OXYGEN AND WOUND HEALING
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Oxygen is essential to several critical mechanisms in wound healing, including bacterial killing, angiogenesis, fibroplasia, and epithelialization. As a substrate, oxygen provides the respiratory burst necessary for white blood cells to kill engulfed bacteria, hastening resolution of inflammation so that a preliminary matrix can be formed for subsequent fibroplasia and epithelialization. Additionally, oxygen therapy makes the wound less hospitable to anaerobic bacteria that interfere with healing and to biofilm-producing bacteria that are more likely to develop antibiotic resistance. Mild, acute local hypoxia is considered angiogenic; however, chronic or severe hypoxia actually interferes with vascularization. Oxygen serves as a signal for angiogenesis, stimulating secretion of macrophage-derived vascular endothelial growth factor and increasing PDGF receptors and cell proliferation. Increasing wound oxygenation increases collagen deposition and wound tensile strength. Oxygen is also necessary for ATP production and protein synthesis.

About 50% of inspired oxygen crosses alveolar membranes and reaches the bloodstream. Total oxygen content within the blood consists of a dissolved (unbound) portion in the plasma and a larger portion that is bound to hemoglobin within red blood cells. Within the capillaries, oxygen moves along a concentration gradient into the tissues, with the unbound oxygen leaving the plasma first, followed by oxygen released as needed from hemoglobin. The dissolved oxygen is what forms the partial pressure of oxygen; therefore, its concentration is much more critical for driving diffusion than that bound to hemoglobin.

Under normal circumstances, pO₂ of subcutaneous tissues in people ranges from 55-70 mmHg. Poor wound healing is associated with decreases in tissue pO₂; for instance, healing after partial limb amputation was noted in only 11% of people with a pO₂ of <20 mmHg but occurred in >95% of people with a pO₂ of ≥30 mmHg.

Oxygen delivery is affected by local factors such as decreased blood supply (e.g., cardiovascular disease, radiation, vascular compression from swelling) or increased tissue thickness (e.g., edema). Most wounds contain pockets of moderate to severe hypoxia; with necrosis of these areas, subsequent inflammation and infection can affect adjacent tissues. Contributors to arterial hypoxia and subsequent delayed wound healing include pain, anxiety, hypothermia, hypovolemia, severe anemia, heart disease, severe liver disease, and respiratory disease.

Oxygen therapy is an adjunct treatment. It must be able to reach a wound; therefore, as a sole treatment it can only be expected to help those wounds in which cellular hypoxia is the only limiting factor to healing. Because of this, clinicians should first focus on the most fundamental aspects of wound care: fluid management, temperature control, analgesia, wound debridement, normalization of PaO₂, nutritional support, and treatment or prevention of infection. Tissue perfusion and oxygenation may require IV fluid administration, warm environmental temperature, and anxiolytics or analgesics to reduce peripheral vasoconstriction. Eschars, necrotic tissue, and debris must be removed from the wound to reduce inflammation and infection and improve vascularization. For systemic oxygen administration, the distance between the capillary bed and the wound must be minimized by reducing tissue edema. Appropriate nutrition must be provided so that substrates are available for wound healing and maintenance of oncotic pressure.
Topical Oxygen Therapy

Compared with other organs, skin consumption of oxygen is relatively low, accounting for only 2% of the total oxygen consumed by the body. Oxygen can and does diffuse through the skin from outside to inside. The total surface area of the skin is smaller and thicker than lung, so total oxygen exchange through the skin is not significant in a global sense. Locally, however, oxygen’s role may be more important, since atmospheric ambient oxygen can be directly absorbed into the superficial dermis and epithelium.

Topical oxygen therapy is less expensive and more readily available than HBOT and is not hampered by the effects of edema or cardiovascular dysfunction. By direct delivery to the wound, topical oxygen therapy also eliminates the systemic side effects associated with HBOT. Local increase in pO_2 is only modest; therefore, its use is best limited to hypoxic superficial wounds. Topical oxygen therapy does not penetrate intact skin, bone, or petroleum based dressings. As with HBOT, there are no large, randomized, case controlled studies on effectiveness of topical oxygen therapy.

Topical oxygen therapy is provided locally by gaseous or dissolved oxygen delivery systems. Gaseous oxygen is administered within an enclosure that surrounds the wound. The gas must penetrate the tissues and transform into a liquid, dissolved phase before it can be effective, so it must overcome several types of resistance before reaching cells. Despite this, it does seem to improve epithelial healing. In studies of humans with diabetes and refractory venous ulcers, local wound therapy with gaseous oxygen resulted in mean reduction of ulcer surface area of 96%, compared with 61% for conventional compressive dressings, and resolution of 80% of ulcers by 12 weeks, as compared to 35% for conventional dressings. Healing was likely a result of angiogenesis stimulation based on increased wound VEGF concentrations. In another study, 65% of complex, chronic surgical wounds (median wound duration, 4 months) healed with localized delivery of pure oxygen through a plastic inflatable device. In that study wounds were treated with 100% O_2 at 1 ATA for 90 minutes, 4 days consecutively. Wounds least responsive were neuropathic ulcers, postsurgical lower extremity wounds, and pressure ulcers.

Experimentally, wounds in rabbits treated with topical gaseous oxygen therapy showed significantly greater healing after 5 and 8 days of treatment, with epithelial coverage twice that of controls. Corneal burns in rabbits were less likely to ulcerate or perforate with treatments of 1 hour per day. In wounds created by full thickness excision, topical oxygen increased central wound pO_2 from 5-7 mmHg to >40 mmHg 2 mm below the wound surface. As a comparison, collagen synthesis is half maximal at a pO_2 of 20-25 mmHg cellular, and “respiratory burst” needed by white blood cells to lyse phagocytized bacteria is lost at pO_2<20 mmHg.

Contraindications for local gaseous delivery include presence of extensive fistulous tracts and, in people, patients that refuse to refrain from smoking.

Dissolved oxygen can be delivered by systems that catalytically produce dissolved oxygen, contain dissolve oxygen bound to a carrier, or allow a reservoir of gaseous oxygen to diffuse through a vehicle. Experimentally, topical dissolved oxygen treatments produced transcutaneous levels of oxygen 4 to 6 times that of normal subcutaneous oxygen and penetrated to a depth twice that of gaseous oxygen therapy. Some oxygen emulsions use perfluorocarbon droplets to carry and disperse dissolved oxygen. Experimentally, topical oxygen emulsions significantly enhanced rate of epithelialization of partial-thickness wounds and second degree burns in pigs compared to vehicle-treated or untreated controls. Oxidase enzyme iodinated hydrogel dressings react with oxygen in the air to generate a steady flux of hydrogen peroxide within the wound, which interacts with iodine in the dressing and is subsequently converted to 417
dissolved oxygen. Purported effects include local production of molecular iodine, which creates a hostile environment for local bacteria; maintenance of a moist wound; and local surface oxygenation. Comparisons with vehicle (hydrogel dressing) alone are not available.

Normobaric Supplemental Oxygen

Application of supplemental oxygen (FIO2, 80%) in the perioperative period decreases the incidence of surgical wound infections and improves collagen synthesis. People undergoing colonic resection that received 80% O2 for 2 hours after surgery had infection rates less than half of those of people receiving 30% O2 (infection rates of 5.2% and 11.2%, respectively). Local wound perfusion must be optimized for promotion of healing; in the colonic resection study, patients received fluids at rates of 3.5 ml/kg/h for the first day and 2 ml/kg/h over the second day. Without maintenance of patient temperature and fluid administration, no benefit is seen from supplemental oxygen treatment, no matter what delivery method is used.

Hyperbaric Oxygen Therapy (HBOT)

Atmospheric pressure alters the partial pressure of a gas that is dissolved in a liquid; therefore, increasing or decreasing atmospheric pressure will increase or decrease the number of oxygen molecules dissolved in the blood, respectively. The inspired oxygen content of a diver breathing 21% oxygen 33 feet below seawater (2 ATA) would essentially be the same as a person breathing 42% O2 at sea level, while a climber would be breathing the equivalent of 15.75% O2 at an elevation of 8000 feet (0.75 ATA). HBOT is the application of pressure greater than 1 ATA to an environment that is 100% oxygen. Because hemoglobin is saturated at a pO2 of 100 mmHg, HBOT at 2.5 ATA during inhalation of 100% O2 will increase the amount of dissolved oxygen in the blood from 0.3 vol% to 5.4 vol%, which is enough to sustain basal metabolic function in the complete absence of hemoglobin. With inspiration of room air, HBOT will increase dissolved oxygen content three-fold. Although normal arterioles and venules constrict at pO2 >500 mmHg to protect tissues from oxidative damage, ischemic tissues lack this protective mechanism and therefore continue to have improved oxygen delivery.

By increasing the driving force of systemic oxygen, greater oxygen delivery should occur within the tissues, as long as there is a functional blood supply to the area. Greater pressures will also increase the depth to which oxygen penetrates. Oxygen tensions remain high for several hours after HBOT treatment, improving angiogenesis and transcutaneous oxygen tension to unhealthy tissues, such as chronic wounds or irradiated sites. HBOT works synergistically with growth factors such as PDGF to stimulate healing of ischemic wounds. It also may provide topical oxygen therapy.

In people HBOT is recommended for treatment of air or gas embolism, decompression sickness, carbon monoxide or cyanide poisoning, gas gangrene, acute crush injuries, necrotizing fasciitis, chronic refractory osteomyelitis, osteoradionecrosis, burns, intracranial abscesses, blood loss anemia, and diabetic extremity ulcers or other select nonhealing wounds. Most treatments last for 90 minutes and are given, at least initially, two or more times per day. Treatment is ineffective if the local vascular network is nonfunctional; in people, transcutaneous oxygen measurement is evaluated when initiating treatment to confirm the patient’s ability to respond to HBOT. Nonresponders are not considered candidates.

Currently most claims for HBOT effectiveness rely on empirical results, experimental studies in normal animals, and uncontrolled clinical studies. Comparisons have not been made to treatment with sub-pure systemic oxygen under normobaric conditions, which could reduce the
risk of oxygen toxicity. In one study of hyperoxic normobaric therapy, treatment with 100% O₂ at 1 ATA resulted in healing of 75% of wounds that had marginal hypoxia (30-39 mmHg) and 50% of wounds that had moderate hypoxia (20-29 mmHg).

Experimentally, HBOT increases fibroblast and endothelial cell proliferation and keratinocyte differentiation and migration. In rat studies, twice daily treatment of burn wounds resulted in greater neovascularization and less edema at 5 days; however, no effect on breaking strength and collagen concentrations of esophagojejunal anastomoses was seen. In rabbit studies, HBOT improved mandibular bone density during distraction angiogenesis but did not significantly affect the rate of open wound healing. In horse studies, use of HBOT resulted in more inflammation and less superficial viability of full thickness skin grafts and had no protective effects as a pretreatment for endotoxemia.

In clinical studies of people, HBOT decreased mortality rates in patients with gas gangrene and necrotizing fasciitis, as long as appropriate surgical debridement, antibiotics, and supportive care were provided. People with crush wounds were more likely to heal with HBOT treatment and required fewer surgical treatments, and people with chronic, refractory osteomyelitis had a 70-85% remission rate. HBOT reduced the risk of major, but not minor, amputation for distal limb ulcers, decreased the size of venous diabetic foot ulcers at 6 weeks but not 18 weeks, and decreased the size of diabetic leg ulcers at 15 days but not 30 days. In one study of people with diabetic ulcers, there was no statistically significant improvement in wound size because response to treatment was so variable and, thus, patient-dependent. Mixed results were reported in people receiving HBOT for burn treatment, skin graft take, or neoplasia. In regards to traumatic brain injuries or strokes, the strongest papers indicated either no effect or actual harm from HBOT.

The only absolute contraindication to HBOT therapy is untreated pneumothorax. Others contraindications include patient size, intolerance to treatments (e.g., claustrophobia), recent ear or sinus surgery, seizure disorders, febrile disorders, pulmonary disease, certain chemotherapies that cause pulmonary toxicity, upper respiratory infection, emphysema, pacemakers, optic neuritis, otosclerosis, viral infections, hyperthermia, and pregnancy. Complications of HBOT include reversible myopia, middle ear barotrauma, seizures, pulmonary complications (tension pneumothorax, apnea with COPD, pulmonary edema if heart failure), and hypercapnea. Experimentally, HBOT is associated with decreased red blood cell function, mutations in human blood DNA, and arrested development of fibroblasts and hemopoietic cells.

Oxygen toxicity is one of the most common concerns. Pulmonary oxygen toxicity has an initial nonclinical, latent period. Early clinical signs include acute tracheobronchitis, which occurs after 4 to 22 hours of 100% O₂ treatment at normal atmospheric pressure and as early as 3 hours after breathing 100% O₂ at 3ATM. With longer exposure (more than 48 hours at 1 ATA), alveolar damage occurs. CNS toxicity occurs at pressures of 2.8 ATM; the most dramatic sign is seizures because of decreased seizure threshold and hypogycemia. Conditions that also decrease seizure threshold, such as febrile disorders, are therefore considered contraindications to HBOT.

Fire hazard is always possible when gaseous oxygen is delivered at supra-atmospheric concentrations or pressures. Within HBOT chambers, energy required to ignite a fire is lower, flames spread more rapidly, and any fire increases chamber pressure. Fire requires an ignition source, oxygen, and a combustible material. Fire prevention therefore focuses on reducing ignition sources and fuel. Most fires are caused by electrical sources; faulty wiring; overheating of equipment or light bulbs; ignition of polyester clothing from welding sparks; electrostatic charges from synthetic and wool clothing, fiberglass trays, or titanium plates; exothermic
chemical reactions (e.g., hand warmers); spark-generating toys; microwave-heated blankets; and, of course, open flames (smoking). In animals, metal (collars, skin staples, horse shoes, etc.) is a common concern and should be removed or covered. Fuel sources include adhesives, aerosols, aftershave, hair detanglers or conditioners (e.g. ShowSheen®), cleansing powder, clothing, stuffed toys, bedding, newspaper, petroleum based lubricants or grease, dust, and sugar and other flammable food stuffs. Cotton towels, clothing, and bandaging materials, while still flammable, are preferred since they are less likely to cause static electricity.

Effect of concurrent medications must also be considered when planning HBOT. On a positive noted, HBOT is thought to act synergistically with some antibiotics such as sulfonamides, aminoglycosides, fluoroquinolones, vancomycin, penicillins, and trimethoprim to improve clearance of infection. Leukocyte mediated killing of bacteria is impaired when oxygen tension falls below 30-40 mmHg, and antibiotic transport across cell walls does not occur with oxygen tensions less than 20-30 mmHg. As a negative effect, however, patients concurrently receiving hydrocodone, codeine, or tramadol may have additive CNS depressive effects. Effectiveness of digoxin is reduced by HBOT, while levothyroxine and certain chemotherapeutics may enhance effects of oxygen toxicity. HBOT decreases cardiac output because of decreased heart rate and experimentally reduces kidney and splenic perfusion. Concurrent use of beta blockers may result in increase in blood pressure and decrease in heart rate in people with hypertension; therefore, drugs such as atenolol should be given after instead of before treatments.

Selected References:
- Smith RG: An appraisal of potential drug interactions regarding hyperbaric oxygen therapy and frequently prescribed medications. Wounds 2011;23:147-159