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Evidence-Based Recommendations for the Use of Topical Oxygen Therapy in the Treatment of Lower Extremity Wounds

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Abstract

Topical oxygen therapy provides another tool in the armamentarium of clinicians treating refractory lower extremity wounds. Devices suitable for providing topical oxygen therapy in a clinical setting have recently become available. This article reviews the evidence to justify the use of this treatment modality, including in vitro, preclinical data, and clinical data. It also provides a protocol for how to administer topical oxygen therapy as well as guidance on patient selection and management to optimize outcomes. Randomized controlled trials are not yet reported and clearly necessary. The current body of evidence suggests that topical oxygen therapy may be considered as a second line of therapy for refractory wounds.

Keywords

oxygen; reactive oxygen species; angiogenesis; wound

Oxygen (O_2) therapy could potentially provide tremendous benefits for the treatment of lower extremity wounds.[1] However, most health care providers view oxygen therapy as being outside the mainstream of clinical care. Reliance on empiricism and a paucity of data that meets the highest criteria for evidence-based medicine has hindered the general acceptance of oxygen therapy as a standard modality in wound care. Embracing the concept of oxygen therapy depends not only on favorable clinical outcome but also on detailed mechanistic insight that explain those outcome results. It is generally accepted that correction of wound hypoxia is required to provide enough O_2 that would support growth of regenerating tissues.[1] This article is aimed at summarizing experimental, preclinical and clinical findings that illustrate the mechanisms through which O_2 promotes wound healing with a specific emphasis on the effects of topical oxygen (TO) therapy. The objective of this article is to provide a clear rationale for using TO therapy to treat wounds and provide guidance for the implementation of TO therapy and patient selection.

Effects of Oxygen on Essential Wound Healing Events

Hypoxemia caused by vascular disruption or disease is a key factor that limits wound healing, especially because of its high prevalence in the lower extremity. The central area of the wound is most hypoxic with a progressive increase in the oxygen gradient toward the uninjured tissue at the periphery. The partial pressure of oxygen (po_2) in dermal wounds ranges from 0 to 10 mm Hg centrally to 60 mm Hg at the periphery,[2] whereas the po_2 in the

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arterial blood is approximately 100 mm Hg. Oxygen delivery is a critical element for the healing of wounds.[3–5] Factors that can increase oxygen delivery to the regional tissue, such as supplemental oxygen, warmth, and sympathetic blockade, can accelerate healing.[6,7] Measurement of wound tissue oxygenation has been shown to be the best predictor of wound healing outcome compared with other diagnostic modalities such as ankle–brachial index, segmental pressures, and laser doppler fluximetry that are based on blood flow.[8]

The current practical gold standard for measuring wound tissue oxygenation in the clinical setting is transcutaneous oximetry (TcOM) or TcPo_2 where electrodes are placed on intact skin adjacent to the wound and tissue oxygen tension is measured. TO does not penetrate intact skin, so no changes in TcOM measurements are observed during TO application to intact skin. However, we used tissue oximetry in pigs with full thickness excisional wounds using the Seldinger technique to place a probe (Oxy-Lite, Oxford Optronix, Oxford, UK) directly beneath the wound surface during TO administration and noted that the central wound po_2 increased from a baseline of 5 to 7 mm Hg to levels >40 mm Hg as early as 4 minutes into treatment. The O_2 levels were detected 2 mm below the surface of the wound.[9] These results provide a key proof of principle that TO can oxygenate superficial wound tissue.

Collagen deposition is a fundamental step in wound healing that provides the matrix for angiogenesis and tissue remodeling. There are several posttranslational steps in collagen synthesis that are oxygen dependent. The enzymes prolyl hydroxylase, lysyl hydroxylase, and lysyl oxidase all require molecular oxygen as a cofactor. Prolyl hydroxylase is required to convert proline residues to hydroxyproline, which allows the procollagen peptide chains to assume their triple helix configuration. Without this triple helix configuration, the synthesized procollagen chains accumulate in the rough endoplasmic reticulum and are eventually excreted as nonfunctional gelatinous protein. Once the procollagen has assumed the triple helix conformation and been excreted, the individual collagen fibers are arranged into linear fibrils via the cross-linking effects of lysyl hydroxyalse and finally cross-linking between large fibrils is performed by lysyl oxidase. These extracellular cross-linkages are ultimately responsible for the tensile strength achieved in healed wounds. Of the oxygen-dependent enzymatic processes, the rate of collagen synthesis is reflected by the rate at which prolyl hydroxylation occurs.[10,11] The amount of oxygen at which collagen synthesis is half-maximal (K_m using the Michaelis–Menton equation) has been determined to occur at a po_2 of 20 to 25 mm Hg, with V_{max} occurring at levels approaching 250 mm Hg.[12,13] This represents levels of oxygen availability that exceed the po_2 normally present in wounds and suggests that supplemental oxygen may enhance collagen synthesis. This has, in fact, been shown to be true in both experimental in vivo models, as well as in human subjects. Increasing wound oxygenation results in increased collagen deposition and tensile strength with maximal effects seen at levels in which wound oxygenation is increased above normal physiologic conditions by the addition of supplemental oxygen.[14–16] Among a group of postoperative patients all treated with supplemental oxygen (4 L/min via nasal cannula for 12 hours × 3 days), 3 times as much collagen was deposited in wound cylinders in patients with well perfused and oxygenated wounds compared to those with lower oxygenation and perfusion scores.[3] Thus, supplemental oxygen can optimize collagen deposition that should ultimately translate into increased wound tensile strength.

Oxygen is also a rate-limiting substrate for the production of reactive oxygen species (ROS) that serve as a disinfectant and as intracellular signaling molecules that orchestrate the wound healing response.[17] At the wound-site, ROS are generated from oxygen by almost all wound-related cells. Nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) is the enzyme that generates ROS for signal transduction necessary to promote healing. The amount of oxygen required for half maximal function of NADPH oxidase (the

Michaelis–Menton constant K_m) is 45 to 80 mm Hg with maximal function observed at >300 mm Hg. If the wound pO_2 drops below 20 mm Hg, the NADPH oxidase ceases to function.[18] This may help explain, at least in part, why ischemic lower extremity wounds fail to heal.

In phagocytic cells at the wound site, the ROS produced by NADPH oxidase are used to kill bacteria. Pioneering work done by Bernie Babior[19] in the 1970s linked the explosive production of superoxide (termed "respiratory burst") by NADPH oxidase to bacterial killing. In fact, approximately 98% of the oxygen consumed by wound neutrophils and macrophages is used for respiratory burst.[18] Phagocytosis and lysis of wound bacteria by neutrophils results in a 15-fold to 20-fold increase in O_2 consumption.[20] Thus, heavy bacterial burden within a wound will increase the need for O_2 as a substrate for NADPH oxidase and limit substrate availability for signaling purposes. The ability of contaminated wounds to resist infection has been shown to be directly proportional to tissue pO_2,[21] which is not surprising given the loss of NADPH oxidase function at $pO_2 < 20$ mm Hg. Increasing the wound pO_2 from 20 mm Hg to 100 mm Hg, a level far above what is commonly observed in wounds, can increase NADPH oxidase function 3-fold to 4-fold.[18]

As cellular messengers, ROS may contribute to several facets of wound healing, including angiogenesis.[22–24] Increasing wound pO_2 through the use of TO potentially provides an important substrate to cells for mediating wound healing responses at a molecular level. Numerous wound healing–related growth factors, including platelet-derived growth factor-B (PDGF-B; Regranex gel, Johnson & Johnson, Indianapolis, IN) rely on ROS for the execution of its biological function.[25] Oxidation plays a central role in promoting transforming growth factor-β (TGF-β) function.[26] Indeed, strategies to raise wound pO_2 show a synergistic effect to benefit wound healing in conjunction with both TGF-beta as well as PDGF therapy of wounds.[27]

Wound healing is an angiogenesis-dependent process. Although tissue hypoxia plays a central role in initiating the angiogenic response[28] in wounds, it cannot sustain it.[29] The impact of oxygen therapy on the angiogenic response is a critical feature of its overall benefits. Vascular endothelial growth factor (VEGF) is believed to be the most prevalent, efficacious and long-term signal that is known to stimulate angiogenesis in wounds.[24] In vitro experiments have shown that oxygen treatment induces VEGF mRNA transcription in endothelial cells and macrophages.[30–32] In vivo experimental models have also shown that supplemental oxygen therapy increases VEGF protein expression in wounds[33] and can accelerate vessel growth in wounds.[29] We demonstrated that TO increases VEGF expression in wounds and vessel formation in a preclinical pig model.

Each pig had 2 groups of 5 wounds placed on its back. Each wound removed the full thickness of skin and measured 2.5 × 2.5 cm. Half the wounds were treated with TO given as 100% O_2 at 1 atmosphere of pressure for 3 hours/day × 7 days beginning the day of wounding and the other half of the wounds were treated with room air under the same conditions. A statistically significant difference ($P < .005$, Student's t test) in the size of the wounds and rate of wound closure was seen as early as 5 days postwounding and was maintained over the course of healing. Compared with the wounds treated with room air, those treated with TO had higher levels of VEGF protein expression and greater blood vessel density as detected by immunohistochemistry. The functional outcome of these findings was a wound pO_2 in the TO group (42 mm Hg) that was almost 4 times higher than the room air group (11 mm Hg) at 22 days postwounding and a significantly faster rate of wound closure.[9] The fact that TO-treated wounds had persistently elevated wound pO_2 15 days after the last treatment demonstrates that TO can initiate a powerful angiogenic

response capable of sustaining itself and enabling the wound to progress through subsequent events in the healing cascade.

Another group reported that TO therapy can increase the rate of wound epithelialization using a preclinical pig model. In this experiment, the pigs had second degree burns created on their backs and were treated in a randomized controlled fashion using a superoxygenated perfluorocarbon emulsion to deliver supplemental oxygen topically to the wound. Control sites received either the perfluorocarbon vehicle with no oxygen or were left untreated. The TO emulsion reportedly had an oxygen concentration of 2 mL O_2/mL of emulsion. A statistically significant increase ($P < .01$, χ^2 4-fold tables) was observed in the TO-treated group compared with either control group.[34] This provides additional supporting evidence from a preclinical model that the concept of supplementing oxygen delivery using a topical approach can improve healing outcomes.

We have reported that TO therapy increases VEGF expression and promotes closure in patients with chronic wounds affecting the trunk and lower extremities. The study was designed to investigate the mechanism by which oxygen therapy promotes healing in chronic wounds. Because it was designed to investigate mechanisms and not efficacy, it was not a designed as a randomized trial. Serial wound tissue biopsies were obtained over the course of 12 weeks of TO therapy or until closure, whichever came first. The first biopsy was done prior to initiating TO therapy to obtain baseline levels of VEGF expression. Linear regression analysis, which analyzes the effect of one variable (TO therapy) in context of all the other outcomes being studied, for example, wound size, location, VEGF expression, and so on, found a statistically significant beneficial effect of TO, p value <.001. For each patient who responded to TO, that is, their wounds got smaller, there was a significant and cumulative increase in VEGF expression in the wound tissue over time. The overall response rate to TO was 83%. This is the first time that TO has been linked to VEGF expression and a wound healing outcome in human subjects. Interestingly, we performed this same study simultaneously in patients treated with hyperbaric oxygen therapy (HBO) and there was no consistent increase in VEGF expression among those patients and linear regression analysis did not indicate that HBO contributed to the healing outcome.[35] This suggests that there may be a therapeutic range of pO_2 capable of inducing VEGF. That range may be exceeded by the pO_2 achieved with HBO, which can range from 400 to 1600 mm Hg compared with the 40 to 80 mm Hg range we have observed for TO. The authors believe that these are the first reported results to ever look at oxygen-induced changes in gene expression in wound tissue from patients with chronic wounds.

Tissue Hypoxia and Response

There is a common misperception about the benefits of hypoxia because it promotes angiogenesis. Tissue hypoxia caused by disrupted perfusion creates an oxygen gradient that plays an important role in initiating the angiogenic response to support tissue repair.[28] The role of hypoxia is to initiate the angiogenic response, which is observed only in the acute wound setting. Chronic hypoxia cannot sustain angiogenesis in wounds because cells are deprived of a crucial source of energy.[29] Certainly, any clinician involved in wound care has seen that persistently hypoxic lower extremity wounds will not heal. The conditions for “normoxia” vary based on the location of the cell within an organ and the functional status of the organ itself. Oxygen sensing is required to adjust to physiologic or pathologic changes in pO_2. Whereas acute changes in pO_2 will usually involve changes in the activity of preexisting proteins, chronic responses invariably involve O_2-sensitive changes in signal transduction and gene expression.[36] The fact that we have shown persistent elevation in VEGF expression[35] and wound oxygenation[9] in response to ongoing TO therapy is consistent with this observation.

In ischemic wounds, limited oxygen supply and enhanced oxygen consumption such as to fight infection and fuel repair often leads to extreme hypoxia.[1] Hypoxia, by definition, is a relative term. It is defined by a lower tissue po_2 compared with the po_2 to which the specific tissue element in question is adjusted to under healthy conditions in vivo. Depending on the magnitude, cells confronting hypoxic challenge either induce an adaptive response that includes decreasing the rates of glycolysis to conserve energy or undergo cell death.[37] Generally, acute mild to moderate hypoxia supports adaptation and survival. In contrast, chronic extreme hypoxia leads to tissue loss. Although tumor tissue is metabolically designed to thrive under conditions of hypoxia,[38] hypoxia of the wound primarily caused by vascular limitations is intensified by coincident conditions (eg, infection, pain, anxiety, and hypothermia) and leads to poor healing outcomes.[18,39] Hypoxia sensing and response is activated on exposure to a state of oxygenation that is lower than the po_2 to which the cells or tissue is adjusted to under basal conditions. This response cascade is centrally important in coping with the challenge of O_2 deficiency.

Clinical Results and Considerations for Using TO

Having an appreciation for the fundamental principles regulating O_2 delivery to the wound will substantially increase the likelihood of success when using TO. First and foremost, practitioners need to appreciate that local conditions at the wound site are the ultimate determinant of O_2 delivery. This means that vasoconstriction at the wound site will severely limit wound tissue oxygenation. Any patient who is anxious, smokes, has pain, is cold, or has an inadequate intravascular volume will have decreased O_2 delivery to their wounds. The anesthesia literature provides some of the best studies illustrating this key concept. A randomized controlled trial by Arkiliç et al[40] compared perfusion and O_2 delivery using capillary thermal diffusion and O_2 detection probes placed subcutaneously in the arm of patients given either 8 mL/kg/h or 16 to 18 mL/kg/h of maintenance intravenous fluids perioperatively. Both tissue perfusion and oxygenation were significantly elevated in the patients receiving the supplemental/increased fluid administration.[40] Another double blind randomized controlled trial with 500 patients evaluated healing outcomes in patients undergoing colonic resection that received either 30% O_2 or 80% O_2 during their surgery and for 2 hours postoperatively. The patients who received 30% O_2 had infection rates (11.2%) that were more than twice as high as those observed in patients receiving 80% O_2 (5.2%).[41] The difference in the incidence of wound infection between the 2 treatment groups was statistically significant with a p value <.016 by 2-tailed chi-square analysis. This study was carefully designed to control for patient temperature and intravenous fluid administration to ensure optimal oxygen delivery to the surgical site. When another group repeated this study without controlling for patient temperature or intravenous fluid administration rates, they were unsuccessful and revealed their lack of understanding for the principles of O_2 delivery.[42] A group in Spain was able to repeat the study by Greif et al[41] and verify the effects of supplemental O_2 in decreasing surgical site infection.[43] Although systemic factors such as arterial po_2 and cardiac output do contribute to the wound tissue oxygenation status, their ability to deliver oxygen is regulated by local conditions at the wound site. Therefore, putting a patient on supplemental oxygen via nasal cannula or face mask or endotracheal tube cannot by itself increase wound oxygenation. Local conditions at the wound site must be favorable to permit O_2 delivery and achieve the benefits of oxygen therapy administered systemically. Because TO therapy delivers O_2 directly to the surface of the wound and not through the peripheral vasculature, it is possible that this form of administering supplemental oxygen may not be as tightly regulated by local conditions. However, this has not been proven and it remains in the best interest to follow these rules to optimize wound perfusion that provides the cells and additional nutrients to promote healing.

Other important factors influencing wound tissue oxygenation are diffusion distance and the rate of O_2 consumption. Diffusion distance can either be defined by the distance between the wound bed and the capillaries, or, in the case of TO, between the wound surface and the oxygen source. There are several ways to decrease diffusion distance and increase tissue oxygenation. Appropriate measures should be taken to decrease lower extremity edema to minimize the distance between the capillary bed and the wound. This is especially true for lower extremity ulcers. Multiple different treatment interventions for venous leg ulcers designed to reduce edema have been shown to raise periwound transcutaneous oxygen measurements.[44] When using TO, it is extremely important to remove eschar or debris from the wound surface to allow the oxygen to penetrate a clean wound surface. Also, it is a contraindication to use dressings that are petrolatum based as they create an oxygen impermeable barrier on the wound surface rendering the TO ineffective.

The rate of O_2 consumption in the wound is determined by the availability of O_2 as a substrate and the local metabolic conditions in the wound. This explains why the supplemental O_2 given perioperatively decreases surgical site infections and drives home the rationale for providing supplemental O_2 to wounds. It also explains why wounds that are profoundly ischemic (TcOM < 20 mm Hg) fail to heal and are more prone to infection. Although the studies to document that TO can decrease infection have not been done, the same underlying principle of increasing O_2 availability at the wound site still applies. It seems reasonable to assume that there is probably some benefit from TO in this regard, but perhaps only for the soft tissue at the base of the wound that the oxygen can penetrate. This statement is based up observations from the largest reported case series using TO. In that retrospective review, there were 2 immunosuppressed diabetic renal transplant patients with open hand wounds and osteomyelitis of the metacarpal bone that had progression of their osteomyelitis while receiving TO.[45] These wounds went on to heal following resection of the infected bones, which suggests that TO cannot penetrate the cortex of the bone. HBO therapy with its systemic elevation of arterial po_2 may be a better choice for treating osteomyelitis. Further studies need to be done to definitively determine the effects of TO on bacterial burden in wounds.

There were several other important observations from that TO case series consisting of 32 patients with 58 wounds, of which 2 patients with 2 wounds were lost to follow-up. There were 38/56 wounds (67.8%) that healed with TO alone and 4 more wounds healed when TO was used in conjunction with surgical flaps or grafts for a total healing rate of 75% (42/56). The average length of treatment for wounds that healed with TO was 71 days and there was no significant difference in healing outcome based on the acuity (age) of the wound. There was a 92.7% positive response rate (decrease in size) in wounds treated with TO, but initial wound size was a significant determinant in healing outcome. The average initial wound area for those that went on to heal was 8.1 cm^2 and for those that did not heal it was 25.3 cm^2, which may also explain the 44% healing rate observed in pressure ulcers as they are usually larger wounds.[45] It is important to consider the size of the wound to determine whether TO should be used as an adjunctive therapy in preparation for flap or graft surgery or as a primary treatment modality to achieve a healed wound.

As with any treatment, patient selection plays a key role in the likelihood of achieving success with this therapy. The findings from the case series provide some insight into how to guide patient selection. A randomized placebo controlled trial using TO for the treatment of diabetic foot ulcers is currently in progress. The objective of that study is to meet highest standards in demonstrating clinical efficacy. If it is successful it will move TO therapy for the treatment of diabetic foot ulcers into the mainstream of clinical practice. In general, the following guidelines may also help with patient selection and treatment:

1. Use TO for 90 minutes per treatment once a day for 4 consecutive days followed by 3 days with no treatment. The device we have used for extremity wounds is a disposable boot attached to either an oxygen cylinder or concentrator that delivers 100% O_2 at slightly above 1 atmosphere of pressure (see www.woundrx.com). A valve contained within the device will automatically release excess pressure if overinflation occurs.
2. Optimize conditions for O_2 delivery.
    a. remove necrotic debris from wound surface,
    b. minimize edema,
    c. keep affected area warm, and
    d. keep patient well hydrated/intravascularly replete—if possible.
3. Wound dressing off during TO treatment.
4. Do not use TO on fistulous tracts—they will epithelialize and stay open.
5. Do not use petrolatum-based dressings, which create a barrier to O_2 penetration of the wound surface.
6. Do not use TO in patients with lower extremity wounds associated with significant limb ischemia (TcOM ≤ 25 mm Hg) to avoid using this type of therapy in patients who are not likely to respond.
7. Do not expect to heal large wounds with TO alone.
8. Use TO as an adjunctive therapy to
    a. improve/prepare wound bed for graft or flap coverage, and
    b. salvage flaps with superficial dehiscence— for example, postoperative pressure ulcer flaps.

In conclusion, TO therapy represents an additional tool available to clinicians managing difficult wounds. There is a clear rationale to justify using topical oxygen because supplementing wound tissue po_2 has been shown to increase collagen deposition and decrease wound infection. There are also published mechanistic data documenting that TO can generate a sustained increase in wound tissue po_2 and angiogenesis and in chronic human wounds it can induce a progressively increasing and sustained elevation of VEGF expression. Understanding the principles of O_2 delivery to the wound site is a critical element in using TO appropriately to achieve wound healing success.

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