• REVIEW ARTICLE •

The Role of Hyperbaric Oxygen Therapy in Enhancing the Rate of Wound Healing with a Focus on Axon Regeneration

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Wounds have always afflicted humanity causing pain, suffering and death, and for thousands of years humans have tested and developed various techniques for their ability to induce wound healing. Hyperbaric oxygen therapy (HBOT) refers to placing a patient or their extremity in a chamber in which the pressure is raised several fold above ambient air pressure and the ambient air is substituted with 100% oxygen. HBOT is effective in enhancing the rate and effectiveness of healing of a variety of wounds and injuries. The mechanisms by which HBOT acts are well understood. An important question about HBOT is whether it can heal another is type of wound, nerves after trauma? This review primarily discusses mechanisms by which HBOT induces the complex process of wound healing. It then examines how some of these mechanisms are also involved in promoting axon regeneration. Finally it presents anecdotal evidence suggesting that HBOT promotes axon regeneration, but notes that more extensive and thorough studies are required to determine whether HBOT induces axon regeneration. [*P R Health Sci J 2011;1:35-42*]

Key words: Nerve regeneration, Trauma, Wound healing

Wounds

Wounds and diseases have affected humanity for all time and finding better techniques for inducing their healing or resolution is of critical importance. Wound healing is a dynamic pathway requiring the presence of oxygen for optimal restoration of tissue integrity and function. Healing results from an accumulation and cascade of cellular and biochemical processes including blood coagulation, cellular respiration, inflammation, ground substance and matrix synthesis, angiogenesis, fibroplasia, re-epithelialization, wound contraction, and remodeling, increased collagen production, fibroblast proliferation, enhanced vascularization, increased cell motility, antibacterial action, and the presentation of growth and wound-healing factors. These complex overlapping processes are best organized into 3 phases of healing: the inflammatory phase, the proliferative phase, and the maturation phase, all of which are oxygen dependant. Therefore, arterial occlusion or vasoconstriction, hypotension, hypothermia, and peripheral venous congestion delay or prevent wound.

The physiologic processes underlying wound inflammation begins immediately upon tissue injury. The inflammatory phase of wound healing is clinically characterized by signs of redness, heat, swelling, pain, and loss of function with the inflammation generated by metabolites, and redness caused by vasodilation, primarily a result of prostacyclin (PGI2) (1). The edema is potentiated by PGE2 and prostaglandin F2-alpha (PGF2-alpha), where PGI2 and PGE2 promote local blood flow, causing the localized warmth in the area of inflammation, but also allow for entry of inflammatory cells into the wound, which is due to increased vascular permeability (2). These cells then release cytokines responsible for fever production. Pain is elicited by the effects of PGI2, PGE, and PGE2 on peripheral sensory nerve endings. Simultaneously, the coagulation cascade, the arachidonic acid pathways, and the synthesis and release of growth factors and cytokines, initiate and maintain the inflammatory phase and the sequence of cells involved in the process.

During the progression of the inflammatory phase, eicosanoids interact with cells that are present to increase the ratio of PGF2-alpha to PGE2 during late inflammation, which is a stimulus for fibroblasts to begin to synthesize collagen and ground substance. Additionally, the macrophage-derived

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growth factors are at optimal levels, strongly influencing the influx of fibroblasts, then keratinocytes and endothelial cells, into the wound. The cellular population of the wound becomes predominantly mononuclear, with a declining number of neutrophils and macrophages, signaling the end of the inflammatory phase and the initiation of the proliferative phase. At this time fibroblasts are driven by macrophage-derived bFGF, TGF-beta, and PDGF to proliferate and synthesize glycosaminoglycans and proteoglycans, the building blocks of the new extracellular matrix of granulation tissue, and collagen (3), which fibroblasts assemble extracellularly into collagen fibers. These fibers are then cross-linked and organized into bundles, the major component of acute wound connective tissue. Finally, with decreasing hyaluronic acid concentration and rising chondroitin sulfate levels there is a slowing of the in-migration of fibroblast migration and proliferation, leading to the maturation phase of wound healing.

When the normal reparative process is interrupted, a chronic wound develops. Definitions of wound, acute wound, chronic wound, healing and forms of healing, wound assessment, wound extent, wound burden, and wound severity are well defined in the paper of G. S. Lazarus et al., 1994 (4). Similarly, the cascade of cellular and molecular events involved in wound healing is discussed thoroughly elsewhere and will not be discussed in detail here.

Certain characteristics of wounds (ischemic appearance, a history of a lack of healing, physical examination yielding no pulses, or a transcutaneous oxygen evaluation suggesting tissue hypoxia), identify a wound as hypoxic, or related to arterial disease. What factors allow one to identify and classify patients with arterial wounds? How does one manage those primarily caused by peripheral arterial occlusion or damage? When and how does one use transcutaneous oximetry to evaluate this subgroup of patients and the use of endovascular interventions such as arteriography, angioplasty and arterial stenting? When is the use of HBOT appropriate, and when should it be used to provide arterial revascularization to manage wounds?

Wound Healing

Collagen production is maximal at 250 mm Hg and falls to almost zero in severe clinical hypoxia due to the failure of collagen fibril cross-linking which requires the hydroxylation of proline and lysine to synthesize mature collagen. Cell motility decreases as available cell energy production via oxygen decreases at or below 10 mm Hg pO2. Re-epithelialization, essential to wound healing, is oxygen dependent. Similarly, eliminating bacteria within a wound is oxygen dependent because it results from oxidative killing of bacteria, and reaches its maximal effect at several hundred mm Hg pO2, and drops to almost zero in hypoxic patients. Thus, since enhanced oxygen presentation induces the events required to induce wound healing HBOT which provides enhanced oxygen to tissues is a reasonable place to start wound healing therapy. However, before discussing HBOT itself, it is important to consider some of the potential influences of oxygen on wound healing.

Deposition of Collagen

Collagen synthesis, deposition, and reduced collagen degradation, which are critical for wound healing, require oxygen dependent prolyl-hydroxylase hydroxylation of proline. Wound healing takes place where the rate of collagen synthesis is maximum and is also associated with the enhanced presence of hyaluronic acid (HA) and fibronectin (FN), which lead to an increased number of fibroblasts and an increased deposition of oriented collagen fibers (5).

Bacterial Infection

Although many factors contribute to poor wound healing, the most common is wound infection caused by foreign debris and necrotic tissue. Therefore, debridement of all necrotic tissue and debris, whether performed by surgical means or with the use of enzymatic agents or wound dressings, is critical in achieving wound healing.

Wound hypoxia predisposes tissue to bacterial infection because the leukocyte's oxidative phosphorylation bactericidal activities are severely impeded without normal tissue oxygen levels. Therefore, reestablishing vascularization, or providing enhanced oxygen should lead to increased antibacterial activity within a wound.

Angiogenesis

Angiogenesis is a dynamic, oxygen stimulated and growth factor-dependent process (6), and is directly sensitive to oxygen as a function of local lactate delivery (7). Therefore, once tissue oxygen tension decreases to 10 mm HG there is no angiogenesis, which leads to further oxygen deficiency, preventing tissue granulation and blocking tissue healing.

Growth and Wound Healing Factors

At the moment of trauma associated with vascular injury, tissue factors and intracellular calcium are released, activating factor VII and initiating the extrinsic coagulation cascade. Concomitant reflex vasoconstriction occurs to aid in hemostasis. Hemostasis is ultimately secured by the end product of the coagulation cascade, the fibrin plug. The fibrin fibers become a provisional wound matrix and are the lattice on which platelets aggregate. Activated platelets are the most abundant cells in the wound in the early post-injury period. Platelets release proinflammatory substances, such as tissue growth factor-beta (TGF-beta) and platelet-derived growth factor (PDGF). A host of other wound healing and regeneration-promoting factors are also released by platelets.

Growth factors are peptides that act on inflammatory cells, fibroblasts, and endothelial cells to direct the processes involved

in wound healing, and in promoting axon regeneration (8). They are noted in the earliest period post injury because PDGF and basic fibroblast growth factor are produced by injured cells at the time of trauma. Subsequently, activated platelets release TGF-beta and PDGF to mediate chemotaxis of neutrophils, monocytes, and fibroblasts into the wound (9). Another means of providing a host of wound healing and neurotrophic factors is by the exogenous application of autologous platelet-rich fibrin (10). In this case the platelets, which contain a host of wound healing and tissue regeneration-promoting factors, release these factors directly into the site of the wound to promote healing and tissue regeneration.

Subsequent steps in wound healing involve arachidonic acid metabolites that are derived from cell membrane fatty acids, which play central roles in the regulation of vasomotor and platelet activity after injury, while thromboxane A2 helps with hemostasis by its effects on vasoconstriction and platelet aggregation. However, after the initial insult, vascular permeability is increased.

After hemostasis has been obtained, polymorphonuclear (PMN) leukocytes enter the area of injury, drawn by chemotactic substances released by platelets and release cytokines. Other leukocytes, specifically helper T cells, are sources of the cytokine interleukin (IL)–2 that promote the proliferation of additional T cells, which aid in the immunogenic response to injury. T cells are also important for stimulating and activating macrophages, which are primarily responsible for wound debridement, but which also secrete substances such as basic fibroblast growth factor (bFGF), a chemotactic and mitogenic factor for fibroblasts and endothelial cells, and interleukin (IL)-1, which stimulates the proliferation of multiple cells of inflammation and induces the replication of endothelial cells, promoting angiogenesis.

A Brief History of the Development of Hyperbaric Medicine

In 1662, the British Clergyman Henshaw started recompression chamber history with an organ bellows-driven air control device that could create hyper- (above normal) and hypo- (below normal) - baric conditions within a large chamber. Although he had no scientific basis for his theories, Henshaw believed patients suffering from acute conditions would benefit from increased air pressure, while those suffering chronic ailments would profit from a lower pressure environment. The primary drawback to this device was the lack of oxygen with which to fill the chamber because it was not discovered by Priestly until 1774.

Robert Boyle contributed to understanding the use of pressurized gas by describing the behavior of an ideal gas as stated in Boyles Law (1660) in "New Experiments Physio-Mechanical, Touching the Spring of the air and its Effects". Boyle described the effects of decompression illness in 1670 after using vacuum pump to decompress a snake. Subsequently together with Robert Hooke he designed an air pump to study the "elastic properties of air". In the 1830's the study of hyperbaric medicine started in which hyperbaric chambers were used containing 2 and 4 atmospheres of absolute pressure to increase blood circulation to internal organs, improve the cerebral blood flow, and produce a feeling of well being. However, not until 1917 did Drager design a system in which oxygen under pressure started being used to treat individuals suffering from diving accidents, although it was not until 1937 did Behnke and Shaw started using hyperbaric oxygen to treat decompression sickness and when hyperbaric oxygen therapy (HBOT) became a real research and clinical tool. In 1965, Dr. I. Boerema reported that HBOT assisted in cardiopulmonary surgery, the transposition of great vessels, and for pulmonic stenosis (11). Subsequently, it was shown that anaerobic infections were inhibited by HBOT (12). Boerema then published the article "Life Without Blood" reporting on fatally anemic pigs that were successfully treated with volume expansion and pressurized hyper-oxygenation, which lead to Boerema often being credited as the father of modern-day hyperbaric medicine (13).

Benefits of HBOT

Delayed wound healing leads to increased complications for the patient and significantly increased medical expenses associated with prolonged hospitalization (A Consensus Conference, Ravenna, 2006). Elemental oxygen is required to maintain cellular respiration and allow normal cellular protein production. Therefore, HBOT is considered a method for augmenting oxygen availability to tissues. Oxygen is also an important mediator of wound healing and its availability influences wound healing rates. Tissue trauma leads to decreased oxygen delivery precisely to the damaged tissue which needs the oxygen most because of the tissue's immediate increased demand for oxygen to perform the wound healing process (14). Therefore, trauma-related blood flow reduction or elimination induces hypoxia, which stops cell energy production, stops wound healing (15), and interfere with many components of wound healing causing the slowing of the healing process, especially during the critical inflammatory phase of wound healing (16). The presence of oxygen, especially in increased concentrations, which reduces wound edema (17) significantly enhances the rate of wound healing (14). Thus, there is a direct relationship between the available amount of oxygen in the wound and the rate of the healing processes (18), with part of this being directly related to the need for oxygen in the inflammatory phase of wound healing (16).

HBOT is critical to the treatment of chronic non-healing wounds due to its inducing angiogenesis, which is promoted by the increased oxygen gradient caused by HBOT (19). Decreased edema noted following HBOT allows better diffusion of oxygen and nutrients through tissues while also relieving pressure on

surrounding vessels and structures (20). In this light, HBOT has been used for treating venous and arterial insufficiencies, burn wounds, crush injuries, marginal flaps, and skin grafts. Before initiating HBOT, it is important to optimize the patient's overall medical status, facilitate nursing care of the patient, and address local wound care and dressing (21).

HBOT is advocated for the treatment of severe trauma of the limbs in association with surgery because of its effects on peripheral oxygen transport, muscular ischemic necrosis, compartment syndrome, and infection prevention (22). Thus, HBOT is effective in improving wound healing and reducing repetitive surgery and is a useful adjunct in the management of severe crush injuries of the limbs (22).

Oxygen Mapping

Delivery of 100% oxygen under elevated pressure causes a systemic increase in blood oxygen concentration, while the elevated pressure leads to a significantly increased oxygen transfer from the blood to all body tissues, but with the specific aim of increasing oxygen transfer to tissues under stress to enhance the rate of wound healing, a reduction in wound edema (17, 23), reducing muscular ischemic necrosis and compartment syndrome, and preventing infection by killing bacteria within a wound in an oxygen dependent manner (24), thus leading to recovery from trauma or stress (25). An appropriate candidate for HBOT treatment is a patient who has local ischemia but responds to the oxygen challenge.

Under normal conditions, 97.5% of oxygen is carried in the bloodstream bound to hemoglobin, with the remaining 2.5% dissolved in plasma. Oxygen is combined with hemoglobin in the bloodstream, with each gram of hemoglobin combined with 1.34 cm3 of oxygen, the maximum physiologic maximum carrying capacity. Under normal conditions at sea level, the arterial hemoglobin saturation is 97%, and the venous hemoglobin saturation is 70%. The oxygen content can be calculated according to Henry's law that "at a constant temperature, the amount of a gas that will dissolve in a liquid is proportional to the partial pressure of the gas" (26).

A hyperoxic challenge (100% oxygen for 20 min) normally increases the transcutaneous oxygen reading to greater than 300 mm Hg (25). Generally, responses less than 50 mm Hg require a vascular workup, and HBOT likely is of little benefit. Patients with intermediate responses may benefit from HBOT. The response to the HBOT by further transcutaneous oxygen should be tested after 14-20 sessions of HBOT.

Systemic vs. Topical Hypobaric Oxygen Therapy

It is critical to make a distinction between systemic HBO and topical oxygen, because they are entirely different (27). Topical oxygen involves the use of an airtight chamber or polyethylene bag sealed around a limb or the trunk by a constriction / tourniquet device or tape. High oxygen flow (usually 10 liters per minute) is introduced into the bag and over the wound at a pressure only slightly above 1.0 atmosphere (28). Systemic HBOT involves 100% oxygen presentation in an environment of up to 2.4 atmospheres of pressure (29). An additional difference between the two techniques is that topical oxygen therapy does not provide the oxygen penetration of the tissue to which it is delivered at the same concentration as when it is inspired.

Topical oxygen is advocated for the diffusion of oxygen into the wound adequate to enhance healing, and its delivery is less complex and expensive than HBOT. Data on the influences of topical oxygenation come mostly from small and non-randomized studies on a variety of wound types . Although comparative studies have shown that topical oxygen is effective, more extensive controlled studies are required to be certain about the reliability of its apparent effects, and in which cases it may be more effective and more economical than HBOT.

HBOT benefits the acceptance of ischemic split-thickness skin grafts when there is a risk of their not taking, flap survival and salvage, wound re-epithelization, recovery from techniques in plastic and reconstructive surgery, and repair of crush injuries and acute post-traumatic limb ischemia. HBOT is also useful for healing include: traumatic brain injuries preorbital reconstruction, gas gangrene, compartment syndromes, acute traumatic ischemia, enhancement of healing in selected problem wounds (ulcers and diabetic ulcers), exceptional blood loss anemia, necrotizing soft tissue infections, thermal burns (30). HBOT has been advocated, both as an adjunctive or primary form of treatment, for a variety of disorders, including, osteoradionecrosis, and carbon monoxide poisoning, irradiation non-healing wounds to improve ischemic wounds before skin grafting.

HBOT Protocols

HBOT for wound healing, compromised skin graft and/or flaps, thermal burns, crush injury and/or compartment syndrome, involves 2.0-2.5 atmospheres with 100% oxygen. In some cases, such neuroprotection against transient focal cerebral ischemia, even higher pressures (3 atmospheres), are more effective. However, in some cases, such neuroprotection against transient focal cerebral ischemia even higher pressures, such as 3 atmospheres are even more effective, while for anoxic brain injuries, autism and other brain research, atmospheres of 1.3-1.8 pressure are used.

HBOT induces an 8- to 9-fold increased vascular density over both normobaric oxygen and air-breathing controls and oxygen appears to require hyperbaric pressures to generate its therapeutic effects on chronically hypovascular irradiated tissue. Therefore, researchers conducting wound-healing studies continue to try to take advantage of the angiogenic properties of increasing oxygen gradients resulting from HBOT. Prospective blinded randomized trials and well-executed laboratory studies continue to define further the role of HBOT in medical therapeutics.

Appropriate HBOT use and patient recovery requires proper supervision by a physician trained in its use, and who works closely with a surgeon. When ethically used for appropriate indications, it is a useful adjunct to surgical practice.

Local wound management with appropriate debridement, irrigation, infection control, and daily dressing changes are required to aid in healing. Patient positioning and pressure relief with special beds, orthosis, or splints may be necessary to optimize the local wound milieu. Patients should be advised to stop smoking, since nicotine adversely affects the wound's vascularity and increases potential complications of HBOT. The general approach to these problem wounds is therefore multidisciplinary.

Reperfusion Injuries

The benefits of HBOT on ischemic insults, ischemia reperfusion injuries, and crush injuries have been subject to controversy. These injuries result from the reperfusion that follows an extended period of ischemia. Oxygen free radicals rise, thromboxane A2 and adhesion molecules are activated, platelet aggregation occurs and vascular vasoconstriction activity is increased. The endothelium is damaged, which promotes vascular leakage, edema, and thrombosis. Tissue necrosis ensues, and the activation of white blood cells is pivotal to the reperfusion injury. Using HBOT, which may increase oxygen free radical production, to benefit the reperfusion injury seems paradoxical. But, HBOT promotes hyperoxygenation and vasoconstriction to decrease edema and neurovascularization and inhibits neutrophil activation, preventing margination, rolling, and accumulation of white cells (31). Neutrophils therefore are not permitted to produce detrimental oxygen free radicals.

Basic Requirements for Axon Regeneration

Oxygenation and angiogenesis

Certain characteristics of wounds, such as ischemia and lack of healing, are similar to the hypoxic situations that occur following nervous system trauma that destroy arterial flow to the nervous and associated tissues. These tissues require oxygenation to prevent necrosis, which itself creates a permanent toxic environment that inhibits axon regeneration. Therefore, by its immediate providing enhanced oxygenation to and subsequent induction of angiogenesis of ischemic nervous and tissues associated with axons, HBOT induces the survival and healing of cells critical to axon regeneration, such as Schwann cells and endothelial cells, as well as axons themselves.

Inducing processes required for Axon Regeneration

Initiation of the induction of the axon regeneration process starts with the migration of macrophages into the site of a nerve trauma where they proliferate and phagocytize the degenerating axons and myelin debris (32). Enhanced metabolism is required to promote proliferation of Schwann cells, which both contribute to debris phagocytosis and the synthesis and release of neurotrophic factors required to promote axon regeneration (33, 34).

Axon regeneration requires angiogenesis to permit glycolysis by the surviving axons and associated tissues. Glycolysis is necessary for protein synthesis required for axon elongation, proliferation of macrophages, Schwann and other cells, and to allow Schwann cells to ensheathe and myelinate axons (33, 35). This can be accomplished by HBOT inducing hyperoxygenation of the damaged tissues and angiogenesis as discussed earlier.

Collagen Synthesis and Deposition

Both the synthesis and deposition of collagen are essential for axon regeneration to provide the scaffold of developing new nerve (36). As discussed earlier, HBOT induces collagen synthesis and deposition.

One fundamental challenge in inducing axon regeneration following nerve trauma that creates a nerve gap, lies is the technique required to repair the nerve gap. The standard technique involves bridging the nerve gap with nerve grafts. Vascularized nerve grafts are significantly better at inducing axon regeneration than non-vascularized grafts, but are never used because of the great difficulty in obtaining such grafts. Therefore, non-vascularized nerve grafts are used, and they can rapidly become necrotic, which inhibits axon regeneration. Further, upon reperfusion of the ischemic nerve grafts, reactive oxygen species are generated which inhibit axon regeneration (37). Therefore, HBOT could promote and enhance axon regeneration by reducing ischemia of nerve and associated tissues, ischemia of nerve grafts and their subsequent necrosis, as well as by reducing edema, and suppressing activation of thromboxane A2 and adhesion molecules, platelet aggregation, vascular vasoconstriction activity, free radical oxygen production, inhibiting neutrophil activation, and preventing margination, rolling, and accumulation of white cells (31).

Growth and Wound Healing Factors

Just as wound healing requires growth-, neurotrophic- and wound-healing factors, they are also essential for promoting for promoting axon regeneration the healing of nerve trauma sites (8). Some of these factors are provided by platelet that infiltrate nerve trauma sites, where they promote axon regeneration by mediating chemotaxis of neutrophils, monocytes, and fibroblasts into the wound (9). Similarly, axon regeneration-promoting factors are provided by the infiltration of leukocytes, specifically helper T cells as discussed above, and are involved in stimulating and activating macrophages, responsible for wound debridement and the release of growth and regeneration factors. All of this is induced by HBOT.

Bacterial infection

Like other types of wounds, traumatic nerve injuries and hypoxia make these sites prone to bacterial infections, which contribute to poor axon regeneration. HBOT treatment both pre- and immediately post- surgery would assist in the reduction of bacterial infection which could retard both the wound healing and axon regeneration.

Data supporting the Hypothesis that HBOT Induces Axon Regeneration

HBOT decreases cerebral edema, normalize water content in the brain, decrease the severity of brain infarction, and maintain blood-brain barrier integrity. HBOT attenuates motor deficits, decreases the risks of sequelae, and prevents recurrent cerebral circulatory disorders, thereby leading to improved outcomes and survival (38). For the damaged brain, HBOT inhibits neuronal death, arrest the progression of radiation-induced neurologic necrosis, improve blood flow in regions affected by chronic neurologic disease and aerobic metabolism in brain injury, and accelerate the resolution of clinical symptoms. Hyperbaric oxygen has also been reported to accelerate neurologic recovery after spinal cord injury by ameliorating mitochondrial dysfunction in the motor cortex and spinal cord, arresting the spread of hemorrhage, reversing hypoxia, and reducing edema (38).

HBOT can even reverse hydrogen peroxide gas embolism-triggered mental state deterioration. Clinical studies have shown that following fluid-percussion and cortical contusion brain injury HBOT combined with moderate systemic hypothermia reduced the mortality rate and led to neurological improvements (39), and Hyperbaric oxygen combined with nicardipine administration accelerates neurologic recovery after cerebral ischemia. Finally, the results of HBOT in the treatment of patients with stroke, atherosclerosis, cerebral palsy, intracranial pressure, headache, and brain and spinal cord injury indicate that HBOT is a promising effective technique, and warrants further testing for its ability to induce neurological recovery following CNS trauma.

Nerve regeneration in diabetes is essential for reversal of neuropathy as well as the recovery of nerves from injury due to acute nerve compression and entrapment. Endoneural hypoxia due to hyperglycemia-induced blood flow reductions is observed early in the course of diabetes, and the resultant ischemia plays a role in the diminished neural regeneration. HBOT produces tissue hyperoxia by raising oxygen tensions in ischemic tissues, and is beneficial in the reversal of experimental ischemic neuropathy. In a diabetes model, no benefits of HBOT were found in the early stages of diabetic nerve regeneration (40). Similarly, no difference in axon regeneration was seen in the rate of regeneration following a nerve crush for HBOT treated and control animals (41). In the case of a sciatic nerve transection and entubation in a silicon tube with a gap between the nerve ends, no differences were seen between HBOT treated animals and controls (42). However, in the absence of a matrix within the bridging tube no difference should have been expected.

In the case of the transection of sciatic nerves and the immediate grafting of a 1 cm autologous sciatic nerve graft between the ends of the sciatic nerve, HBOT induces enhanced rates of axon regeneration when the animals were placed at 3.2 atmospheres and treated with 100% oxygen (43). Similarly, HBOT increased the rate of axon regeneration following nerves being crushed or transected and the ends anastomosed (44).

The beneficial effect of HBOT on sensory axon regeneration is not dose-dependent between 0.5 and 2.5 atmosphere of oxygen (45). Although the exposure to 2.5 atmosphere of oxygen moderately enhanced early regeneration of the fastest sensory axons, it decreased the number of regenerating axons in the injured nerves with compromised blood perfusion of the distal nerve stump (45). However, HBOT treated animals showed significantly longer axon growth from crushed nerves than that of control animals (46) and significantly accelerated and more extensive more neurological recovery (47). Clinically HBOT has been shown to induce enhanced axon regeneration (48). In a case study, HBOT was effective in inducing axon regeneration in nerves with longer delays between trauma and HBOT compared to the results with freshly injured nerves (49).

Conclusions

Abundant evidence has shown that HBOT is an extremely important and valuable tool for inducing healing of many types of wounds. The mechanisms by which HBOT induces wound healing are well documented. Some of these mechanisms are the same as those that induce axon regeneration, and anecdotal evidence suggests that HBOT induces axon regeneration. These data suggest that, thorough studies should be performed to determine whether promoting axon regeneration is another form of wound healing that can be induced by HBOT.

Resumen

Las heridas siempre han afligido a la humanidad causando dolor, sufrimiento y muerte. La humanidad por miles de años ha examinado y desarrollado varias técnicas para inducir la sanación de heridas. La terapia de oxígeno hiperbárica consiste en colocar a un paciente o una de sus extremidades en una cámara, en la que se eleva la presión varias veces por encima de la presión ambiental, y el aire ambiental es sustituido por 100% oxígeno. La terapia de oxígeno hiperbárica es efectiva en incrementar el grado y efectividad de la sanación de diversos tipos de lesiones y heridas. El mecanismo por el cual la terapia de oxígeno hiperbárica actúa es ampliamente entendido. Una pregunta de gran importancia es si la terapia de oxígeno hiperbárica es capaz de sanar otro tipo de heridas, como la de daños a los nervios luego de algún trauma. Esta revisión discute

primordialmente el mecanismo por el cual la terapia de oxígeno hiperbárica induce los procesos complejos de la sanación de heridas. Luego, examina cómo algunos de estos mecanismos también están envueltos en promover la regeneración de axones. Finalmente, presenta evidencias anecdotales, las cuales sugieren que la terapia de oxígeno hiperbárica promueve la regeneración de axones, pero entiende que se requieren más extensos y cuidadosos estudios para determinar si la terapia de oxígeno hiperbárica induce la regeneración de axones.

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