How Oxygen Penetrates Open Moist Wounds

Physics of Oxygen Transport into Moist Wounds

Moist Wounds “Breathe” Similar to Alveoli in Lungs – By Diffusion

Oxygen transport into a clean, moist wound occurs via the same transport processes that govern oxygen absorption into the alveoli in lungs during breathing: diffusion. Oxygen is transported from the surrounding air to cells in a clean, moist wound (or alveoli) via the physical driving force of diffusion.

In diffusion, gases (or liquids) move from an area of high concentration (partial pressure) to areas of low concentration (partial pressure). If there is a mixture of gases in a container, the pressure of each gas (partial pressure or concentration) is equal to the pressure that each gas would produce if it occupied the container alone. This applies equally well to the concentration of a gas in a liquid. If a gas (oxygen) is present above a liquid (open moist wound), the gas will diffuse into the liquid until it reaches equilibrium in concentration (partial pressure) in the liquid in proportion to that present in the gas above it.

Increasing Oxygen Concentration Above a Moist Wound Increases Oxygen Concentration in the Wound Proportionally

Oxygen in water obeys Henry's law rather well; the solubility is roughly proportional to the partial pressure of oxygen in the air: \( pO_2 = K_{O_2} xO_2 \), where \( pO_2 \) is the partial pressure of oxygen in Torr, \( xO_2 \) is the mole fraction of oxygen in oxygen-saturated water, and \( K_{O_2} \) is the Henry's law constant for oxygen in water (about \( 3.30 \times 10^7 \text{ K/Torr at 298 K} \)). The air (atmosphere) around us has a total pressure of 760 mmHg (1 atmosphere of pressure). Air is made up of 21% oxygen, 78% nitrogen and small quantities of carbon dioxide, argon and helium. The pressure exerted by each gas is equal to the concentration of the gas multiplied by the total pressure pressure. The pressure of oxygen (\( pO_2 \)) of dry air at sea level is therefore 159 mmHg (21/100 x 760=159).
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Pure Oxygen Above A Moist Wound Can Increase Oxygen in Tissue Up to Five-Fold

In human tissue, oxygen levels contain approximately 50 mmHg pO2 at 3-4 mm below the wound for moist wounds exposed to air which has 21% oxygen (pO2 = 159 mmHg). By increasing the oxygen concentration from 21% (pO2 = 159 mmHg) above the wound to 100% (pO2 = 760 mmHg) above the wound, as is the case with Continuous Diffusion of Oxygen therapy using the TransCu O₂™, the resulting oxygen levels in the tissue can increase to as high as 250 mmHg pO2. These levels have been found experimentally to be optimal for many of the enzymatic pathways involved in fibroblast proliferation, collagen synthesis, phagocytic (antibacterial) activity, angiogenesis (new blood vessel formation) and growth factor signaling transduction in wound repair. For more information, refer to the “How Oxygen Works in Wound Healing” guidance document².

Clinical and Preclinical Evidence of Oxygen Transport into Wounds

Oxygen therapies have been shown to rapidly raise oxygen levels in the wound bed, in both clinical and preclinical settings, when pure oxygen is applied directly to the surface of a moist wound at near-atmospheric pressures (not hyperbaric). The following short summaries are of studies published in peer-reviewed literature supporting the use of directly applying oxygen to moist wound beds:

Four-Fold Increase in Wound Oxygen Concentration in Four Minutes (Pre-Clinical)

Preclinically, pure oxygen applied to an open wound has been shown to increase the pO2 of the superficial wound tissue in pigs³. In this study, an increase of pO2 from less than 10 mmHg to 40 mmHg at a depth of 2 mm in the center of the wound bed was observed in as little as 4 minutes using an implanted probe. Furthermore, the investigators confirmed histologically that the oxygen-treated wounds showed signs of improved angiogenesis and tissue oxygenation.

Vascular Endothelial Growth Factor (VEGF) is Proportional to Oxygen Concentration

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.⁴ VEGF expression has been shown to be proportional to oxygen levels and is used as an indirect measure of oxygen levels in wound repair.⁵,⁶

Increase in VEGF Expression & Angiogenesis (Pre-Clinical)

In-vitro experiments have shown that oxygen treatment induces VEGF mRNA transcription in endothelial cells and macrophages.⁷⁻⁹ In-vivo experimental models have also shown that supplemental oxygen therapy increases VEGF protein expression in wounds¹⁰ and can accelerate blood vessel growth in wounds.¹¹ It was demonstrated that oxygen supplied to the surface of a wound increases VEGF expression in wounds and vessel formation in a preclinical pig model.
Clinical Evidence: Better Wound Closure and Angiogenesis versus HBOT
In a clinical trial treating chronic wounds, it has been reported that directly applying oxygen to a moist wound (OXYGEN group) resulted in significantly better wound closure rates and significantly higher VEGF expression as compared to hyperbaric oxygen therapy (HBOT). A non-random prospective clinical trial compared the effect of HBOT (n=32) and OXYGEN (n=25) on wound closure and VEGF expression in chronic wounds. VEGF was studied as an outcome since it is believed to be the most prevalent, efficacious and long-term signal that is known to stimulate angiogenesis in wounds. The type of oxygen therapy administered was based upon the clinical decision of the physician treating the wound. Analysis of the patients for age, sex, wound location and presence of diabetes revealed no significant differences between the subject populations of the HBOT and OXYGEN study groups. Tissue biopsies for VEGF analysis were obtained from the wound edge at three time points (just prior to treatment with oxygen, after 7 weeks and after 14 weeks) during the 14 week study period. The direct wound oxygenation devices were provided by GWR Medical Inc. (Chadds Ford, PA). Treatment with OXYGEN was conducted for 90 minutes per day for 4 consecutive days, followed by three days of no treatment, each week.

The study concluded that direct wound oxygenation treatment resulted in statistically significant reductions in wound size (83%, p=0.001), whereas HBOT did not. Similarly, direct wound oxygenation treatment showed a statistically significant increase in VEGF expression, whereas HBOT did not. No adverse or toxic effects were reported from using direct wound oxygenation.

Clinical Evidence: Improved Wound Closure, MRSA and Pain Reduction, and Reduced Recurrence in Venous Stasis Ulcers vs. Conventional Compression Dressings
A parallel observational study between the use of conventional compression dressings (CCD) and direct wound oxygen therapy (OXYGEN) in the treatment of refractory venous ulcers was conducted to compare the effect of direct wound oxygenation treatment to a current standard of care. The primary endpoint of the study was to compare the proportion of wounds fully healed at 12 weeks. Secondary endpoints included time to full healing, percentage of reduction in ulcer size, pain reduction, and recurrence rates. Patients had to have a chronic refractory non-healing venous ulcer of more than two years duration and no improvement within the last year to be qualified to participate. Patients were given the choice to be managed with either treatment. Oxygen treatment was performed using the AOTI Hyper-Box (AOTI Ltd, Galway, Ireland) for 180 minutes twice daily at a pressure of 50 mbar. Oxygen was supplied at a rate of 10 l/min with continuous humidification. The wound was left exposed between treatments with no dressings unless the patient decided to leave the hospital, in which case the wound was covered with a non-adherent Profore wound contact layer dressing (Smith & Nephew Ltd, Hull, UK). A total of 46 patients were managed with OXYGEN and 37 were managed with CCD. No significant differences were found between the patient populations.

The primary endpoint showed a significant enhancement of healing by applying OXYGEN, with 89% of the ulcers completely healed versus 35 % for the CCD group (p<0.0001). The mean reduction in ulcer surface area for the OXYGEN group at 12 weeks was 96%, compared with 61% for CCD. Median time to full closure was 45 days in the OXYGEN group, compared to 182 days for CCD (p<0.0001). With regard to reduction of infection, 9 of the 19 MRSA positive ulcers were negative after 5 weeks of OXYGEN therapy, compared to none of the 17 MRSA positive ulcer in the CCD group (p=0.007). The pain score threshold in direct wound oxygenation managed patients improved from 8 to 3 by 13 days. Patients were followed for a mean of 12 months, during which none of the 37 fully healed OXYGEN group ulcers showed signs of recurrence, whereas 5 of the 13 fully healed CCD managed ulcers show signs of recurrence. No local or systematic complications were encountered in either group. The authors concluded that direct wound oxygenation is safe and effective in treatment of refractory venous ulcers, achieving shorter healing times, alleviating pain, and reducing recurrence rates.
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Clinical Evidence: Improved and Faster Closure in Diabetic Foot Ulcers vs. MWT

A prospective, controlled study on the treatment of diabetic foot ulcers with direct wound oxygenation treatment was conducted to examine the clinical efficacy of oxygen therapy applied directly to a wound and assess ulcer recurrence at 24 months. Seventeen patients (the OXYGEN group) were treated with oxygen five consecutive days per week (60 minutes per treatment with the pressure cycling between 45 and 50 mbar) using the AOTI Hyper-Box (AOTI Ltd, Galway, Ireland). OXYGEN treated wounds were covered with saline-soaked gauze between treatments. Eleven patients (the MWT group) chose to receive standard silver-containing dressings (Silvercel™, Johnson and Johnson Inc., Somerville, NJ). There were no significant differences in patient demographics between the two groups, yet the wounds in the OXYGEN group were more severe. This may have been the result of selection bias. The ulcer duration and mean baseline wound area were both greater in the OXYGEN group than in the MWT group: 6.1 months (σ=5.8) vs. 3.2 months (σ=0.4) and 4.1 cm² (σ=4.3) vs. 1.4 cm² (σ=0.6), respectively.

Treatment with oxygen was shown to result in significantly greater amounts of healing as well as significantly faster wound closure. The proportion of the ulcers which completely closed was significantly greater in the OXYGEN group than in the MWT group (82.4% versus 45.5%, p=0.013). Oxygen-treated wounds healed in a median of 56 days, as compared to 93 days for MWT wounds (p=0.04). No adverse events were reported and there was no recurrence at the ulcer site after 24 month follow-up in either treatment group. The authors concluded that the patients treated with direct wound oxygenation were significantly more likely to heal and needed a shorter time to heal. The authors also reviewed many other articles in the published literature and cite that no adverse events were observed in this or previously published studies.

Clinical Evidence Summary

In summary, the above clinical studies have shown the following significantly positive effects of using oxygen diffusion therapy:

- Increased VEGF expression and angiogenesis
- Improved wound closure success rate
- Faster wound closure
- Reduction in MRSA infection
- Pain reduction
- Reduced Venous Stasis recurrence

Additional evidence as to how oxygen is effective in wound healing can be found in the guidance document “How Oxygen Works in Wound Healing”, p/n 690024.
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Comparison of Oxygen-Based Wound Therapies

There are three primary different methods of oxygen-based therapies which are used to treat chronic wounds: Hyperbaric Oxygen, Topical Oxygen and Continuous Diffusion of Oxygen. All three technologies are similar in that they use pure oxygen as an aid to wound healing. Hyperbaric Oxygen Therapy is used to treat a patient systemically with pure oxygen at elevated pressures. Topical Oxygen Therapy is used to treat an area directly surrounding a patient’s wound using pure oxygen at pressures slightly above atmospheric. Both of these technologies only offer treatment for a relatively short period of time: typically 90 minutes per day, 4 or 5 days per week. Furthermore, neither of these technologies allows for patient mobility during treatment and can require significant time and expense associated with travel and preparation time for the patient.

Continuous Diffusion of Oxygen Therapy offers several breakthroughs in oxygen therapy. Foremost, it provides continuous oxygen therapy, which is about 25x the therapy time of competing technologies. Used with Moist Wound Therapy dressings, it maintains a moist wound environment and allows for full patient mobility. Furthermore, the TransCu O₂™ device is silent, lightweight (nine ounces), handheld, and rechargeable. The TransCu O₂™ device also incorporates continuous monitoring of oxygen flow rates and pressures to ensure efficacious delivery of the oxygen.

Table 1. TransCu O₂™ (CDO) Advantages

<table>
<thead>
<tr>
<th>Modality</th>
<th>Continuous Diffusion of Oxygen (CDO)</th>
<th>Topical Oxygen Therapy (TOT)</th>
<th>Hyperbaric Oxygen Therapy (HBOT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment at Home</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Patient Mobility</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Maintains Moist Wound Bed</td>
<td>Yes</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td>Direct Wound Treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Therapy Time</td>
<td>Continuous</td>
<td>~90 min/day</td>
<td>~90 min/day</td>
</tr>
<tr>
<td>Flow Rate</td>
<td>3-10 ml/hr</td>
<td>5-60 L/min</td>
<td>Up to 600 L/min</td>
</tr>
</tbody>
</table>

Notes:  
A – also referred to as Topical Hyperbaric Oxygen Therapy  
B – can be treated at home, yet patient immobile during treatment  
C – treatment typically treats portion of limb, not just wound: limb may be constricted

The TransCu O₂™ is intended for use with lower-cost wound dressings as an adjunctive therapy to moist wound therapy. The goal of the therapy is to continuously diffuse pure oxygen into an oxygen-compromised wound to aid in wound healing while maintaining a moist wound healing environment, maintaining patient mobility and significantly reducing costs.
REFERENCES