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Case Report

Topical Oxygen Therapy in Wound Healing: A Narrative Review of Mechanisms and Modalities

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Abstract:

Wound healing is a dynamic and intricate physiological process requiring adequate oxygenation to support cellular functions critical for tissue repair. Oxygen plays an essential role in all phases of wound healing, including inflammation, angiogenesis, collagen synthesis, and epithelialization. Inadequate oxygen supply, often observed in chronic wounds such as diabetic foot ulcers and pressure sores, can lead to delayed healing, infection, and poor clinical outcomes. As a result, therapeutic strategies aimed at improving oxygen availability in wound tissues have gained increasing attention.

This narrative review explores the physiological role of oxygen in the wound healing process and examines the clinical utility of oxygen-based interventions. A focused literature search was conducted using online databases including PubMed, Scopus, and Google Scholar to identify relevant studies, reviews, and clinical guidelines on oxygen therapy in wound management. The review discusses key modalities of topical Oxygen delivery and innovative oxygen-delivery systems.

While these techniques promise to promote healing in hypoxic and non-healing wounds, their use requires careful patient selection and clinical judgment. By summarizing current evidence and emerging trends, this review aims to provide clinicians and researchers with a comprehensive understanding of how oxygen therapy can be integrated into effective wound care strategies.

Key words: wound healing; chronic wounds; topical oxygen therapy; continuous delivery of oxygen; hemoglobin spray; higher cyclical pressure oxygen; low constant pressure oxygen

Introduction

Chronic or hard-to-heal wounds are those that do not heal properly within a time that is normally sufficient for healing.[1] The rising number of patients with chronic non-healing wounds has resulted in a change in medical research towards therapeutic techniques to hasten wound healing and allow home-based care in an attempt to bring down hospital costs and to improve patient compliance.

Wound healing is a complex biological process involving a coordinated sequence of events, including hemostasis, inflammation, proliferation, and re-modelling. Oxygen plays a pivotal role in each of these stages, serving as a critical substrate for energy production, cell proliferation, angiogenesis, collagen synthesis, and defence against pathogens. The understanding that local tissue hypoxia and low oxygen tension at the wound bed are key factors contributing to wound chronicity has led to the development of various modalities of oxygen delivery to the wound surface to promote wound healing, broadly termed topical oxygen therapy.

This review explores the physiological role of oxygen in wound healing, evaluates the clinical efficacy of different oxygen therapy modalities, and highlights emerging innovations in oxygen delivery systems. Understanding these approaches is essential for optimizing outcomes in patients with complex or non-healing wounds.

Physiological Role of Oxygen in Wound Healing

Oxygen and its derivatives contribute to wound healing through various mechanisms (Figure 1):

1. Energy generation: Cellular respiration in the electron transport chain within mitochondria synthesises adenosine 5'-triphosphate (ATP). ATP is the fundamental energy currency of the cell, and is a prerequisite for cellular metabolism, protein synthesis, and collagen maturation

2. Nitric Oxide synthesis: essential for the regulation of local vascular tone
3. Oxidative burst and Phagocytosis: Reactive oxygen species (ROS) such as Superoxide and Hydrogen peroxide are generated by the action of NADPH oxidase and Superoxide Dismutase enzymes, respectively, in phagocytic cells, which have bactericidal and bacteriostatic properties. Hydrogen peroxide is acted on by Myeloperoxidase to generate hypochlorous acid, which has local disinfectant actions. [2]
4. ROS, in addition, helps in cellular signalling, migration, and upregulation of platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF).

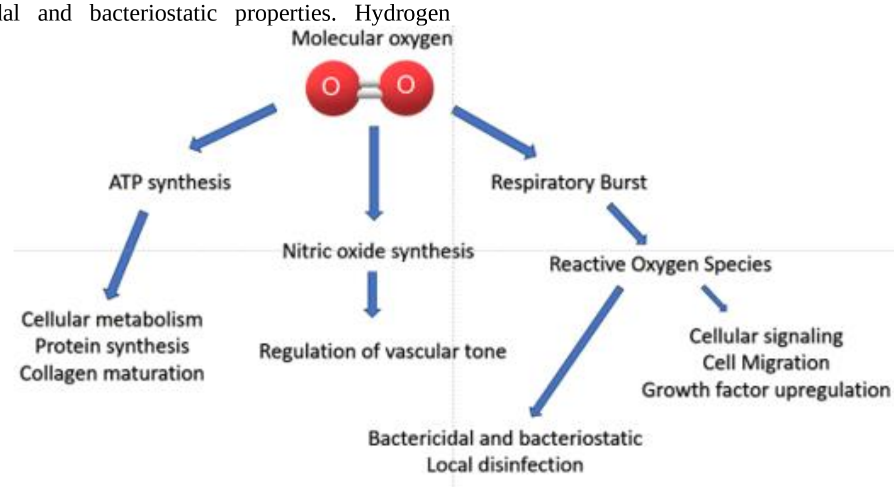

Figure 1: Physiological Role of Oxygen in Wound Healing

The oxygen inflow to the tissue by arterial perfusion and the rate of oxygen consumption determine the local oxygen tension. [3] In the subcutaneous tissue, where the capillary network is less dense and consumption of oxygen is relatively low, cellular diffusion of oxygen is driven by the arterial oxygen tension. Oxygen tension in normal tissues reaches around 100 mmHg. Disruption of microcirculation in a wound impairs oxygen transport, causing oxygen tension to drop to 10-30 mmHg in the centre of a wound, contributing to wound chronicity. [2]

Effect of Biofilm on wound oxygen tension

Chronic wounds have depleted oxygen levels owing to increased local metabolism, tissue edema, impaired perfusion, and bacterial oxygen consumption. A bacterial biofilm is an organized assembly of bacteria that are embedded in a self-generated extracellular matrix, typically made up of substances like polysaccharides, proteins, and extracellular DNA. These communities attach to various surfaces, whether biological or inert, and the surrounding matrix shields the bacteria, enhancing their resistance to antimicrobial agents and immune responses. Neutrophilic activity in the wound microenvironment in response to infection results in the generation of large quantities of ROS, thereby depleting the local oxygen. [4] This response is usually temporary and the oxygen consumption decreases once the inflammation settles. However, in chronic wounds where the biofilm persist, neutrophil recruitment and activation is sustained resulting in oxygen depletion. [5]

Clinical indicators of Low oxygen tension at the wound

Isolation of obligate anaerobic species from the wound may be a surrogate marker for persistent low oxygen tension. [6] High lactate levels in the wound exudate also indicate increased anaerobic glycolysis. [7] Newer modalities such as Transcutaneous oximetry (TcPO2), Near-infrared Spectroscopy, and Hyperspectral imaging with Remission spectroscopy may be used, wherever available, to estimate local oxygenation and guide therapy. [8–10]

Topical Oxygen Therapy Modalities

A 2022 expert consensus panel defined Topical Oxygen Therapy (TOT) as ‘the administration of oxygen applied topically to wounds by either mechanical or non-mechanical means to promote tissue healing. [11]

Topical Oxygen Therapy (TOT) differs technically from Hyperbaric Oxygen Therapy (HBOT), which is a systemic therapy wherein the patient inhales oxygen at supraphysiological tension (1800 mmHg) in a hyperbaric chamber (2.4 ATA). [12] Hence, the two techniques may be combined for a synergistic effect.

TOT is based on the principle that maintaining higher wound oxygen tension can improve pathogen clearance by phagocytic cells, optimise enzymatic activity, improve cellular metabolism and tissue regeneration, ultimately resulting in the promotion of wound healing. [13]

We discuss various techniques for the topical oxygen therapy reported in scientific literature.

1. Continuous Delivery of Oxygen (CDO)

This technique is essentially the addition of a sustained supply of low-flow humidified pure oxygen to moist wound therapy. A portable electrochemical unit generates pure oxygen from the surrounding air, which is delivered to the wound through a flexible cannula and a wound contact layer of occlusive oxygen diffusion dressing (Figure 2). Purified oxygen is delivered at a constant low flow rate of 3- 15ml/hour for 24 hours a day for 7 days a week. [14,15]

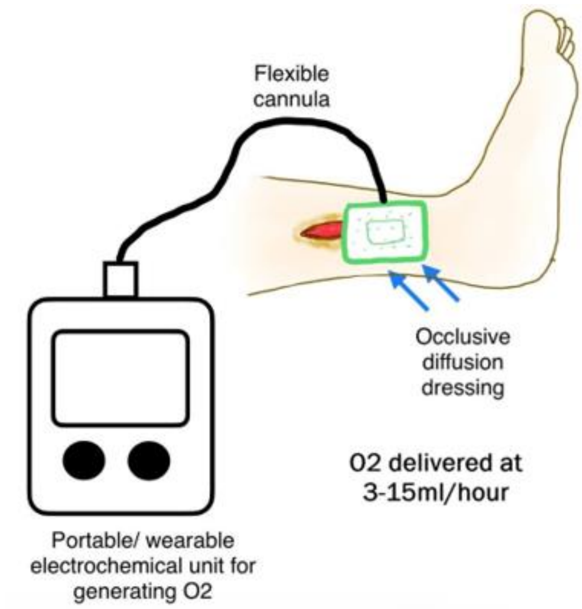

Figure 2: Schematic representation of Continuous delivery of Oxygen (CDO)

2. Disposable Continuous Delivery of Oxygen (DCDO)

These devices are a disposable variant of conventional CDO machines, and comprise of tape-based electrochemical oxygen generators intended to be used for 15 days following which they are to be replaced. They offer the advantage of being lighter and wearable. The rate of oxygen delivery and frequency of use are identical to conventional CDO systems. [16,17]

3. Higher Cyclical Pressure Oxygen

These devices deliver oxygen into a disposable plastic chamber placed around the wound, at pressures cycled between 10 mbar and 50 mbar at 10L/min with the help of a computer-controlled concentrator. The treatment is delivered for 90 minutes for 5 days per week. [18] The non-contact cyclical compression simulates a level 3 conventional compression dressing (CCD) and helps to reduce both peripheral edema and the hydrostatic pressure in the lower leg that is a frequent component of lower extremity peripheral vascular disease. [19]

4. Low Constant Pressure Oxygen

Low constant pressure oxygen (LCPO) devices deliver a high flow (2–5 I/min) of low-pressure oxygen at 29 mbar to a disposable plastic extremity chamber placed around the wound. The treatment is delivered for 60-90 minutes for 3-7 days a week. [20]

5. Hemoglobin Spray

Topical hemoglobin spray uses a liquid containing 10% purified Hemoglobin. Hemoglobin is sprayed directly onto the wound, where it functions as a carrier facilitating diffusion of oxygen from the surrounding air into the wound tissue, effectively bypassing the diffusion barrier formed by wound exudate. The treatment is used as an adjunct to standard-of-care wound care and can be repeated during each dressing change. The treatment works concomitantly with conventional moist wound dressings, but care should be taken to avoid occlusive dressings so as to allow for oxygen diffusion. [21–24]

6. Oxygen Dressings

These are specialised dressings which deliver topical oxygen without the need for an external oxygen source. They may be of two types:

a. Continuous release dressings

These are multilayer dressings that are prefilled with pure oxygen embedded in a reservoir at >2800 ppm or in foam vesicles. They comprise a barrier layer that holds the oxygen in the wound and a semipermeable contact layer that allows oxygen diffusion into the wound surface. Oxygen diffusion is facilitated by the moisture from the wound and is sustained for around 5 days. [25]

b. Hydrogel dressings

These dressings rely on controlled biochemical reactions for the release of oxygen. Various products are available that differ in the substrates utilised for oxygen synthesis, many of which are based on the breakdown of hydrogen peroxide into oxygen and water. Optimal results are obtained when such dressings are used concomitantly with standard cleaning and debridement. [26,27]

Current Indications, Contraindications, and Practice Recommendations

Positive results reported in various randomised trials and systematic reviews have resulted in TOT being recommended with the highest level of evidence rating by the ADA and the International Working Group on the Diabetic Foot (IWGDF) in 2023. [28,29]

TOT may be used as an adjunct therapy in non-healing wounds that have failed to show a size reduction of at least 50% after 4 weeks of optimal standard of care treatment. This may be extrapolated to all chronic wounds, such as diabetic foot ulcers, pressure ulcers, and venous ulcers, which are known to have local hypoxia. Current evidence is insufficient to recommend its use in critical limb ischemia.

Wounds that show satisfactory healing should be continued on standard of care therapy without using TOT and reassessed every 1-2 weeks. TOT may be considered if wound healing stalls after initial progress. Compression, pressure relief, and vascular procedures should be implemented based on individual needs, with appropriate management of pain and infection.

TOT should be deferred if the wound is covered with eschar, on wounds with an untreated infection or osteomyelitis, in the presence of a malignancy, or un-debrided wounds. Hydrogels, foam dressings, multilayer compression, petrolatum-based salves, or occlusive dressings should not be used under the TOT treatment device as they may hinder oxygen transfer. [30]

Future Directions

With growing evidence supporting the various modalities of delivering topical oxygen for chronic wound healing, focus should now be directed towards making the technology universally accessible and cost-effective. Research should also focus on the development of diagnostic tools to measure wound oxygen tension, such as Near Infrared Spectroscopy, which can help identify wounds at risk of hypoxia and monitor therapy. With the advent of artificial intelligence, AI-enabled smart dressing devices that can monitor wound oxygen levels in real time and administer oxygen as per deficit have the potential to enable home-based or ambulatory healthcare.

Conclusion

In conclusion, while the current body of evidence on topical oxygen therapy (TOT) is heterogeneous and several questions regarding its optimal integration with other treatment modalities remain unanswered, the therapy shows considerable promise. Existing studies—ranging from case reports to randomized trials—support its safety and efficacy as an adjunct to standard wound care. Growing endorsement from expert panels and inclusion in recent clinical guidelines further reinforce its clinical relevance. This review has provided an overview of the underlying principles, evolving delivery methods, and clinical applications of TOT. As research advances, greater clarity on patient selection, treatment protocols, and long-term outcomes will help optimize its use and expand access, particularly in underserved settings.

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