Using Topical Intermittent Wound Oxygen TWO2® in Wound Healing

The unique component is cyclical compression.

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Disclaimer: *Dr. Garoufalis is CMO of AOTI, Inc.*

Abstract

Chronic wounds are a significant burden on healthcare systems and patients worldwide. Topical oxygen therapy, specifically intermittent cyclical pressurized topical wound oxygen (TWO2) therapy, represents a proven modality in the management of complex wounds. This article explores the scientific rationale, clinical benefits, and mechanisms behind TWO2 therapy, with particular emphasis on the synergistic effect of cyclical compression. Supported by recent clinical studies and mechanistic insights, TWO2 therapy is emerging as a valuable tool in modern wound care.

Introduction

Chronic wounds such as diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and pressure injuries are challenging to treat due to impaired oxygen delivery, infection, and prolonged inflammation. Acute wounds in individuals who have certain co-morbidities or might otherwise be compromised are also at risk for healing complications or slow-to-heal processes. Oxygen is critical for most wound healing processes, including collagen synthesis, angiogenesis, fibroblast proliferation, and immune responses.

While hyperbaric oxygen therapy (HBOT) has long been used, its limitations in accessibility and systemic effects have led to interest in localized alternatives like topical oxygen. We can take what we have learned from the use of HBOT and apply it to those patients who may not have access or the ability to undertake HBOT, so that they may benefit from this technology.

TWO2 therapy combines high-pressure delivery of oxygen, with non-contact cyclical compression in a sealed chamber, with humidification, allowing for transcutaneous oxygen diffusion and absorption, and enhanced tissue perfusion. This multi-modality approach offers a unique physiological and therapeutic benefit for wound healing.

Oxygen and the Wound Healing Cascade: Oxygen is essential throughout the phases of wound healing:

1) Hemostasis and Inflammation: Oxygen supports reactive oxygen species (ROS) production for bacterial killing and signaling.

2) Proliferation: Oxygen enhances angiogenesis by upregulating hypoxia-inducible factor-1 alpha (HIF-1α) and vascular endothelial growth factor (VEGF), stimulating endothelial cell migration.

3) Remodeling: Collagen cross-linking by prolyl and lysyl hydroxylase enzymes is oxygen-dependent.

Hypoxia is a hallmark of chronic wounds, often exacerbated by diabetes, vascular disease, and infection. While we can still heal wounds in a hypoxic state, correcting local oxygen deficiency improves the rate of wound healing as well as the wound durability going forward, resulting in fewer recurrences.

Topical Wound Oxygen (TWO2) Therapy Mechanism of Action: TWO2 therapy involves placing the affected limb into a chamber where 100% oxygen, at 10 L/minute is intermittently pressurized and released in cycles. This cyclical compression enhances oxygen diffusion through the skin and wound bed, while promoting interstitial fluid movement, thereby reducing edema. Nitric oxide production is stimulated while also increasing vasodilation. The mechanical stimulation of tissues also enhances angiogenic signaling with the tissues.

Advantages of Cyclical Compression: TWO2 therapy's unique component is the cyclic pressurization of the limb chamber. As a result, we get improved perfusion as the cyclic pressure mimics intermittent pneumatic compression (IPC), enhancing venous return and arterial inflow. There is also a reduction in periwound edema and a restoration of capillary exchange. Because of the

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New Concepts and Studies

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mechanical signaling, there is the phenomenon of tissue stretch coming from the active cycling. The resulting pressure differentials increase transcutaneous oxygen delivery and retention in hypoxic tissues.

Biological Pathways Affected by TWO2 Therapy

- ***HIF-1α Regulation:*** TWO2 therapy modulates hypoxia signaling, promoting angiogenesis without overwhelming oxidative stress.
- ***Beta-Defensin 3:*** This antimicrobial peptide is upregulated in response to oxygenation, supporting defense against MRSA and other pathogens.
- ***NADPH Oxidase Activation:*** Enhances ROS production for bacterial killing and signaling, critical in infected or biofilm-laden wounds.

Applications in Special Populations: TWO2 therapy has shown efficacy in populations with complex comorbidities:

- ***Dialysis Patients:*** Despite the challenges of poor perfusion and multiple comorbidities, TWO2 therapy has demonstrated good healing outcomes in renal patients, as shown in the subgroup analysis of the TE02 study.
- ***Post-Surgical Wounds and Skin Grafts:*** TWO2 therapy supports skin graft take by enhancing oxygenation and reducing shear from edema.
- ***Osteomyelitis:*** Case reports and mechanistic data suggest a role for TWO2 therapy in managing infected, ischemic bone wounds.

Comparison with Other Modalities Compared to HBOT and standard care:

- ***TWO2 therapy vs. HBOT:*** TWO2 therapy is localized, reducing systemic risks (e.g., oxygen toxicity, barotrauma) and is easier to administer at home.
- ***TWO2 therapy vs. Standard Care:*** Enhances healing without requiring surgical intervention or prolonged inpatient stays.

Safety and Tolerability TWO2 therapy has a favorable safety profile:

- Non-invasive and well tolerated.
- No systemic oxygen toxicity observed.
- Can be used in conjunction with compression wraps (e.g., for VLUs).

Economic and Operational Benefits

- Reduces hospital admissions and amputations.
- Promotes faster healing, minimizing dressing costs.
- Suitable for home use, improving adherence.
- Valuable in telemedicine-supported wound care programs.

Clinical Evidence Supporting TWO2 Therapy: Numerous studies support the use of TWO2 in chronic wound care:

1) TE02 Study (2020): Published in the *Journal of Wound Care*, this large real-world evidence study evaluated 145 patients with DFUs treated with TWO2 therapy. Healing rates significantly improved, with a 73% healing rate versus 40% in matched controls (Frykberg et al., 2020).

2) Randomized Controlled Trial (2011): Blackman et al. demonstrated that 80% of DFU patients treated with TWO2 therapy healed within 12 weeks, compared to 35% in the standard care group.

3) Systematic Review (2022): A review by Dissemond et al. summarized the benefits of topical oxygen, showing consistent improvement in healing metrics for VLUs, DFUs, and pressure injuries.

Conclusion

Topical oxygen delivered via TWO2 therapy with cyclical compression provides a multifaceted approach to chronic wound healing. By addressing local hypoxia, reducing edema, and activating healing pathways, TWO2 therapy demonstrates both clinical efficacy and economic value. As healthcare moves toward outpatient, home-based management of chronic conditions, TWO2 therapy stands out as a safe, evidence-based tool for wound care. **PM**

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