Oxygen Therapy and Wound Management: Thinking Outside the Chamber

Editorial Summary

Oxygen is a vital component of basic and advanced wound healing. It plays a major part in intricate cellular processes involved with healing all types of wounds. Understanding the pathophysiology of a hypoxic situation at the tissue level is vital in establishing the types of wounds that will benefit from oxygen therapy. The options for comprehensive therapy are discussed in depth; indications such as venous leg ulcers and chronic venous insufficiency, as well as diabetic foot ulceration are also reviewed in this article. A summary of recent topical oxygen therapy evidence is presented, as well as the myths surrounding oxygen therapy. This guide is aimed at providing support for clinicians wishing to incorporate oxygen into their practice.

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Introduction

Advanced, or 'smart', technology continues to be utilized in all facets of healthcare, up to and including for delivery of oxygen to the body. And while the use of smart technology is said to make life increasingly more convenient from both a personal and professional standpoint, it does not relieve wound care providers of having to understand the many nuances associated with caring for patients living with hard-to-heal wounds. From the mechanism of action and the administration of oxygen therapy, to the available research that offers proven pros and cons to oxygen's use, providers must be comprehensively well versed with this modality regardless of how much today's technology might be able to 'think' for us humans. What's more, topical oxygen presents a myriad of challenges despite how sophisticated today's technology is. This continues to place emphasis on the basic facts and best practices surrounding this important life-sustaining element.

Oxygen's Important Role

Oxygen is crucial in all phases of the wound healing cascade of events. Cellular and biological processes depend on oxygen, especially during the repair process. These include cell proliferation, angiogenesis, collagen deposition, resistance to infection, and protein synthesis needed to restore tissue integrity and function.[1] Tissue oxygenation can trigger healing responses as well. Oxygen keeps cells nourished, oxidizes food during cellular respiration, is involved in the production of cell energy, and is an overall essential element to wound healing.[2] Hypoxia, a lower level of oxygen than normal, is caused when there's an impaired delivery of oxygen or an impaired cellular oxygen uptake.[2] In the human body, normal blood oxygen level is categorized in the 94 - 98% range, while levels below 90% are considered dangerous and require intervention.[3]

Negative Effects of Decreased Oxygen

Limiting oxygen to the cells could have negative consequences, such as impaired healing and respiratory issues. Consider chronic obstructive pulmonary disease (COPD), which compromises lung function due to damage to the airways that renders breathing difficult. As COPD and breathing difficulties advance, a lack of oxygen to vital organs could lead to hypoxia. Symptoms include shortness of breath, frequent respiratory infection, fatigue, lower-extremity swelling, and reduced muscle strength.

Another condition that restricts the flow of oxygen and can impact wound healing is obstructive sleep apnea (OSA), a serious disorder that causes breathing to stop repeatedly during sleep when the body should be receiving extra oxygen. If left untreated, OSA can lead to hypertension, development of diabetes, heart conditions, and strokes, among other maladies. The importance of recognizing diminished oxygen levels has led clinicians to utilizing the delivery of oxygen as a treatment. COPD patients, depending on severity, can be prescribed supplemental oxygen, while patients with OSA can be treated with positive airway pressure devices that prevent breathing

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interruptions.

Another form of oxygen as a treatment is hyperbaric oxygen therapy (HBOT), the roots of which actually date back to the 1600s. In the late 1930s, the military began using hyperbaric chambers to treat deep-sea divers who experienced decompression sickness. In 1967, the Undersea Medical Society, now known as the Undersea and Hyperbaric Medical Society (UHMS), was founded and later reviewed available evidence supporting the use of HBOT for a number of conditions. A listing of approved indications for HBOT by the U.S. Food & Drug Administration includes[4]:

Approved Indications for HBOT:

- Air and gas bubbles in blood vessels
- Anemia (severe anemia when blood transfusions cannot be used)
- Burns (severe and large burns treated at a specialized burn center)
- Carbon monoxide poisoning
- Crush injury
- Decompression sickness
- Gas gangrene
- Hearing loss (complete hearing loss that occurs suddenly and without any known cause)
- Infection of the skin and bone (severe)
- Radiation injury
- Skin graft flap at risk of tissue death
- Vision loss (when sudden and painless in one eye due to blockage of blood flow)
- Wounds (non-healing, diabetic foot ulcers)

It is reported that there are more than 8 million chronic wounds that are more likely to be stuck in the inflammatory phase.[5] The longer that it takes to manage these wounds effectively will increase likelihood of complications - time is tissue.

Options for Comprehensive Treatment

An arsenal of modalities is available that can impact cellular dysfunction in chronic wounds. These modalities could include electrical stimulation, high frequency ultrasound, low frequency contact and non-contact ultrasound, low level laser, shockwave therapy, pulse lavage, negative pressure wound therapy, diathermy, deep oscillation devices, and others that can be conducted in conjunction with sharp debridement, compression, and complete decongestive therapy (CDT). The goal with these modalities mainly includes the ability to 'jump start' chronic wounds into the progressive healing cascade and removing nonviable tissue to alter the wound environment.

Altering the chronic wound environment can move the wound along the healing path. Chronic wounds have an alkalic pH level of 7.15 - 8.9, while wounds that make progress have a much lower pH level.[6] If we are successful in decreasing the pH level by one numeric point, this increases the oxygenation level at the wound dramatically.[6] Necrotic tissue is a medium for bacteria to proliferate and produce inflammatory mediators that inhibit healing. Without adequate local tissue oxygenation, the respiratory burst is impaired and the result is increased susceptibility to infection.[7]

Clinicians should also aim to assess arterial perfusion in lower-extremity wounds to establish adequate delivery of oxygen-rich blood to tissue. The delivery of oxygen is dependent on adequate blood flow at the capillary level. Without adequate perfusion, tissue death is eminent as the environment could become ischemic. Acute hypoxia is needed for cellular signaling, but chronic hypoxia will maintain the wound in an inflammatory phase. Treatment through revascularization can reestablish adequate levels of oxygen delivery to tissue.

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Another important and often missed component in wound care is recognizing the negative effects of edema. Edema impairs the healing process because it delays the delivery of oxygen and nutrients to tissue. The endothelial glycocalyx plays an important role in fluid management, but increases endothelial cell permeability and leukocyte infiltration when injured. There's also an increase in inflammatory cytokines, matrix metalloproteinases, reactive oxygen and nitrogen species, iron deposition, and tissue metabolites.[8] When interstitial space increases due to endothelial glycocalyx damage or with an edematous condition, the distance from the capillaries to the cells requiring oxygen increases, therefore delaying oxygen transport. This increase in diffusion distance robs the wound of oxygen, which ultimately impairs the healing cascade of events. Patients with chronic venous leg ulcers (VLUs) and edematous lower extremities suffer from frequent infections, skin changes, and poor outcomes.

Chronic Edema and VLUs

Studies have validated the fact that patients with chronic edema have a difficult time healing. Rafetto et al. describe that the incidence of VLUs is 70 - 80% of all clinical ulcers, with recurrence rates of 50 - 70% at 6 months.[8] VLUs pose a significant problem to our population, but new findings indicate that the numbers will continue to increase. The standard of care for VLUs consists of compression. With the recent changes in the Starling principle, it is understood that the lymphatic system is responsible for removing fluid and resolving edema. If a patient has a healthy lymphatic system, edema management will not pose a problem. However, if a patient's lymphatic system fatigues, fails, or is damaged, any long-standing VLU edema will lead to a condition known as phlebolymphedema. A condition that indicates venous damage, phlebolymphedema when present with ulcers will lead to difficult healing due to the presence of stagnant protein-rich fluid and due to the longstanding fluid volume within the lower extremities. Essentially, the lymphatic system is working overtime and eventually fails. Margolis et al. discuss a prognostic model for VLUs, indicating that a wound that is < 10 cm2 and less than 12 months old at the first visit has a 29% chance of not healing by 24th week of care, while a wound > 10cm2 and > 12 months old has a 78% chance of not healing.[9] This could be our answer as to why VLU patients with prolonged unresolved edema could have a poor chance of healing. If patients with VLUs have a lymphatic system that fails due to prolonged edema, compression will not suffice as the standard of care. The treatment at this point, along with compression, should be aimed at moving lymph to another quadrant with a normal lymphatic system. A 2022 article indicates that all edema is related to lymphatic dysfunction, whether transient or permanent, thereby creating a lymphedema continuum.[10] Untreated lymphatic dysfunction will also lead to an increase in diffusion distance, thus decreasing the amount of oxygen delivered to the skin and/ or wound.

The Impact of CVI

In their 2020 study, Dean et al. established that lower-extremity lymphedema is predominantly caused by chronic venous insufficiency (CVI) and not the commonly encountered cancer.[11] This also underscores that when the cause of edema is not addressed properly, patients will encounter frequent infections, chronic wounds, and other complications while not allowing oxygen to diffuse adequately. Tests such as transcutaneous oximetry (PtcO2) can assess the peri-wound oxygen tension of wounds. Fife et al. determined oxygen tension < 40mm Hg to be defined as tissue hypoxia.[12]

Patients with edema, inflammation, and/ or infection could have initial Ptc02 readings < 30 mm Hg, due to the increased diffusion distance. When adding supplemental oxygen under

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normobaric conditions, if the PtcO2 is > 100mm Hg, there could be an edematous condition at fault, as opposed to an arterial condition, decreasing the delivery of O2. Noting the important role of oxygen throughout the healing process, focusing on adequate arterial perfusion and decreasing the diffusion distance of edematous legs can be of value to bringing wounds out of the inflammatory phase and into the proliferative phase. Additionally, wound bed oxygenation can increase by revascularization, debridement of necrotic tissue, address infection, and address edema.

A study published in 2003 found that the percent change in wound area at 4 weeks in those who healed was 82%, whereas the percent change in wound area was 25% in those who failed to heal.[13] The percent change in foot ulcer area after 4 weeks of observation is a robust predictor of healing at 12 weeks. This study concluded that this can serve as a clinical decision point in care for diabetic foot ulcers to identify patients who may not respond to standard care requiring additional treatments. If limited or no progress is made at 4 weeks, it is recommended to reassess the wound for arterial perfusion, infection, and other factors that delay healing and potentially consider the use of advanced modalities.

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The Emergence of Topical Oxygen Therapy

Topical oxygen therapy (TOT) is another valuable option that has been available for some time, but early research was lacking. As such, TOT was often labeled as 'topical hyperbaric oxygen therapy', which is incorrect based on its function.

More recently, there has been a great deal of available research on the effectiveness of TOT and its ability to help heal chronic wounds. TOT is not likely to replace HBOT, but should continue to produce optimal evidence-based results. What follows is a list of top challenges that exist related to the use of TOT.

Top 10 Challenges of Oxygen Therapy

1. The use of TOT at Home Doesn't Alter Treatment at an Outpatient Wound Clinic

During the past 3 years, I've had the opportunity to use long wave infrared thermography and Near Infrared Spectroscopy on chronic hard to heal wounds. Medical thermography has over 800 published articles and this allows me to not only look for physiological anomalies in the nonvisible light spectrum but also to assess tissue oxygenation. These objective findings assist providers with their clinical assessments, while requesting further objective tests, validates treatment interventions and utilized in preventative measures not only for pressure injury but also for patients with diabetes. As we consider chronic wounds to have a decrease in oxygenation in the wound bed, I am also noting a decrease in thermal energy when imaging chronic wounds, classifying them in a hypoperfusion state. Thermographically, it is evident that technology can assist us with determining which wounds may not progress due to a lack of oxygen, whether the lack of oxygen is due to arterial disease of a problem with increased diffusion distance, as in an edematous extremity. In addition, dehiscence of incisions may occur when there's increased diffusion distance, therefore minimizing the amount of oxygen needed to maintain surgical incision health.

Patients can utilize TOT at home and continue wound care treatments at an outpatient clinic and/ or with home health, without altering the plan of care. Providers can continue treatment,

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such as debridement and other modalities, just as if they were performing HBOT treatment. The only exception would be negative pressure wound therapy and/ or occlusive dressings, as oxygenation might not reach the wound bed due to the occlusive barrier. To be mindful of successful interventions, chronic wounds could require additional modalities, as long as the basic tenets of wound care have been implemented and not overlooked.

2. Recent TOT Evidence

There is growing evidence of the benefits of TOT. A sampling of studies includes:

Benefits of TOT

- Evidence of TOT promoting collagen formation and VEGF expression promoting angiogenesis[26]
- Use of a special probe to measure the superficial pO2 at the center of the wound (2mm depth) after exposure to topical oxygen[27]
- A comparison of a variety of chronic wounds being treated with HBOT versus TOT for 14 weeks and assessing healing outcomes[19]
- A study that examined VLUs being treated with TWO2 versus compression[28]
- A report that TOT can generate sustained increased in wound pO2 supporting angiogenesis and increased VEGF[29]
- A DFU study noting that at 12 weeks with TWO2 with a mean baseline wound area of 4.1 cm2, there was a healing rate of 82.4%, with a median of 56 days to heal; versus the control group with a mean baseline wound area of 1.4 cm2, there was a healing rate of 45.5%, with 93 median days to heal in the standard of care group[30]
- A study of VLUs with > 2 years onset, with no improvement over the previous year, demonstrating improved healing rates and median time to heal when using TWO2[31]
- A multinational, multicenter, randomized, double-blinded, sham-controlled trial supporting cyclical pressurized TOT for the treatment of DFUs[32]

3. TOT Being Misunderstood

As indicated by a recent consensus statement on guidelines for the use of TOT in the treatment of hard-to-heal wounds[25], there's a growing body of evidence suggesting that topical oxygen is valuable in healing DFUs.

4. Indications

As with any product, following manufacturer's indications to ensure proper use is imperative. Indications for TOT includes the use for chronic, hard-to-heal wounds such as DFUs, VLUs, pressure ulcers (stage 3 - 4), and post-surgical and burn wounds. TCOT and/ or CDO list indications to treat such as skin ulcerations resulting from diabetes, venous stasis, post-surgical infections, gangrenous lesions, pressure ulcers, infected residual limbs, skin grafts, burns, and frostbite. Research lists wound types that are indicated and/ or have demonstrated successful outcomes for TOT,[21] including diabetic ulcers, vascular ulcers, post-surgical infections, pressure injuries, amputations and infected stumps, skin grafts, ischemic tissues, burns, and frostbite. The utilization of various products and modalities as intended could alter the healing trajectory of chronically stalled hard-to-heal wounds.

5. Understanding TOT Contraindications

Contraindications for topical oxygen include:

Contraindications

- Inadequate perfusion to support wound healing
- Acute thrombophlebitis
- Ulcers due to Raynaud's disease
- Presence of necrotic tissue if debridement is not attempted. Necrotic wounds with eschar or slough
- Wounds with fistulas or deep sinus tracts with unknown depth
- Wound dressings that are occlusive, including the use of petrolatum products

"The importance of oxygen is also recognized in the numerous biological processes occurring throughout the healing cascade, such as cell proliferation, angiogenesis, protein synthesis, and resistance to infection, which are required for restoration of tissue function and integrity."[21,22]

Also consider including untreated osteomyelitis, and malignant wounds.

6. TOT Safety & Precautions

Although there are benefits for using oxygen in the wound management field, the hazards and side effects of oxygen must be considered. Oxygen should be administered cautiously, as with any medication.

Generally, oxygen supports combustion, so smoking should not be permitted near the source of oxygen and it should be kept away from any heat source. Ensure that any electrical equipment involved is in safe working condition. Unlike precautions and possible complications with HBOT, TOT presents no risk for oxygen toxicity, ear barotrauma, pneumothorax, temporary change in vision, or a decrease in glucose levels. Devices that are worn continuously are recommended to be disconnected during a shower or bath. A recent systematic review and meta-analysis study on the efficacy and safety of TOT for DFUs concluded that TOT is effective and safe for chronic DFUs.[23] Another 2022 study describes TOT to be considered safe with no known risks to the patient above moist wound therapy alone with no reported serious adverse events or reactions in the literature.[21,24]

7. Failing to Recognize and Address Importance of Oxygen

Oxygen levels affect the quality of new blood vessel growth, collagen formation, and the signaling of growth factors. Chronic wounds are found to have low oxygen levels. Adequate circulation should be determined with objective testing in lower-extremity wounds to ensure there's oxygenation and nutrients reaching tissue. The importance of oxygen is also recognized in the numerous biological processes occurring throughout the healing cascade, such as cell proliferation, angiogenesis, protein synthesis, and resistance to infection, which are required for restoration of tissue function and integrity.[21,22]

8. Uncertainty About TOT Changing Wound Environment

It is known that chronic wound beds have higher-than-normal pH levels. Dissemond et al. acknowledge that pH values influence wound healing and that insight into this allows for more individualized therapy.[14] Percival et al. mention how pH has been shown to affect matrix metalloproteinase activity (MMP), tissue inhibitors of MMP, fibroblast activity, keratinocyte proliferation, microbial proliferation, and immunological responses in a wound.[15]

The pH of chronic wounds has been described to be between 7.15 and 8.9 (7 being neutral, above that as alkaline and below as acidic). For perspective, a pH of 4 is 10 times as acidic as a pH of 5, representing a 10-fold in H+ concentrations.[16] The same study describes how pH level decreased as the wound progresses.[17] Since there's a higher number of MMP and necrotic tissue in the wound bed, there's also an increased metabolic load resulting in tissue hypoxia.[18]

The pH also influences oxygen release to the tissue. By lowering the pH, there's an increase of oxygen diffusion. Tissue oxygen tension (pO2) > 40mmHg increases the likelihood of healing. Gordillo demonstrated that tissues must have a pO2 of at least 40 mmHg to promote the production of VEGF, collagen, and restore angiogenesis.[19] Fries et al. utilized a special probe at a depth of 2mm in the center of a wound, to determine if TOT raises pO2 levels. Another study utilized an oxygen aerosol delivery system, which could continue to answer questions on oxygenation penetration.[20]

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9. Understanding Available TOT Therapies.

There are various types of topical oxygen therapy (TOT) delivery systems, including intermittent TOT, continuous TOT (TCOT), and continuous diffusion of oxygen (CDO), to deliver oxygen to the tissue. There are differences, however, in how oxygen is supplied to the wound bed and the equipment. TOT uses a high-flow oxygen concentrator connected to a disposable boot or bag, supplying oxygen to the area for 90 minutes, five days per week. The pressure on one device that's available cannot be controlled, while the other device can control the pressure from 0 - 50 mmHg to help oxygen diffusion to the wound bed. The concentrator is connected to a power source and it's capable of being used at multiple settings, including the patient's home. The patient will be immobile during therapy. While oxygen could desiccate a wound bed, a humidifier is utilized to maintain the moisture level inside this boot or bag. Oxygen transfer requires the wound to be moist. One product utilizes non-contact cyclical compression to aid in edema management and the use of humidification, to maintain a moist wound barrier to aid in oxygen diffusion while preventing desiccation.

TCOT uses oxygen generators to continuously provide oxygen from the air to the wound 24 hours per day, 7 days per week. Tubing can be placed within a wound dressing. This continuous system requires a minimum relative humidity level and the level of humidity must be met for normal operation. CDO is a lightweight, handheld device using an oxygen generator providing continuous delivery of oxygen to the wound bed. It delivers oxygen via a cannula that is placed under a moist wound dressing indicated for 24 hours, 7 days per week therapy time. There are two types of CDO systems available: CDO with oxygen distribution system. These systems will produce oxygen even at lower levels of humidity.

10. Realizing TOT is Not HBOT

Topical oxygen is not and should not be classified in the same category as HBOT, nor 'soft' or 'mild' chambers. Although HBOT and TOT interventions deliver oxygen to the wound bed, HBOT mechanism of action is to deposit an increase of oxygen to the wound bed, HBOT mechanism of action is to deposit an increase of oxygen to the wound through the plasma as the patient breathes 100% oxygen. On the contrary, TOT is diffusing oxygen across the wound bed and can be utilized in various settings, including the patient's home, making it convenient when there are barriers such as lack of transportation, rising gasoline prices, the pandemic, lack of resources, and no access to advanced modalities.

Topical oxygen pressures are slightly higher than normobaric pressure, equivalent up to 1.1 atmosphere absolute (ATA). HBOT pressures will be higher than normobaric pressures consisting of >1.4 ATA with treatments typically ranging from 2-3.0 ATA. There's data indicating the effectiveness of TOT, especially for treating DFUs. But if the goal is to increase the tissue pO2 to a hyperoxygenated level systemically, HBOT will be the choice.

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