The Role of Hyberbaric Oxygen Therapy in Wound Healing

BY Martine Albert

Adequate oxygenation is vital for all of the steps involved in wound healing. Oxygen plays a fundamental role in the angiogenesis process, in fibroblast function, epithelialization and bacterial management. Hypoxia can be defined as an insufficient supply of oxygen to support biological processes. However, hypoxia can sometimes be seen at a level capable of supporting basal tissue maintenance, but not enough to allow for tissue growth or healing.[1] Hyperbaric oxygen therapy (HBOT) is a method of administering a higher dose of oxygen at an increased atmospheric pressure. The Undersea and Hyperbaric Medical Society describes HBOT as "the inhalation of 100 per cent oxygen while the entire patient is enclosed within a chamber at pressures of at least 1.4 atmosphere absolute or greater."[2] HBOT provides a pharmacological dose of oxygen needed to stimulate and support wound healing for recalcitrant hypoxic wounds.

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History

The therapeutic use of oxygen under pressure—known as hyperbaric oxygen therapy—is not a new modality; it has been used to assist wound healing for over 40 years, and even longer to treat other disorders. In the 1940s, HBOT was used to treat decompression sickness. In the 1950s and 1960s, gas poisoning, carbon-monoxide, poisoning gangrene and anemic states were treated with HBOT and showed good response. It was only in the 1960s that physicians started to use hyperbaric oxygen on wounds. HBOT is currently recognized and used as a primary treatment for decompression illness, air embolism and carbon-monoxide poisoning.[3] It is regarded as an adjunctive therapy for certain types of wounds: clostridial myonecrosis, crush injury, necrotizing soft tissue infections, chronic refractory osteomyelitis, radiated tissue, compromised skin grafts or flaps, and diabetic foot ulcers—all of which share a common pathophysiology of local hypoxia.

Physiological Effects of Oxygen in Wound Healing

Healing occurs in a predictable sequence of events that rests on a successful cellular and biochemical chain of events. Any disruption to these events can have a detrimental effect on the healing process. The key to successful management of any type of ulceration lies not only with the accurate identification of the underlying cause of the ulcer but also with the appropriate measures to remove or modify the causative factors interfering with healing.

To obtain closure on a recalcitrant wound, clinicians need to consider advanced treatments: biologic modalities and adjunctive therapies such as HBOT.

Any interruption of normal healing will result in a chronic wound. In many cases the pathological environment can be remedied with best-practice interventions aimed at correcting the offending agents, and with the judicious consideration of the local wound-care needs: i.e., debridement, moisture balance and bacterial balance. However, some chronic wounds still do not respond and become recalcitrant to any type of intervention. Tissue hypoxia is a key element of healing failure.

Adequate oxygenation fuels the cellular function essential to the tissue-repair process. As the wound enters the inflammatory phase initiating the healing process, the requirements for oxygen increase and are

accelerated due to oxidative cellular mechanisms. During normal wound healing, the fibroblasts are stimulated to make collagen. This supports the development of a collagen matrix, which forms a scaffold that supports new blood vessels (angiogenesis). Angiogenesis enables the delivery of oxygen and nutrients required to promote the healing process.[4] The probability of wound healing is extremely high if the tissue oxygen tension (pO_2) at the wound site is 40 mmHg, where fibroblastic activity and cellular interactions are supported.[5]

Oxygen moves from areas of high concentration (pressure) to areas of low concentration (pressure). Wounds naturally have a hypoxic central zone that is surrounded by normal perfusion in the adjacent tissue.[6] This produces an oxygen gradient from the peripheral tissues to the centre of the wound. The central hypoxic zone therefore creates a demand for oxygen and engages the adjacent tissue to provide oxygen to support the healing process through angiogenesis. Subsequently, hypoxic peri-wound tissues cannot provide adequate levels of oxygen to support cellular proliferation and the creation of new vessels to the central zone. A lack of oxygen, or poor oxygenation, prevents a normal healing pattern.

Oxygen is key to the phagocytosis and killing of bacteria by neutrophils or polymorphonuclear cells (PMNs).[1] Neutrophil phagocytosis creates a 25-fold increase in oxygen consumption.[7] As the oxygen tension falls below 30 mmHg the efficiency of bacteriocidal action of PMNs begins to drop off dramatically.[1] Therefore, hypoxia weakens the tissues' resistance to bacteria. Oxygen also stimulates macrophages to produce angiogenic substances—as vascular endothelial growth factor (VEGF)—that attract and stimulate endothelial cells. Therefore, hypoxia weakens the neovascularization process.[3]

When wound hypoxia is the systemic cause of the healing failure, providing oxygen at the wound site is, essentially, treating the cause. Hyperbaric oxygen therapy is an adjunctive therapeutic modality in which the patient is given a high volume of pure oxygen to breathe in an environment of elevated atmospheric pressure, which leads to an increase in tissue oxygen pressures at the wound site.

HBOT stimulates fibroblast activity by providing an environment rich in oxygen, which supports the formation and deposition of collagen. The tissue's tensile strength is then improved. HBOT reduces wound infection and potentiates the effect of antibiotics through its direct impact on anaerobic bacteria so they cannot proliferate and will eventually die, as well as through its indirect impact on aerobic bacteria by enhancing the microbicidal function of the PMNs.

Mechanism of Oxygen Transport with HBOT

At sea level, the air that we breathe is composed of 20 per cent oxygen and 80 per cent nitrogen, and the Earth's atmosphere exerts 101.325 kPa (14.7 psi) of pressure. This pressure is defined as 1 atmosphere absolute, abbreviated 1 ATA. HBOT provides an environment where the patient breathes 100 per cent oxygen at greater than normal atmospheric pressures of at least $\geq$1.4 ATA. The effects of HBOT are two-fold: those associated with high pressure and those associated with high pO_2. Each haemoglobin molecule in a human red blood cell has four oxygen binding sites. At sea level or at normal atmospheric pressures, most healthy individuals naturally reach saturation of these red-cell binding sites, consequently reaching a predetermined cellular amount of oxygen. When a patient receives hyperbaric oxygen, the haemoglobin binding sites are quickly saturated and there is no significant increase in the amount carried by haemoglobin, which is already $\geq$95% saturated with oxygen. The oxygen can then independently travel to the injured tissues without having to rely on red blood cells for transport. This excess of oxygen is dissolved into the plasma, creating an elevated tissue oxygen tension at the wound site. It is important to note that the oxygen diffusion is directly proportional to the increased partial pressure of oxygen (pO_2) present in the circulating plasma caused by HBOT.[8] Warriner states that the radius of the oxygen diffusion from the capillaries into the extracellular compartment increases four-fold when oxygen is breathed at 3 ATA.[8]

HBOT consists of a patient breathing 100 per cent oxygen while the entire body is enclosed in a pressure chamber large enough to accommodate either one person (monoplace) or more than one person (multiplace). The topical application of oxygen is not recognized as a hyperbaric therapy. Topical oxygen therapy that encloses a body part (e.g., a lower extremity with wounds) lacks strong clinical evidence at this time.[9]

Patient Selection

HBOT is an adjunctive modality to enhance evidence-based practice and is not a substitute treatment for other therapeutic measures. The role of the health-care professional working in HBOT is to rigorously and discriminately select those patients that need and that will most likely benefit from this therapeutic intervention and, thereafter, to safely provide the hyperbaric treatment. The indication for HBOT is evidenced by the presence of tissue hypoxia either as a causal or as a contributing factor to impaired healing. Measuring transcutaneous pressure oxygen, $TcPO_2$, in tissue adjacent to the wound can be useful in discriminating those patients without significant hypoxia who do not require HBOT from those who do.[10] $TcPO_2$ is a quick, simple, reliable non-invasive diagnostic technique for an objective assessment of local cutaneous oxygenation.

It is always important to ascertain if large vessel disease is a contributing factor in the hypoxic state of the peri-wound tissues. Impaired perfusion of the larger vessels will decrease the oxygenation of the tissues surrounding the wound, and HBOT will not reverse this state of hypoxia. A referral to a vascular specialist is then indicated.[2] It is also imperative to ensure that all of the local underlying factors that impede healing are corrected; otherwise, HBOT could be used erroneously.

Conclusion

Hyperbaric oxygen therapy is an adjunctive treatment to enhance best-practice wound care. HBOT allows the reversal of a hypoxic state by increasing the oxygen diffusion within the plasma, consequently promoting angiogenesis, encouraging fibroblastic activity and supporting the tissues to resist against bacteria.

The medical use of oxygen under pressure is an evolving specialty. Many types of recalcitrant wounds have responded favourably to HBOT. However, despite its long history of therapeutic use and the literature supporting HBOT as an effective adjunctive modality for hypoxic recalcitrant wounds, skepticism still shadows the effectiveness of HBOT for wound healing due to the small number of well-executed controlled randomized trial studies, as well as the high cost associated with this treatment. It is important to note that many Canadian health-care systems will cover the cost of HBOT, but that the hidden costs to the patient and their families can be overwhelming. This includes the costs of accommodation, food, transportation/travel and, possibly, lost wages. Consequently, many clinicians remain guarded in recognizing HBOT as an adjunctive therapy to support wound healing. For further details on HBOT and to locate a HBOT clinic near you, visit www.uhms.org.

$TcPO_2$ provides clinical information to determine

- if a patient does not need HBOT
- if a patient needs HBOT and responds to an O_2 challenge
- if a patient is hypoxic and HBOT will not reverse the condition

HBOT session

A typical HBOT treatment for a wound is capable of providing tissue oxygen levels greater than 11 times normal.

- patient is placed either in a monoplace or a multiplace chamber
- lasts two hours
- 100% delivery of oxygen at 2.0-2.4 ATA (45 feet under sea level)
- three periods of 30 minutes at 2.0-2.4 ATA
- two periods of five minutes for air breaks
- HBO treatments are sometimes called "dives" by patients

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