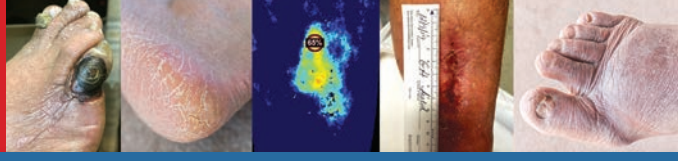

Oxygen as an Adjunct to Closing DFUs

Both HBOT and the newer TO2 treatments have been found to be generally safe and efficacious.

BY ADAM R. JOHNSON, DPM

As the epidemic of diabetes mellitus continues to grow, so does the number of individuals with diabetic foot ulcerations that fail to heal. Efforts to provide quality wound healing are advancing across the spectrum of medicine. It is important that these efforts continue. It is estimated that the risk of an individual with a diabetic foot ulceration having it progress to an outcome that requires a lower extremity amputation is upwards of 10%.[2] A well-known adjunct to assisting in the closure of diabetic foot ulcerations (DFUs) is oxygen delivery treatment. This can be achieved via either traditional hyperbaric oxygen therapy (HBOT) or through the new wave of local oxygen delivery devices (topical oxygen, or TO2). In this article we'll first take a look at HBOT and then discuss TO2 options.

Figure 1: Wagner 4 diabetic foot ulceration

Figure 2: Ulceration after failing to respond to 30-day standard-practice wound healing

A well-known adjunct to assisting in the closure of diabetic foot ulcerations (DFUs) is hyperbaric oxygen therapy (HBOT).

Case Presentation

A 66-year-old female with T2DM presented with a Wagner 4 ulceration (Figure 1). Gangrene of the right forefoot was complicated by underlying critical limb ischemia. An endovascular angioplasty procedure was completed and restoration of arterial supply to the distal extremity was achieved. Amputation of the necrotic digit was performed with tissues left open for secondary healing. After 30 days of standard-practice wound healing, the surgical ulceration failed to show signs of healing. The ulceration was fibrotic, and tendon and fascia began to desiccate (Figure 2). Transcutaneous oxygen measurements to the right forefoot were measured at 13 mmHg. The patient consented to starting hyperbaric oxygen therapy and completed 40 treatments utilizing treatment table 9 (US Navy 6th ed.) with 100% O2 at 2.5 Atmospheres Absolute (ATA) for 90 minutes plus two five-minute air breaks in a monoplace chamber. While undergoing treatments, this previously non-healing ulceration showed significant increase in healthy granulation tissue (Figure 3). The patient healed her ulceration shortly thereafter (Figure 4).

Standard-Practice Wound Healing

The standard-practice of wound healing for diabetic foot ulcerations includes a well-established protocol

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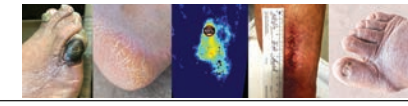

Figure 3: Ulceration with improved appearance after HBOT initiated

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and remains to be the preferred initial care-plan. These steps include, but are not limited to, routine washing and cleaning of an ulceration with soap and water, or manufactured wound sprays and irrigants. There should be regular dressing changes to ensure a moist, healing environment so that tissues do not macerate or desiccate. Of importance is serial debridement of devitalized and contaminated debris and slough to reduce risk of infection. The off-loading of pressure and reduction in shear friction at the site of healing should be maintained. In addition, ongoing evaluation of adequate vascular supply should be ensured, and finally, aggressive medical management of the core medical issues related to diabetes should be addressed.

Physiological Effects of Hyberbaric Oxygen

When wound healing is not progressing, augmentation with hyperbaric medicine may provide additional support to reach closure. This occurs due to multiple physiological effects that occur with the use of supplemental oxygen.

When oxygen is in an environment of increased pressure, it behaves like a drug, having specific indications and side-effects. Placing a patient in a hyperbaric chamber at 2.5 ATA O2 may raise the oxygen tension to more than 10 times above normal physiological levels. This effectively saturates the plasma and causes hemoglobin to remain fully oxygenated, even on the venous side. Even though high levels of oxygen cause vasoconstriction, the increased blood oxygen levels more than compensate for this. Areas of delayed wound healing may be hypoxic due to lack of necessary vasculature. These hypoxic tissues do not respond with normal vasoconstriction, and this leads to a beneficial redistribution effect that further oxygenates this tissue.[3]

Oxygen also stimulates collagen synthesis, which is a necessary step for healthy tissue to form in a healing wound bed. Collagen synthesis occurs when fibroblasts are triggered by the lactate produced by macrophages located in the wound environment. Increases in oxygen also lead to increases in VEGF gene expression.[4] VEGF, otherwise known as Vascular Endothelial Growth Factor, stimulates neoangiogenesis, the process of new blood vessel growth into the wound. Fibroblasts are unable to synthesize collagen in a hypoxic state. An oxygen-rich environment is required to produce the necessary cross-linking of collagen.[5]

When oxygen levels are low and collagen framework stalls, neoangiogenesis also stalls. This leads to subsequent formation of a chronic, non-healing wound. However, within 15 minutes of hyperbaric oxygen therapy, endothelial cells begin to proliferate; and after 120 minutes, fibroblasts begin to produce a response that can last up to 72 hours post-exposure.[6] Effects are also seen in red blood cells as hyperbaric oxygen improves the cells' ability to pass through narrow capillaries. Furthermore, leukocytes use oxygen to create high-energy radicals, and the rate that these radicals are formed is directly proportional to the amount of oxygen available. Leukocytes can then lend these radicals to neutrophils for increased phagocytosis of bacteria, which in turn cleans the wound and prevents infection.[7]

Patient Criteria

Standard-practice wound healing modalities should be initiated with all diabetic foot ulcerations. With traditional hyperbaric oxygen therapy, CMS guidelines[8] require that the wound be staged at a Wagner III (a full thickness ulceration having bone and/or soft tissue infection present) and have failed the standard-practice wound healing for at least 30 days.

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Figure 4: Closure of ulceration

Transcutaneous oxygen pressure (TcPO2) measurements (TCOMs) are a simple and non-invasive diagnostic technique that can be performed to provide a reliable objective assessment of the local skin perfusion in room air as well as with supplementing the patient with 100% O2 via mask or nasal cannula. The results of this test may show if the patient has the ability to heal a wound by way of

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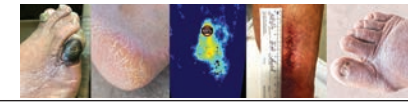

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tissue perfusion in a setting of room air.[9]

This test is specifically useful when considering the use of adjunct oxygen. If TCOMs near a non-healing ulceration are significantly low, it may signal a lack of oxygen reaching the ulceration. When supplementation with oxygen is provided via a mask or nasal cannula is performed, it helps to determine if the delivery to the affected site may be altered via systemic circulation. While more difficult to accomplish, this test may also be performed inside an HBOT chamber to determine what effects increasing ATA may have. Just as adding supplemental oxygen may alter TcPO2 levels, it is also important to understand that levels may change due to local tissue swelling and inflammation. For instance, in the presence of infection, a local decrease in tissue oxygen perfusion may occur leading to a low TCOM reading.[10] Repeat testing may be necessary to determine an accurate representation.

Contraindications

Hyperbaric oxygen therapy is not without risks, however, so proper patient screening and selection is important. The following list provides some known concerns but should not be considered complete. Consultation with a physician board-certified in hyperbaric medicine is recommended before starting therapy. The concurrent use of the chemotherapeutic drug doxorubicin is contraindicated as cardiotoxicity may occur leading to death. Bleomycin, another treatment for lymphoma and other forms of cancer, is a relative contraindication as its use may lead to decreased pulmonary diffusion capacity. Performing a pulmonary function test should be considered with any patient having previously received this therapy.

Sulfamylon® cream use on a wound is also contraindicated while a patient undergoes hyperbaric oxygen therapy. This medication leads to local CO2 buildup. A different topical wound agent should be employed or the ointment should be removed from the wound before starting a treatment. If its use is desired, it may be re-applied once the treatment is completed. Untreated pneumothorax is also a contraindication and it is of benefit to screen patients by a chest radiograph before starting hyperbaric oxygen therapy to rule this out.

Other conditions that present a risk during hyperbaric oxygen therapy include: seizure disorders, emphysema with CO2 retention, uncontrolled high fevers, history of spontaneous pneumothorax, chronic sinusitis and upper respiratory tract infections, viral infections, a history of optic neuritis, previous otosclerosis surgery and congenital spherocytosis.[3]

Topical Oxygen as an Option

For patients that do not meet criteria for the systemic delivery of supplemental oxygen, a new wave of local oxygen delivery devices has been developed. Many proponents of topical oxygen (TO2) argue that it is safer and more effective than traditional HBOT. For HBOT to work, the patient requires breathing 100% oxygen at increased atmospheric pressures, which has its own risks. Furthermore, the delivery of oxygen to the wound requires systemic circulation to deliver the oxygen-rich blood. TO2 locally increases oxygen at the wound bed, thus delivering the oxygen where it is needed most, and performs this while the patient remains at room pressure. The increase in oxygen around the wound bed creates increased oxygen solubility and dissolution via increases in O2 partial pressures.[11]

TO2 may also be delivered in the patient's place of residence, limiting the burden of care and improving the ability for compliance. It is also true that HBOT requires the use of monoplace or multiplace pressure chambers that many hospitals and medical centers do not have access to, eliminating the option of HBOT for many patients altogether. HBOT typically requires that a patient present to an equipped medical center 5 days per week for up to 40 treatments; treatments last around two hours. TO2 may be delivered intermittently, or continuously, allowing for longer sessions of therapy; treatments may occur in a patient's own residence. While HBOT may remain the standard for delivery of supplemental oxygen in non-healing diabetic foot ulcers, new research continues to show promise for TO2.

The TO2 Research

A 2008 retrospective study[4] compared the results of wound healing patients treated with HBOT and those treated with TO2. While the HBOT group appeared to show improvement in the wound healing, no significant difference was found. In contrast, the TO2 group did show significance in improvement in wound size.

Many proponents of topical oxygen (TO2) argue that it is safer and more effective than traditional HBOT.

In 2018, a landmark randomized, double-blind, multicenter study[12] was published looking at the effects of TO2 on diabetic foot ulceration healing. Many impressive findings of significance included: 18.4 mean days to closure for the TO2 group compared to 28.9 days for the placebo ($p = 0.001$) and 32.4% closure of wounds being treated with TO2 compared to 16.7% for the placebo ($p = 0.033$).

A newly released Multinational, Multicenter, Randomized, Double-Blinded, Placebo-Controlled study[13] also found significant results. The 2020 study found an impressive 41.7% closure rate at 12 weeks for the TO2 group comparted to only 13.5% for the sham group ($p = 0.010$). Perhaps even more impressive was a post-study follow-up at one year where 56% of the TO2 group closed and remained closed compared to 27% for the sham group ($p = 0.013$).

Conclusion

As the epidemic of patients with diabetes mellitus continues, the need for effective options to heal and keep diabetic foot ulcerations closed will

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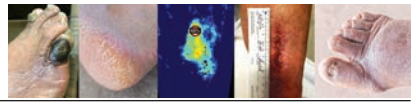

Oxygen *(from page 92)*

continue to be a pressing need. Supplemental oxygen has shown to be efficacious. How we will deliver this oxygen will continue to evolve. **PM**

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