissues by increasing its abundance in the body. Hyperbaric Oxygen Therapy has recently been used to heal more than just external tissue damage. New research has been studying the effects of HBOT on brain damage caused by strokes, traumatic injury to the brain and even clinical trials on Alzheimer patients.

Physiology of HBOT:

Pressurized oxygen increases the oxygen tension in both arterial blood and tissues. This causes an increase in the cellular oxygen supply because the tissue-cellular diffusion gradient is raised (Leach et al., 1998). This increase in oxygen in the body is known as hyperoxia which is the primary effect of hyperbaric oxygen therapy. The secondary effects are a result of controlled oxidative stress. HBOT produces both reactive oxygen species (ROS) and reactive nitrogen species, which both work to signal pathways that promote wound healing (Heyboer et al., 2017). ROS in excessive amounts in the presence of Fe^{2+} can result in cellular damage (Dennog et al., 1999). To counteract this potential for damage, antioxidant systems in the body are activated to control and reduce damage of the ROS. Antioxidants work to reduce the production of ROS or by removing the species themselves (Dennog et al., 1999).

The principles of HBOT depend on gas laws, and how oxygen behaves under changing pressures within the tissues. This can be explained by Henry's Law, which explains how the pressure of gas affects its concentration within a tissue or fluid. The concentration of a dissolved gas equals the pressure times the solubility coefficient of that gas (Edwards et al., 2010). The more pressure applied to oxygen the higher the dissolvability into the tissues.

Decompression Therapy:

Hyperbaric Oxygen Therapy was historically used to treat decompression sickness. Decompression sickness is a disorder in which nitrogen dissolved in the blood and tissues from

high pressure, begins to form bubbles as the pressure decreases to normal at a rapid rate. These bubbles can cause mechanical distortion of tissue, leading to tissue hypoxia as the bubbles cause a vascular obstruction (Hadanny et al., 2015). This is commonly seen in divers who ascend from below-sea level too quickly for the nitrogen to properly diffuse out of the blood and tissues before forming bubbles. Hyperbaric Oxygen chambers were used to rapidly recompress the patients to alleviate the symptoms and safely return the body to normal pressure allowing the nitrogen to diffuse naturally without causing harmful bubbles (Leach & Rees & Wilmshurst, 1998). The use of oxygen with an added pressure component to accelerate gas diffusion in humans was first suggested in 1897, not tested on divers until the 1930s (Moon et al., 2014). This timeline shows that the use of pressurized oxygen is a relatively new development that is beginning to branch into new forms of treatment for other illnesses and injuries.

Wound Healing:

Wound Healing is a complicated pathway that requires the presence of oxygen for optimal healing of tissue function and integrity. Healing is a positive feedback system that begins with an accumulation and cascade of cellular and biochemical processes that include; blood coagulation, inflammation, matrix synthesis, wound contraction, increased collagen production, fibroblast proliferation and angiogenesis (Kuffler, 2011). Healing results from all of these processes that are organized into three oxygen-dependent phases; the inflammatory phase, the proliferative phase, and the maturation phase. A key determinant to tissue healing outcomes is the state of oxygenation at the site of the wound. Optimization of wound perfusion to providing oxygen to the wound in the peri-operative period reduces the progression of post-operative infections (Sen, 2009).

Hyperbaric Oxygen Therapy has been shown to have a healing effect on tissue wounds. It is thought that hypoxia, lack of oxygen in the injured tissue, suppresses myofibroblast differentiation which causes the wound healing to slow (Andre-Veligne et al., 2016). Myofibroblasts that have been subjected to low oxygen resulted in downregulating contraction (Modareressi et al, 2010). Myofibroblast differentiation is important in the healing process, because without the differentiation of fibroblasts the wound site would be unable to regenerate extracellular matrix, leading to the inability for skin cells to proliferate over the wound site. This can be reversed when oxygen levels are re-established (Modaressi et al,, 2010; Andre-Veligne et al., 2016).

A study was conducted with normoglycemic and hyperglycemic animals that were treated with HBOT to test the effects on wound repair/reduction. It was observed that the HBOT was able to counteract the negative effects of wound closure, significantly enhancing the healing process in ischemic and hyperglycemic conditions. HBOT was able to counteract these effects by increasing blood perfusion rates in the wound area, leading to a decreased tendency of limb necrosis following arterial resection (Andre-Veligne et al., 2016). The increase in blood perfusion allows for a larger blood volume to flow through the injured tissue and deliver oxygen and nutrients to aid in the healing process.

HBOT has also been found to increase collagen mRNA (Kuffler et al., 2011) and improve granulation tissue formation (Sheikh et al., 2000; Kalani et al., 2002). Collagen is the most abundant protein in the human body that is found in bones, muscles, skin and tendons, it is a major component of the extracellular matrix that supports cells. Collagen production decreases due to severe hypoxia because of the inability for collagen fibril cross-linking which relies on the hydroxylation of proline and lysine to synthesis collagen (Kuffler et al., 2011). Without oxygen,

this hydroxylation process is inhibited resulting in the decrease of collagen production which is detrimental for wound healing. Collagen synthesis is directly proportional to the concentration of molecular oxygen (PO2) which is normally within a range of 0 mm Hg to 200 mm Hg (Sheikh et al., 2000). The increase in oxygen in the blood from HBOT is able to counteract the negative effects of ischemia on early collagen deposition during wound repair (Andre-Veligne et al., 2016; Al-Waili et al., 2005).

Diabetic Foot Ulcers:

Diabetic foot ulcers have become much more prevalent in recent years. Diabetic foot ulcers and other chronic wounds increase amputation risk in patients with diabetes (Zhao et al., 2017). The three most common causes of amputations are ischemia, infection, and retarded wound healing (Boulton et al., 1994). This has increased the need to find treatments to help avoid amputations and reduce dangers specifically of diabetic foot ulcers. There are multiple reasons as to why ulcers in patients with diabetes do not heal. The main causes are due to edema, anemia, or poor perfusion which all have been proven to prevent normal wound healing (Liu et al., 2013). Hyperbaric oxygenation therapy has been shown to decrease tissue hypoxia helping to treat chronic foot ulcer. Those treated with HBOT have reported fewer infections based on their lower bacterial colony counts which can demonstrate that the oxygenation therapy indirectly demonstrates better infectious outcomes (Liu et al., 2013). This is because the treatment can stimulate oxygen-dependent components that enhance host antimicrobial responses to stimulate the tissue repair (Zhao et al., 2017).

Hyperbaric oxygen therapy is used as an adjunctive treatment for the diabetic foot because of its beneficial effects on the microenvironment of the wound. High oxygen pressure over a long period of time stimulates abnormal angiogenesis, while studies have shown that

cycling through high and low oxygen pressures over shorter periods of time is able to stimulate a physiological angiogenesis at the specific site of the diabetic ulcer (Kessler et al., 2003). This is due to the release of fibroblasts and vascular growth factors that are enhanced by macrophages at the ulcer site (Kessler et al., 2003: Sheikh et al., 2000; Duzgun et al., 2008). The hyperbaric oxygen chamber can lead to hyperoxia which triggers the onset of signal transduction pathways that regulates the gene expression of certain growth factors, in this case the platelet-derived growth factor. This regulation of genes leads to an increase of strength in microbiocidal capacity of endogenous defense mechanisms (Kessler et al., 2003). Hyperbaric Oxygen Therapy is able to increase the healing process in foot ulcers through the enhancement of angiogenesis as well as the reduction in hypoxia to the damaged area.

Traumatic Brain Injuries:

Traumatic Brain Injuries and strokes are the main causes of brain damage. Traumatic Brain Injury, also known as TBI, is defined as damage to the brain as a result of external mechanical force, such as rapid acceleration, deceleration, impact, or penetration of an object. Immediately after an injury to the brain, the brain cells become inactivated either temporarily or permanently by local, injury related trauma such as ischemia and edema because the local perfusion has been compromised (Sahni et al., 2011). The brain receives 15% of the cardiac output, the amount of blood the heart pumps through the circulatory system in a minute, consumes 20% of the total oxygen in the body and utilizes 25% of the total body glucose. This energy supply is only sufficient enough to maintain 5-10% of the neurons in the brain active at a given time (Boussi et al., 2013). Therefore, when the brain is injured the regeneration process requires a much greater energy usage. HBOT is able to increase the level of oxygen in the blood and body, to supply the brain with the energy needed to begin repairing the damage. This therapy

has been shown to have significant effects on cognitive functions and improve quality of life for patients who have suffered mild TBI (Wang et al., 2016). HBOT has been shown to induce neuroplasticity leading to significant neurological improvement for post-stroke patients from months to years after the original event. HBOT can reactivate neuronal activity in the stunned areas of the brain (Calvert & Cahill & Zhang, 2007). It is able to promote new neuron and blood vessel regrowth, improve cellular metabolism and cell survival (Sahni et al., 2012). The increase in plasma oxygen concentration through the oxygen therapy allows for the increase of oxygen being delivered to the brain to promote sufficient tissue repair (Boussi et al., 2013). It is important to begin HBOT as early as possible after severe head injury, to rapidly increase blood flow which has the best results in mortality and neurological recovery (Niklas et al., 2004).

Cerebral ischemia is a condition in which a blockage of an artery restricts the delivery of oxygen-rich blood to the brain, resulting in brain tissue damage. Blood flow is a critical factor of oxygenation, and a rapid decrease in oxygen availability is an inevitable result of severe ischemia (Niklas et al., 2004). In cerebral ischemia, local anoxia leads to cellular damage which results in a complete stroke (Al-Waili et al., 2005). The ability to increase the amount of oxygen in the brain is why HBOT has been thought to be an attractive treatment option for cerebral ischemia. Ischemic episodes have been reported to lead to mitochondrial membrane alterations and intermittent cerebral blood flow reductions (Calvert & Cahill & Zhang, 2007). These both can impair the flow of oxygen from the capillaries into the tissue, neurons, and mitochondria, all of which may contribute to the aerobic metabolism. The use of hyperbaric oxygen therapy increases the amount of dissolved oxygen in the blood plasma, thus elevating the supply of oxygen to be delivered to the tissues and mitochondria (Calvert & Cahill & Zhang, 2007).

An ischemic stroke occurs when an artery that supplies blood to the brain is blocked by a clot. Approximately 80% of all strokes that occur are ischemic (Al-Waili et al., 2005). The stroke results in impaired cerebral blood flow and possible irreversible injury within minutes following the stroke. Cell death and neuronal activity can result from any ischemic event and can be attributed to excitotoxicity, oxidative stress, and inflammation which are all related to hypoxia (Rosario et al., 2018). Decreased oxygenation to the damaged areas, specifically blood vessels, halts tissue repair and blocks the generation of new synaptic or neuronal connections. Hyperbaric Oxygen Therapy is thought to be a neuroprotective treatment, especially in ischemic stroke with the therapies ability to improve oxygen supply (Lee et al., 2013). The use of HBOT for brain injuries is based on the idea that injured or possibly inactive neurons will benefit from increased blood flow and oxygen delivery to the tissues which would act to metabolically reactivate the dying cells. It has also been shown that HBOT increases cerebral blood flow which is beneficial after an ischemic stroke (Huang & Obenaus, 2011 & Sahni et al., 2012). HBOT has been shown to promote oxygen delivery, decrease cerebral edema and maintain blood-brain barriers integrity (Al-Waili et al., 2005).

HBOT has also been showed to improve neurogenesis, with longer and more repetitive HBOT resulting in inducing greater degrees of neurogenesis. Longer and more repetitive HBOT also showed significant improvement of functional outcome in a study done on rats following ischemic stroke (Lee et al., 2013). As with most studies the HBOT enhanced brain tissue oxygenation during treatment. One study tested six subjects who had suffered from an ischemic stroke at least 12-months ago and exhibited some functional impairments. After the use of HBOT the researchers observed a significant effect of treatment on improving both verbal and nonverbal memory. Specifically, there was a significant effect of HBOT on CVLT, essentially

the measurement verbal memory, as well as WMS, measurement nonverbal memory (Rosario et al., 2018). Another study however, found that after the termination of HBO treatment, when returning to normal oxygenation levels, the body temporarily enters a hypoxic state. The change from hyperoxia to hypoxia resulted in the hypoxia inducing factor-1(alpha HIF) production (Lee et al., 2013). The preconditional hypoxia was shown to decrease ischemic stroke related injury, and that the oxygen cycling helping in traumatic brain injury. These studies both suggest that the oxygen cycling that occurs after HBOT may attenuate ischemic injuries (Lee et al., 2013). The brain requires a lot of energy to function, and even more to heal, therefore the addition of hyperbaric oxygen therapy helps to increase the amount of oxygen flowing to the brain to stimulate the healing process.

Alzheimer's Disease:

Alzheimer's disease (AD) is the most common form of dementia found in the elderly, accounting for approximately 60-80% of all dementia cases (Ashery et al., 2018). Alzheimer's disease is an irreversible, progressive brain disorder that causes disruptions in memory, cognition, personality and other functions. These disruptions are caused by the loss of connection between neurons in the brain. Excess production of Beta-amyloid (Aβ) occurs at the beginning of the disease process (Zhang et al., 2015). Beta-amyloid is a protein fragment, that forms amyloid plaques when they accumulate and clump together between the neurons in the brain. The excessive deposition of Aβ causes apoptosis in hippocampus neurons, which is what leads to the symptoms of impairment in memory (Zhang et al., 2015).

HBOT has been found to improve neurological function of life following incidents including stroke and traumatic brain injury. A specific study used Alzheimer's diseased mice who were exposed to 14 days of HBOT to observe the neurological effect. These mice showed

reduced hypoxia, neuroinflammation, reduction of beta-amyloid plaques and phosphorylated tau (Ashery et al., 2018). At the cellular level, it has been determined that HBOT can improve mitochondrial redox, preserve mitochondrial integrity, alleviate oxidative stress and increase levels of neutrophils and nitric oxide via an enhancement of mitochondrial function in both glial cells and neurons (Huang et al, 2011).

Hypoxia leads to the activation of microglia and astroglia to induce pro-inflammatory cytokine secretion. The increase of oxygen from HBOT reduced microgliosis, astrogliosis and the secretion of these cytokines including; tumor necrosis factor alpha (TNFa) and increased the production of anti-inflammatory cytokines which are beneficial to the healing process. Ultimately this suggests that HBOT attenuates neuroinflammation by repressing inflammatory variables (Shapira, 2018). The most difficult part for treating AD is that those patients who have been diagnosed tend to already have significant brain atrophy, meaning that the tissue that has been lost cannot be recovered. Therefore, it is very important to identify the subpopulation of patients with AD that would benefit most from the treatment and produce enhancing results.

Treatment Risks/Costs:

Oxygen, like any other known drug, can both have significantly beneficial effects as well as life threatening effects, depending on its use (Speit, 2002). Oxidative stress is a situation in which the abundance of reactive oxygen species increases the free radical formation in the body, likely to cause significant damage if the antioxidant defenses are not prepared (Speit, 2002). A study has shown that after a single HBO session the oxygen exposure caused oxidative DNA damage (Dennog, 1996) but no further damage after repeated HBO exposures (Speit, 2002). HBOT has been studied as a therapeutic method for healing tissue damage, it can also have undesirable side effects if too high an abundance of oxygen leading to DNA damage. According

to Boyle's Law, the volume of a gas at a fixed temperature is inversely proportional to the ambient pressure. In reference to HBOT the effects of the pressure change are experienced within the bodies air cavities. One of the most common side effects of HBOT is middle ear barotrauma (Heyboer, 2017). During middle ear barotrauma, the patient has difficult equalizing the ear, feeling the pressure of the therapy. This can be avoided by teaching the patient the proper mechanics of equalizing the ears while experiencing pressure changes.

Conclusion:

Hyperbaric Oxygen Therapy is a relatively new groundbreaking treatment that has been shown to have healing properties on a number of different injuries and illnesses. The high pressurized oxygen chamber allows for hemoglobin to be fully saturated and deliver oxygen to tissues as well as increase the amount of physically dissolved oxygen into tissues. HBOT has been found to increase healing in tissue wounds by enhancing blood perfusion rates in the wounded area (Andre-Veligne et al., 2016). The increase in oxygen to the damaged tissues has been shown to increase myofibroblast differentiation (Modaressi et al., 2010). Other forms of wound injuries, such as diabetic foot ulcers have reported improvements after the use of HBOT. This therapy can increase oxygen-dependent components which enhance host antimicrobial responses which help stimulate tissue repair (Zhao et al., 2017). HBOT has not only been responsive in helping wound repair, but also in treating traumatic brain injuries. It has been proven to induce neuroplasticity which leads to neurological improvement in post-stroke patients (Calvert & Cahill & Zhang, 2007). More recently, HBOT has been used to treat patients with Alzheimer's disease. It has been shown that this therapy can reduce the beta-amyloid plaques that clump between neurons causing the memory, cognition and personality dysfunctions (Ashery et al., 2018). Similar to other therapies and drugs, HBOT has risks. These risks such as

oxygen toxicity and middle ear barotrauma can be prevented if the correct active measures are taken (Heyboer, 2017). Oxygen has been shown to work as a drug, enhancing the bodies ability to heal wounds, treat ulcers, improve brain function after a traumatic brain injury, and has positive effects in the therapy for Alzheimer's Disease.

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