JWC
journal of wound care

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ISSN 0969-0700
Printed by Pensord Press Ltd, Blackwood, NP12 2YA

How can we deliver oxygen to wounds?

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How does oxygen work in wound healing? We are all familiar with how necessary oxygen is for life in general. A few minutes of holding your breath (if you can last that long) proves the point quickly. We are taught the basics of how oxygen is important for essential processes such as energy conversion in the adenosine triphosphate (ATP) cycle, yet not typically processes in which oxygen plays a critical role in wound healing.

Oxygen boosts vitality to support increased demand during healing: intracellular processes such as biosynthesis, movement, and transport need energy to be functional. Mechanisms that are more specific to wound healing itself include cell proliferation, angiogenesis, collagen formation, respiratory burst and growth factor signaling transduction, which we'll discuss in more detail.

The practical implications of these mechanisms of action related to oxygen are faster wound healing and closure, with collagen formation that is not only faster, yet stronger, more organized and hence more normal appearing (less scarring). These processes begin shortly after the application of oxygen to a wound. With the continuous, topical application of oxygen, there are several clinical indications that appear within hours or days of application, including pain relief, increased exudate and a general reddening of the wound.

Pain relief is an interesting effect since it can be rapid and dramatic – sometimes within hours of application.[1] The most likely explanation is that hypoxia can induce pain and relief of the hypoxia through introduction of a hyperoxic environment eliminates the source of the pain. The increased exudate normally happens within a few days of oxygen application and is a sign that oxygen is reactivating the wound healing process. The wound typically will redden dramatically in the first week or two, which is a sign of new capillary formation in the wound bed. These effects were recently demonstrated at a molecular level in a study by Lavery et al. on the effect of continuous diffusion of oxygen (CDO) on cytokine and growth factor levels.[2] At one week after application of CDO, growth factor levels increased significantly (Fig 1), with VEGF increasing over 400% and TGF-β over 800% relative to baseline levels.

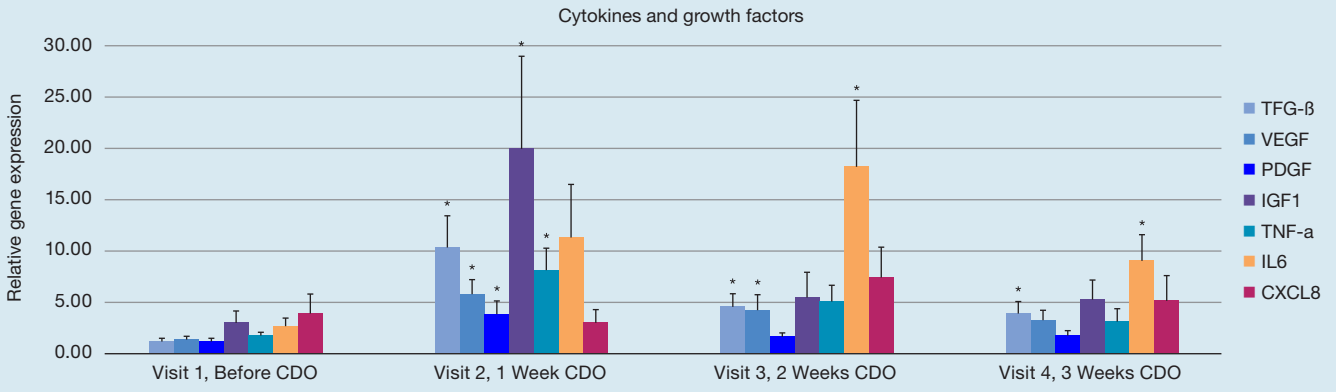
Cytokines associated with the inflammatory response increased significantly and peaked around 1–2 weeks before decreasing. This pattern for growth factors and cytokines is necessary for stalled wounds to get back to the normal processes of wound healing, converting a chronic wound to an acute wound. These scientific findings closely follow the clinical experience of increased exudate levels that typically peak around 1–2 weeks before decreasing, as well as the increasing redness, indicating new capillary growth, starting in the first couple of weeks.

Aside from what has been mentioned already, oxygen is involved in quite a few wound healing processes. For example, oxygen is essential to make and properly organize collagen, which is the primary component of skin. Collagen accounts for 70–80% dry weight and acts as the structural scaffold of skin.

Organized collagen is bundled into fibers (like strands in rope), which are interwoven and can be stretched in multiple directions without tearing (the collagen fibers are woven similar to fabric). The cross-linking of triple-helices, fibers and linear fibrils are all oxygen dependent and involve various oxidases such as prolyl and lysyl hydroxylase. Correct collagen synthesis (posttranslational hydroxylation) is also required for proper capillary tube assembly. An interesting finding is that the rate of collagen synthesis is directly proportional to oxygen levels in injured tissues. Conversely, hypoxic wounds have been shown to deposit disorganized collagen poorly and become infected easily.

On the topic of infection, oxygen is essential for respiratory burst, the production of reactive oxygen species (ROS), which are used by phagocytes such as neutrophils and macrophages in bactericidal activity and the removal of necrotic cellular debris (autolytic debridement). NADPH oxidase, also known as leukocyte oxidase, produces ROS for

Fig 1. Cytokines and growth factors at each visit. Asterisks indicate significant increase from baseline



bactericidal activities and enables dead cell cleansing by phagocytosis. Similar to the rate of collagen production, leukocyte activity has been shown to be directly proportional to local oxygen concentration, with optimum rates at levels only achievable with supplemental oxygen. Interestingly, the efficacy of supplemental oxygen in achieving bactericidal activity has been shown to be similar to antibiotic administration.[3] ROS are also essential for the signalling processes of growth factors and cytokines, and associated processes such as leukocyte recruitment, cell motility, angiogenesis, extracellular matrix formation and remodelling, granulation tissue stimulation, and cell growth and division, to name a few.

There are several excellent overview articles on the effects of oxygen in wound healing that go into further detail regarding the topics covered here, with references.[3–6]

Finally, you may ask how oxygen gets to a wound, especially if it is ischaemic as is the case for many chronic wounds (and some surgical wounds).

The modalities for delivering oxygen in wound care include intermittent inspired oxygen (hyperbaric, forced oxygen, etc.) or direct topical application, intermittent or continuous.[8] For inspired oxygen, the treatment is intermittent and is typically performed in hyperbaric oxygen chambers using pure oxygen (~100%) at highly elevated pressures (>2.4 atmospheres) for sessions which last 90 minutes a day (including ramping the pressure up and down) for 5 days a week. For direct application to a wound, what we traditionally refer to as 'topical oxygen' follows a treatment regimen similar to hyperbaric oxygen: 90 minutes a day for 5 days a week, yet at pressures only slightly above atmospheric.

Traditional topical oxygen uses a high flow oxygen concentrator (~93% oxygen) connected to either a chamber or bag which covers the wound. A newer type of topically applied oxygen is continuous and uses an electrochemical oxygen generator to constantly generate pure (~100%), humidified oxygen from ambient air and deliver it within an oxygen diffusion dressing or a delivery system for use with standard dressings (aka moist wound therapy plus oxygen). This therapy is termed continuous diffusion of oxygen (CDO) since it directly diffuses oxygen into a wound within a dressing. CDO is silent, lightweight, wearable and delivers over 20 times the amount of oxygen therapy time versus traditional intermittent therapies.

Most often, people think of oxygen in the form of breathing it in, especially since this is how we typically get oxygen into our bodies and to the affected tissues. However, in the case of a moist wound environment, the oxygen can penetrate directly into the tissue via diffusion.

Diffusion is a physical process that follows Henry's law: the rate (and amount) of oxygen diffusing into the tissue is proportional to the concentration levels in the tissue (low) and above the tissue (high, up to near 100% in some cases). With application of topically applied oxygen which is pure and humidified, the rate of oxygen transfer increases approximately five-fold over that of room air, which is ~21% oxygen. For ischaemic wounds underneath an occlusive or semi-occlusive dressing, the increase would be significantly higher since the oxygen levels would be very low (near zero in chronically ischaemic wounds).

It is an exciting time for the direct delivery of oxygen to wounds. The current, advanced modalities for topically applying oxygen directly to wounds are demonstrating not only strong clinical outcomes, yet are also demonstrating the repeatability and robustness of the therapies with multiple double-blind, placebo-controlled studies. The clinical outcomes are reinforced with physiologic evidence from scientific studies. The tide is turning: direct oxygen application expands on current available therapies and enables new treatment options for clinicians in wound care. **JWC**

References

1 Bowen J, Ingersoll MS, Carlson R. Effect of CDO on Pain in Treatment of Chronic Wounds. Wound Central 2(4);186-195 2018.
2 Lavery LA, Killeen AL, Farrar D, Akgul Y, Crisologo PA, Malone M, Davis KE. The effect of continuous diffusion of oxygen treatment on cytokines, perfusion, bacterial load, and healing in patients with diabetic foot ulcers. Int Wound J. 2020;1–10. https://doi.org/10.1111/iwj.13490
3 Knighton D, Halliday B, Hunt T. Oxygen as an antibiotic. Arch Surg 1986; 121: 191–195.
4 Sen CK. Wound Healing Essentials: Let There Be Oxygen. Wound Rep Reg 2009; 17: 1–18.
5 Tandara AA, Mustoe TA. Oxygen in Wound Healing – More Than a Nutrient. World J Surg 2004; 28: 294–300.
6 Gordillo GM, Sen CK. Revisiting the Essential Role of Oxygen in Wound Healing. Amer J Surg 2003; 186: 259–263.
7 Schreml S, Szeimies RM, Prantl L, Karrer S, Landthaler M, Babilas P. Oxygen in acute and chronic wound healing. Brit J Derm 2010; 163: 257-268.
8 Howard MA, Asmis R, Evans KK, Mustoe TA. Oxygen and wound care- A review of current therapeutic modalities and future direction. Wound Rep Reg. 2013; 21(4):503-511.