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The Role of Hyperbaric Oxygen Therapy in Crush Injuries

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Hyperbaric oxygen therapy has been approved for primary or adjunctive care in 14 indications. A hyperbaric environment exists when a patient's whole body is physically exposed to 100% oxygen and pressure that is greater than one atmosphere absolute. Hyperbaric oxygen therapy works through the ideal gas laws and is effective as an adjunctive therapy in the treatment of crush injuries. Oxygen is considered a drug and can have contraindications and adverse effects. Hyperbaric therapy works through several different mechanisms in the crush injury. Effects of hyperoxygenation, reduction of edema, infection control enhancement, blood vessel and collagen formation, and reduction of free radicals and reperfusion injury help in healing in patient with crush injuries. **Key words:** *acute traumatic ischemia*, *angiogenesis*, *crush injury*, *crush syndrome*, *hyperbaric oxygen therapy*, *reperfusion injury*

IT LOOKS LIKE A "high tech" submarine with some serious size portholes. The "dives" are scheduled depending on the indication. It works through the laws of oxygen theory. For those with a crush injury, it could mean the difference between limb salvage and an amputation. Hyperbaric oxygen therapy (HBOT) can be the answer that makes the difference.

HYPERBARIC OXYGEN THERAPY

A hyperbaric environment exists when a patient's whole body is physically exposed to 100% oxygen and atmospheric pressure that is greater than 1 atmosphere absolute (ATA).[1] The typical hyperbaric oxygen treatment takes place at a pressure of 2.0 to 2.4 ATA. The duration of the treatment depends on the indication but is generally 90 to 120 minutes long and 1 to 2 treatments per day, 5 days a week. The indication dictates the longevity of the treatment.

Hyperbaric oxygen therapy is delivered in either monoplace chambers or multiplace chambers with hoods.[2] Monoplace chambers are cylindrical Plexiglas tubes with metal end caps. The patient reclines during his or her treatment and converses with the technician through an intercom. They are able to watch TV mounted to the outside of the chamber. The disadvantages are lack of quick access during patient compromise and the small space that may trigger anxiety from claustrophobia. Multiplace chambers allow the patient to enter a chamber that can hold up to 12 patients seated comfortably. A technician enters the hyperbaric chamber with them during the "dive." The multiplace chamber is pressurized with ambient air and not oxygen, so the patients place an oxygen hood over their head that will deliver 100% oxygen during the treatment. The disadvantages are the high initial cost and space for the chambers and the possible trauma to the technicians secondary to the effects of pressurization. Due to the high level of nitrogen in the inspired air the technician breathes, decompression sickness is possible.

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Because of the oxygen-rich environment, the patients must be carefully screened for any product on their body or clothes that could generate a spark.[2] Strict guidelines are in place during hyperbaric treatments. Patients wear 100% cotton fabrics and do not apply lotions or wound care products that contain petroleum or alcohol-based products.

Hyperbaric oxygen treatment costs at the average US hospital are a charge of $1800.00 per 90-minute HBOT treatment.[3] Many insurance companies will reimburse for HBOT services for approved indications; however, they may have different guidelines and should be consulted. Overall, there are limited cost analysis studies done for HBOT. Future studies should also identify and analyze the impact of HBOT on factors such as pain scores, patient satisfaction, quality of life, and activities of daily living.[4]

PHYSICAL LAWS OF HBOT

It is necessary to understand the gas laws to understand HBOT. At the end of the 18th century, scientists began to notice a relationship between pressure, temperature, and volume of gas that held true for all gases. When pressure of gases is discussed, the pressure of 1 atmosphere (ATM) is equal to 760 mm Hg, or 14.7 lb/in^2 being applied to your body.[5] When a patient is placed in a hyperbaric chamber, it is equivalent to him or her diving to 33 ft below sea level where a diver would be at a pressure of 2 ATA.

The mechanical effect of HBOT follows the physical law described by Robert Boyle in 1662, which states that as barometric pressure increases, the density of the gas molecules increases.[5] When a patient is in the hyperbaric chamber, the amount of space that the gas molecules occupy in an enclosed body space, such as the sinus, gastrointestinal tract, lung, and ears, will contract or decrease as the pressure increases and allow for more oxygen molecules to enter the space. If the pressure is doubled, then the gas will be drawn closer together and only occupy half the space, doubling the number of gas molecules, if the pressure is tripled, and then it will contract to about a third of the original space occupied and triple the amount of gas molecules. During decompression, the gases will begin to expand and the gas molecules will occupy the same space as before the therapy. This law also explains some unwanted effects that occur on decompression, such as sinus and middle ear squeeze or a burst lung if a patient holds his or her breath during decompression. Positive effects in HBOT created by Boyle's law cause the oxygen molecules in the alveolus to become more dense and present more oxygen molecules to diffuse to the blood.

In HBOT, the physiologic effect follows the physical law described by William Henry in 1803, Henry's law. This law states that the amount of gas dissolved in a liquid is directly proportional to the partial pressure of the dissolved gas that has contact with it.[6] By raising oxygen tension in inspired air in the alveolus, this would then increase the blood oxygen level. For example, sea-level air contains 21% oxygen, 78% nitrogen, and 1% other gases. When the percentage of oxygen the patient receives is increased to 100%, it increases the oxygen pressure in the alveoli 4.8 times. When the patient is placed in HBOT at 2.0 ATA with 100% oxygen, the oxygen pressure is increased to 9.6 times greater than air at sea level. With the oxygen pressure (tension) far greater in the alveoli than in the systemic blood vessel, it diffuses into the capillary blood and hyperoxygenates it.

Normally, oxygen is transported from the lungs to the rest of the body attached to hemoglobin, with a small amount dissolved in the blood plasma.[5] At sea level, 97% of the hemoglobin attaches to oxygen and forms oxyhemoglobin. Breathing air at sea level, the blood plasma carries a small amount of oxygen, approximately 0.31 mL of dissolved oxygen per deciliter of blood. Exposing patients to HBOT increases the oxygenation in the blood plasma but does not significantly affect the hemoglobin. The amount of

dissolved oxygen in the blood plasma increases linearly as the partial pressure of oxygen increases.[5] As the pressure increases from the HBOT, the more oxygen can be dissolved in the blood plasma and disbursed to the rest of the body. When breathing 100% oxygen at sea level, the blood plasma carries about 2.1 mL of dissolved oxygen per deciliter of blood. When the patient is then subjected to 2 ATA, the blood plasma carries about 4.4 mL of dissolved oxygen per deciliter of blood. This hyperoxygenation increases blood plasma oxygen content to the level where at 3 ATA it could support human function nearly devoid of erythrocytes.[7]

Dalton's law describes that in a mixture of gases, each gas exerts its own pressure in relationship to the proportion of the total volume of that gas. Then, the sum of the individual gas pressures equals the total pressure exerted. For example, in air at sea level, approximately 21% of the air is oxygen and approximately 78% is nitrogen.[6] The pressure exerted by oxygen in the air we breathe at sea level is 21% × 760 mm Hg, or 159.6 mm Hg. Adding 100% oxygen at sea level increases oxygen pressure to 100% × 760 mm Hg, or 760 mm Hg. If the patient is exposed to HBOT at 2 ATA, then the pressure of 100% oxygen (760 mm Hg × 2) would be 1520 mm Hg. That is 9.6 times greater oxygen pressure than at sea-level breathing air.

Graham's law states that oxygen and carbon dioxide move independently from an area of greater pressure to an area of lower pressure. As the blood passes through the capillaries in the alveoli, the higher gas pressure (concentration) of oxygen in the alveoli moves oxygen into the blood, which is a lower oxygen pressure (concentration). If the concentration or pressure of oxygen can be increased in the alveoli through HBOT, then more oxygen will saturate the blood plasma to be carried throughout the blood. In the peripheral circulation, the blood will also have a higher oxygen pressure than the surrounding tissue oxygen pressure and therefore will diffuse into the tissues.

CONTRAINDICATIONS

An absolute contraindication to hyperbaric oxygen therapy is an untreated pneumothorax. Relative contraindications to therapy include pregnancy, emphysema, pneumonia, bronchitis, cardiac disease, recent thoracic surgery, and hyperthermia. Upper respiratory and viral infections, implanted pacemakers, and optic neuritis are also relative contraindications.[2] There was a concern that HBOT may promote cancer growth. Studies by Feldmeier et al[8] concluded that a history of malignancy should not be considered a contraindication for HBOT.

Chest radiographs should be ordered on patients with a strong suspicion of obstructive lung disease to rule out any significant trapping of air in the lungs or untreated pneumothorax.[1] Patients with a history of seizure disorder should be assessed for seizure activity and control. Patients receiving chemotherapy drugs, cyclophosphamide and the anthracyclines, Daunorubicin (Daunamycin) and Doxorubicin (Adriamycin) that exert their tumoricidal effects through the generation of oxygen-free radicals are contraindicated in HBOT.[2,9] HBOT enhances the toxicity of these drugs and is therefore contraindicated. The reason a history of bleomycin therapy is contraindicated is that it is thought to pose a possible lifelong threat of oxygen toxicity.[2] HBOT is also contraindicated for patients on medication therapy with disulfiram (Antabuse), mafenide topical (sulfamylon) and cisplatin.[10] Torp et al[11] recently conducted a retrospective study of 14 patients that had received hyperbaric oxygen therapy within 2 years of their last bleomycin exposure. There were no adverse pre- to post-HBOT changes in arterial blood gases, spirometry, chest radiograph findings, or clinical reports. There were no persistent post-HBOT pulmonary complications on follow-up. Through discussion, the authors recognize that bleomycin and oxygen can individually cause acute pulmonary toxicity. However, based on this study, they feel that

evidence for increased long-term susceptibility based on the synergy may be overstated.

ADVERSE EFFECTS

Any time that oxygen is delivered, it is considered a medication or therapy and can have adverse effects as well as therapeutic effects.[12] Cerebral oxygen toxicity, barotrauma to the middle ear, and anxiety in a closed space are possible effects of HBOT. Seizures are not common when oxygen pressures are below the threshold for seizures and a pretreatment examination is completed. Patients having trouble equalizing the pressures on either side of the tympanic membrane may need to pinch the nose and perform the Valsalva maneuver.[2] Approximately 1% to 4% of patients are unable to clear their ears and will require myringotomy tubes or risk trauma to the eardrums.[9]

INDICATIONS

Hyperbaric oxygen therapy is a primary and adjunctive therapy for 14 health care problems.[13] Primary indications for hyperbaric therapy are air/gas embolism, carbon monoxide poisoning and/or complicated by cyanide poisoning, and decompression sickness. Hyperbaric therapy is used as an adjunctive therapy for crush injury, compartment syndrome, and other acute traumatic ischemia, clostridial myositis, and myonecrosis (gas gangrene) in which there is an acute compromise to the oxygenation of tissues. Hyperbaric therapy is also useful for the treatment of arterial insufficiencies, such as central retinal artery occlusion and enhancement of healing in selected wounds problem (Wagner 3 and higher grade diabetic foot wounds), severe anemia, intracranial abscess, necrotizing soft tissue infection, and chronic refractory osteomyelitis. Other indications are compromised skin grafts and flaps, delayed radiation injury (soft tissue and bony necrosis), acute thermal burn injury, and idiopathic sudden sensorineural healing loss. Of interest for acute care would be crush injury, compartment syndrome, and other acute traumatic ischemias.

CRUSH INJURY, COMPARTMENT SYNDROME, AND ACUTE TRAUMATIC ISCHEMIA

Crush injuries vary from skin tissue trauma to injury of the bone, muscles, and tendons and describe a defect caused by a high pressure force.[14] Crush injuries most commonly occur after natural or man-made disasters.[15] The most severe case of muscle injury is called a "crush syndrome" while less severe forms of crush syndrome are compartment syndromes and Volkmann ischemic contracture (McCance & Huether, 2006).

Crush syndrome received increased attention during treatment of injuries after the London air raids of World War II were publicized.[16] In more recent years, it has been seen in patients who have been found unresponsive and immobile in alcohol and drug overdoses. The weight of an immobile limb alone can cause enough pressure to decrease blood flow to the muscle in that area. Rhabdomyolysis is a severe complication that can result from severe trauma or crush to muscle tissue. When the sarcolemmal membrane of the muscle cell incurs disruptions, called "holes or delta lesions," myoglobin, creatine kinase, and phosphate are released. The release of myoglobin into the systemic circulation and into the kidneys creates myoglobinuria. Rhabdomyolysis can also occur in viral illnesses, status epilepticus, anesthetic drugs, cholesterol lowering drugs, electrolyte disturbances, tetanus, and fractures. Complications can also be seen after heat stroke, in athletes after intense workouts, and high-voltage shock.

In addition to rhabdomyolysis, generally crush injuries will have decreased blood flow related to damage to the tissue and edema.[14] Skeletal muscle compartment syndrome involves muscle and nerve damage. With this syndrome, edema and bleeding within the compartment rise and exceed the capillary

perfusion pressure and create an ischemic environment to the muscles and nerves within the compartment.

Once the tissue ischemia starts, the compartment can become more edematous and create tremendous pressure that will damage muscle and neural cells.[16] In addition, the damage to the blood vessels can lead to decreased arterial flow, transudation (edema formation), interstitial bleeding, and obstruction.[17] Resulting ischemia and hypoxia can then in turn cause interruption in the cell metabolism, disrupting the cell membrane and releasing cellular water, increasing edema. As edema increases and compartment pressures begin to exceed arteriolar pressures, a physical collapse of the arterioles and diminished oxygen transfer across the capillary endothelium take place.

Priority in therapy is treating the underlying disease and preventing renal failure.[16] Compartment syndrome, secondary to edema, may require emergency treatment due to increased venous pressure, decreased arterial flow, and ischemia. Immediate fasciotomy and clinical debridement are indicated and are the standard of care for acute compartment syndrome and venous pressures greater than 30 mm Hg.

Hyperbaric therapy has been proposed to be the sole therapy to prevent compartment syndrome in early stages and to decrease the tissue fluid pressure within the compartment.[13] Although not recommended during the "suspected" stage of injury, HBOT is suggested when objective signs are noted, such as pain, weakness, pain with passive stretch, and/or tense compartment with or without fasciotomy.[18] Adjunctive HBOT is an effective treatment of severe and refractory musculoskeletal injuries and may improve outcomes in lifesaving and limb-saving events in appropriate candidates.[19] When HBOT was used as an adjunctive therapy, it was found to be an effective treatment modality causing a reduction in length of stay, a reduction in surgical procedures, and wound care costs.[19]

Latham et al[18*] suggest that HBOT should be started as soon as possible, ideally within 4 to 6 hours after injury or surgery at 2 to 2.5 ATA for 60 to 90 minutes. The patient should receive HBOT 3 times daily for 2 to 3 days, followed by twice daily for 2 to 3 days, and finally daily for 2 to 3 days.[18] Many insurance companies will reimburse for HBOT services for approved indications; however, they may have different guidelines and should be consulted. Nelson et al[20] demonstrated that when HBOT is delayed greater than 16 to 18 hours post–crush injury, it could decrease the effectiveness of the treatments. This study reinforced previous studies by Strauss et al[21] that demonstrated efficacy in crush injuries in dogs that received immediate HBOT and repeated 1-hour sessions every 4 hours for 10 hours.

Hyperbaric therapy works through several different mechanisms in crush injury—hyperoxygenation, reduction of edema, infection control enhancement, blood vessel and collagen formation, and reduction of free radicals and reperfusion injury in crush injuries.

HYPEROXYGENATION EFFECTS OF HYPERBARIC THERAPY ON CRUSH INJURY AND COMPARTMENT SYNDROME

Ischemic tissue

The gas law described by William Henry explains the physiological effect taking place during HBOT that impacts ischemic tissue. Oxygen tension upon a cell is affected by an equilibrium that is created by the oxygen requirements of the cell versus the oxygen supply of the tissue around the cell.[22] The oxygen tension is also impacted by the atmospheric oxygen tension and the amount of circulating blood in the lungs. Survival of

*As found in Kindwall E, Whelan H. *Hyperbaric Medicine Practice*. 2nd ed. Flagstaff, AZ: Best Publishing Company; 2004: chap 1, 18, 19, 20, 25, 29, 30.

tissues is directly dependent on the oxygen tensions.[23] Increased oxygen tension around the alveolar capillary forces oxygen from an area of higher pressure to an area of lower pressure in the blood. As discussed previously, the HBOT increases the oxygen tension approximately 10 times that at sea level and then in turn hyperoxygenates the blood plasma. Blood and blood plasma that are hyperoxygenated are then able to circulate through the body to damaged tissue and increase oxygenation to those cells. Volumetric levels of diffusion achieved with hyperbaric oxygenation are 2 to 3 times those obtained under standard conditions.[1] Studies by Bowersox et al[24†] found that oxygen to threatened ischemic tissue was increased by a factor of 3 when treated with HBOT at 2.0 ATA in a 100% oxygen atmosphere twice daily for 90 minutes approximately 5 to 7 days and then 120 minutes daily until sustained clinical improvement was seen. Cell ischemia is directly dependent on the perfusion to the crush injury and indirectly affected by surrounding edema and compartment syndrome.

Transcutaneous oximetry (TCPO2) can measure the amount of oxygen that diffuses from the arterial capillary bed to the epidermis of the skin surface, known as oxygen tensions in the tissue.[25] Mathieu et al[25] discovered that the bilateral perfusion index which is calculated by taking a ratio of the TCPO2 pressure of the injured limb and the TCPO2 pressure of the uninjured limb in hyperbaric oxygen was a strong predictor of recovery or a need for amputation in traumatic wounds. TCPO2 can be measured on room air at sea level and during HBOT to determine effectiveness of the HBOT therapy.[26] Campagnoli et al[26] showed that there was a correlation in healing based on the rise and fall of the TCPO2 values under HBOT conditions and therapy. The faster the rise in the TCPO2 level on initiation of the HBOT treatment, the better the evidence of a strong microcirculation. A fast fall at the end of HBOT treatment was more indicative of an absence of microcirculation.[26] During HBOT at 2.0 to 2.4 ATA, TCPO2 values that reached a minimum of 200 mm Hg within 10 minutes in the affected limb accurately predicted healing success in 78% of the patients in a recent retrospective cohort study by Feldman-Idov et al.[27] Oxygen levels can remain elevated up to 1 to 3 hours after treatment depending on variables and metabolic rate.[28]

Edema/vasoconstriction

Edema is an accumulation of body water in the interstitial spaces.[16] Two-thirds of the body's water (28 L) is in the intracellular fluid and one-third (14 L) is in the extracellular fluid compartments. The main compartments of the extracellular fluids are the interstitial fluid and the intravascular fluid or the blood plasma. Increased capillary membrane permeability, as in a crush injury, can lead to edema. The damage to the capillaries secondary to crushing injury causes a release of proteins from the blood plasma and a decrease in oncotic pressure, therefore, a subsequent loss of fluids out of the vascular system. An increase in proteins in the interstitial fluid draws the fluid into that space. As the interstitial fluid increases, the pressure can exceed the pressure of small arterioles and capillaries and diminish microcirculation. Edema impacts the healing of wounds by (1) decreasing the blood flow through the collapse of arterioles and (2) increasing the distance through which the tissue oxygen must transit to get to the tissue needing repair. As swelling continues, compartment syndrome can occur if the fluid is confined to an area and creates high pressures.

Edema can be decreased by HBOT by increasing the partial pressure of oxygen which causes vasoconstriction and a reduction of blood flow by 20% in injured muscles.[29] Vasoconstriction of the capillaries is caused by the effects of a high oxygen concentration having a direct vascular smooth muscle contractile stimulus causing arteriolar vasoconstriction[9] and the effect of high arteriolar oxygen

†Found in McCrary B. Hyperbaric oxygen treatment for a failing flap. *Postgrad Med J*. 2007;83(975):e1-e3.

tension in the chemoreceptors.[30] Despite the 20% reduction in blood flow, the plasma oxygen tension levels are so high, it does not impair the oxygen delivery to the tissue. The vasoconstriction, however, does help to decrease capillary leakage, diapedesis, compartment syndrome, and edema.[30] This change in the capillary blood pressure will affect the flow of fluid across the capillary and increase the resorption of extravascular fluid, decreasing the pressure on the capillaries and improving the blood flow.

Studies by Strauss et al[21] showed that edema was decreased in compartment syndrome through vasoconstriction. In this study, dogs with induced compartment syndrome were exposed to HBOT at 2 ATA for 1 hour, then a 4-hour break, which was repeated 2 times. Their findings showed that the HBOT significantly reduced muscle damage in the experimentally produced compartment syndrome in dogs. They concluded that HBOT may be useful when immediate surgical decompression is not possible, when there is an impending compartment syndrome but surgery is not yet indicated, and after surgical decompression. Following this study, another canine study by Skyhar et al,[12] in 1986, showed that HBOT significantly reduced edema and tissue necrosis after an induced compartment syndrome even in a hypotensive state. The mechanisms of HBOT that affected the edema were postulated to be through vasoconstriction as is in the normotensive state. Sukoff and Ragatz[31] conducted a multifaceted therapeutic study of 50 patients with traumatic cerebral edema and found that HBOT was effective in reducing intracranial pressure by reducing cerebral blood flow, yet increasing cerebral oxygenation.

Infection

HBOT has a direct effect on infection control through the high oxygen concentrations that have a direct killing effect on anaerobic bacteria. In addition, HBOT assists indirectly at a cellular level providing needed oxygenation for intracellular killing.

Knighton et al[32] demonstrated that role of oxygen on bacterial host defense is significantly impacted by oxygen tissue perfusion surrounding infected tissue. The areas of tissue necrosis increased in experimental animals that received 12% and 21% supplemental oxygen but slightly decreased in animals receiving 45% oxygen. The number of bacteria present in the infectious necrosis showed a significant decrease with 45% inspired oxygen between 24 and 48 hours.

Babior[33] reported that neutrophil phagocytosis of bacteria triggers a series of metabolic changes that can result in a greater than 50-fold increase in oxygen consumption at the infected site. Hyperoxia enhances the oxygen-dependent neutrophil in its role of bacterial defense and also protects the injured tissue from ischemia, while the neutrophils consume oxygen to kill bacteria. Phagocytic killing of *S. aureus* was markedly decreased at 23 mm Hg of oxygen but significantly increased at 45 mm Hg and continued to improve as oxygen tensions increased.[34]

Mendel et al[35] experimented with rats with inoculated *S. aureus* to create osteomyelitis in the tibial bone. The rats were treated with hyperbaric therapy alone, cefazolin therapy, and a combination of cefazolin and HBOT, and improvement was found in all the groups. However, the largest improvement was in the group with the cefazolin and HBOT. Their results showed that HBOT alone was effective in the treatment of osteomyelitis and also had an additive effect when used in conjunction with an antibiotic.

Angiogenesis/blood vessel formation

During the acute inflammation period, macrophages (derived from monocytes) release angiogenesis factor to attract epithelial cells and vascular endothelial cells to begin the formation of vascular and lymphatic buds that will progress to new vessels.[16] Angiogenesis factors, vascular endothelial growth factor (VEGF), and basic fibroblast growth factor will stimulate the vascular endothelial cells to create capillary buds that will grow to promote healing in the injury. These buds are often referred to as "cobblestone" in the granulation tissue in a chronic wound.

There is a balance of proangiogenic (blood vessel forming) and angiogenesis inhibitors that keep blood vessel formation in check except for wound healing and pregnancy. Several proangiogenic factors that have been identified are VEGF, transforming growth factor-alpha, basic fibroblast growth factor, and angiopoietins. Specific inhibitors of angiogenesis are platelet factor-4, angiostatin, endostatin, canstatin, tumstatin, thrombospondin, and interferon alpha/beta.

In a study by Knighton et al,[36] angiogenesis was observed in a rabbit study with controlled oxygen gradients. These results showed that increasing the oxygen concentration caused an initial slowing of the capillary growth but then an increased growth rate after the first day. Decreasing the oxygen concentration initially resulted in increased rate of capillary growth but then progressively decreased. It was also noted that the density of the capillaries was also in direct relationship to the oxygen concentration delivered. They postulated that hypoxia in the wound stimulates the release of growth factors, one of which is the VEGF that stimulates increased capillary bed formation. This may have caused the initial slowing of capillary formation in this study; however, as time progressed, increasing the oxygen concentration led to a steeper oxygen gradient and increased angiogenesis.

Collagen production

Macrophages debride a wound through phagocytosis, and they also secrete several factors that promote healing.[16] Some of the factors are growth factors or cytokines, and they transmit signals to other cells or within one cell. One factor from the macrophage is transforming growth factor-beta that stimulates fibroblasts to secrete procollagen, a collagen precursor in a wound. Collagen is a prominent protein in the body and is made up of amino acids glycine, proline, and lysine. These amino acids are enzymatically changed during the synthesis of collagen. Cofactors needed for this synthesis and proper collagen function are iron, ascorbic acid, and molecular oxygen. Absence of these results in impaired or incomplete wound healing. Fibroblast growth factor, produced by multiple cells including fibroblasts, promotes cell survival and inhibits collagen synthesis. Other factors are fibroblast growth factor-2 and VEGF that stimulate vascular endothelial cells to create capillary buds that will grow into a wound.

Tompach et al[37] observed fibroblast proliferation in patients exposed to HBOT. They discovered that increased partial pressure of oxygen through HBOT led to an increase in fibroblast proliferation after exposure for 120 minutes. The fibroblast proliferation continued for up to 72 hours after the HBOT. The most effective response from the fibroblasts was at 2.4 ATA.

Kang et al[38] prepared human dermal fibroblasts in a serum-free medium and exposed them to 1.0, 1.5, 2.0, 2.5, and 3.0 ATA for 7 days. Fibroblast cultures that were exposed to 2.0 ATA showed a marked relative increase in proliferation after day 3 that proved to be statistically significant. They also observed the growth factors and found the secretion of basic fibroblast growth factor was significantly increased by HBOT on day 1 but then decreased to the same levels as the control. They concluded that daily HBOT enhances the growth of fibroblasts when administered to a critical degree since fibroblasts did not increase over the control at any pressure except 2.0 ATA. They postulated that fibroblasts possess the ability to respond to hyperoxia and HBOT affects growth factor production and fibroblast proliferation.

Reperfusion injury

Restoration of oxygen or reperfusion can cause additional trauma to a crush injury.[16] During an ischemic episode, excessive adenosine triphosphate consumption creates a buildup of purine catabolites, hypoxanthine, and xanthine. Upon reperfusion and the introduction of oxygen, these catabolites are metabolized by xanthine oxidase to create large amounts of superoxide and hydrogen

peroxide. In addition, a highly reactive free radical, nitric oxide is created. These radicals can all cause membrane damage. Neutrophils are extremely sensitive to these radicals and neutrophils attached to the endothelium enhance the process. These reactive free radicals can combine with lipids and affect bonds in the cellular membranes and cause cellular destruction.

HBOT reduces the occurrence of the biochemical processes that create a no reflow phenomenon or the failure of blood to reperfuse an ischemic area after the physical obstruction has been removed or bypassed.[9]

EVIDENCE-BASED PRACTICES

Systematic review

A systematic review was completed by Garcia-Covarrubias et al[39] using Eastern Association for the Surgery of Trauma recommendations for evidence-based reviews. After careful selection of published data, 9 documents fulfilled the criteria for a total of approximately 150 patients. One prospective controlled randomized trial with some limitations on design and 8 retrospective, uncontrolled, class III trials were evaluated. Lacking stronger studies, the committee concluded that adjunctive HBOT is not likely to be harmful and would be of most benefit if administered early. The evidence warrants further investigation into studies that include an accepted injury scoring system, standardized HBOT protocol, amputation and wound infection rate, healing time, long-term function, and cost-effectiveness. From their studies, they also determined that TCPO2 may be beneficial in triaging patients who are candidates for amputations.

Randomized controlled trial

Hyperbaric oxygen therapy and crush injuries were observed in a randomized controlled trial by Bouachour et al.[40] This trial was carried out to evaluate the effectiveness of HBOT as an adjunctive measure in the treatment of crush injuries in human limbs. Participants were randomized to receive HBOT or a placebo on admission. Participants were included in the study if they met the following criteria: acute injury of the limb classified as a type II or III depending on soft tissue injury per the Gustillo soft tissue injury classification, surgical management within 6 hours after injury, and no history of peripheral arterial disease. Patients were excluded if they were enrolled in another trial, suspected pregnancy, or neurological, pulmonary, or otorhinolaryngologic diseases contraindicated in HBOT. Thirty-six participants were enrolled in the study, 18 in each group. The hyperbaric treatments consisted of 90 minutes of 100% oxygen via facial mask at 2.5 ATA twice daily for more than 6 days. The placebo group received 90 minutes of air breathing via facial mask at 1.1 ATA twice daily for 6 days. The 4 primary study end points were wound healing (1) without tissue necrosis requiring surgical excision, (2) new major surgical procedures in relation to progressive and massive revitalization after entry in the trial, (3) time of healing, and (4) length of hospitalization. Evaluations of the effects of the treatments were measured by TCPO2 measurements at the first, fourth, eighth, and twelfth sessions. A bilateral perfusion index was calculated by determining the ratio between the TCPO2 of the injured limb and the TCPO2 of the uninjured limb. Complete wound healing without tissue necrosis requiring surgical excision was obtained for 17 patients in the HBOT group versus 10 patients in the placebo group. Adverse effects showed 2 additional surgical procedures needed in the HBOT group, while 8 additional surgical procedures were needed in the control group. In a subgroup of patients older than 40 years with a grade III soft tissue injury, wound healing was obtained in 87.5% of the patients versus only 30% in the placebo group. Secondary outcomes of the study evaluated amputations. There were no amputations in the HBOT group versus 2 in the control group. The results of this study suggest that HBOT is a useful adjunct in the management of crush injuries, especially in

the subgroup of patients older than 40 years with grade III soft tissue injury.

The Cochrane review by Eskes et al[4] assessed HBOT for treating acute surgical and traumatic wounds. After detailed study of the trials, only 3 were found that the authors felt met the inclusion criteria for their review. Because of the limited randomized controlled trials, they had insufficient data to support or refute the effectiveness of the HBOT. The limitations with their review were that the studies were small and did not have comparable studies. The Cochrane study group recommended further high-quality randomized controlled trials for acute surgical and traumatic wounds that are powered to meet FDA guidelines. The authors recommend that future studies include endpoints such as mortality, pain scores, quality of life, patient satisfaction, activities of daily living, TCPO2 increase, amputation and length of hospital stay and costs.

In conclusion, HBOT has a long history of primary and secondary treatment efficacy. The concepts are based on long-established gas laws and physiology and create effects in the human on a cellular level. Established and new concepts in the pathophysiological effects of HBOT are making it a more attractive adjunct for many indications. It is an effective wound care adjunctive therapy for crush injuries and compartment syndrome. Further studies will continue to expand on the cellular effects of the hyperoxia and the cost-effectiveness in wound closure. As HBOT becomes more available to institutions, cost-effectiveness and convenience will improve and create better opportunities for patients with crush injuries.

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