PERSPECTIVE ARTICLE

Oxygen and wound care: A review of current therapeutic modalities and future direction

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ABSTRACT

While the importance of oxygen to the wound healing process is well accepted, research and technological advances continue in this field and efforts are ongoing to further utilize oxygen as a therapeutic modality. In this paper, the authors briefly review the role of oxygen in wound healing and discuss the distinct mechanism of action as well as the advantages and disadvantages of the three major oxygen-based therapies currently in clinical use (Hyperbaric Oxygen and Topical Oxygen and Continuous Diffusion of Oxygen), as well as review the existing literature regarding these distinct therapeutic modalities.

The understanding of oxygen's role in wound healing has grown in recent years, from basic knowledge of oxygen's importance in cellular metabolism and host defense to recognized roles in the regulation of signal transduction pathways and cell functions. The *relative* absence of oxygen in a wound, hypoxia, is clearly associated with reduced, or absent wound healing.[1,2] As such, today, much clinical effort is focused on correction of hypoxic wound conditions in order to optimize wound healing.

To meet the daily energy demand, humans use dioxygen (O_2) to combust or "burn" carbon-based compounds in food to extract approximately 2250 calories per day. This process requires approximately 22 moles of O_2 per day, or 2.5×10^{-4} mol/s.[3] Assuming the typical 70-kg person consists of 1×10^{14} cells, than the average oxygen consumption rate is 2.5×10^{-18} mol cell^{-1} s^{-1} i.e., 1.5×10^{6} O_2 molecules per cell per second. Oxygen utilization depends on the biological status of a cell and varies dramatically between different cell types. Rates of oxygen utilization can therefore range from < 1 to > 350 10^{-18} mol cell^{-1}/s. For example, large cells with high numbers of mitochondria such as hepatocytes exhibit much higher oxygen utilization rates than small red blood cells without mitochondria which rely on glycolysis instead of respiration for their energy needs.[3] Aside from mitochondria, other cellular processes also consume O_2. This nonmitochondrial O_2 consumption varies considerably ($< 0.1 \times 10^{-18}$ to $> 1 \times 10^{-18}$ mol cell^{-1} s^{-1}) and in some cell types can exceed 10% of total oxygen consumption. Under normal conditions, the vast majority of O_2 used by mitochondria is reduced to water, but a small fraction (~1%) is converted into superoxide, a reactive

oxygen species (ROS) that can escape the respiratory machinery and if unchecked will promote cell damage.[4]

Oxygen demand and utilization rates are increased during tissue repair and wound healing. O_2 is not stored in the tissue, therefore, adequate and continuous O_2 supply to the site of injury is critical for wound healing and repair. Physiological oxygen delivery to wounds is dependent on multiple factors including blood perfusion of the tissue, capillary density, arterial partial oxygen pressure (pO_2), oxyhemoglobin dissociation conditions and local oxygen consumption.[5] Oxygen diffuses into the tissue and the concentration decrease is inversely proportional to the square of the diffusion distance, resulting in pO_2 as low as 0–5 mmHg in devascularized central regions of a wound. Depending on the tissue and the size of blood vessel supplying the tissue, oxygen gradients between 0.1 mmHg/μm up to 1.5–2 mmHg/μm have been measured.[6] Measurements from healthy rat mesentery suggest that at a distance of only 40 μm away from the blood vessel pO_2 drops below 10 mmHg and at 70 μm reaches 5 mmHg.[7] Reduced oxygen supply due to impaired blood flow would reduce these distances dramatically.

A minimal pO_2 is required for normal cell functions so that even partial O_2 deficiency can result in impaired energy synthesis and ATP depletion. For example, normal cell division in fibroblasts requires pO_2 of at least 15 mmHg.[8] At a pO_2 of 25 mmHg the O_2-dependent hydroxylation of proline and lysine required for collagen synthesis is impaired. Once $pO2$ decreases below 20 mmHg, cells switch to anaerobic metabolism, resulting in increased lactate production and reduced tissue pH, which further inhibit wound healing.[9–11] Prolonged

O$_2$ deficiency and the associated restricted availability of ATP will prevent the effective synthesis, repair and turnover of essential macromolecules (proteins, DNA, RNA) and cell components (membranes), ultimately resulting in cell death and tissue necrosis.

It is therefore not surprising that increasing oxygen delivery to wounds has been reported to improve wound healing and tissue repair. Oxygen can directly impact wound healing due to its antimicrobial properties.[12,13] However, the major benefit of delivering O$_2$ directly to wounds appears to be the ability of O$_2$ to affect multiple molecular targets and cell types, restore cellular functions and thus accelerate tissue repair. O$_2$ has been reported to: increase fibroblast migration and replication,[14] increase the rate of collagen production and tensile strength of collagen fibers[11,15] stimulate angiogenesis[14] and promote macrophage chemotaxis.[16] O$_2$ also enhances the antibacterial activities of leukocytes, including phagocytic function,[17] thereby increasing the removal of cell debris and promoting physiological wound debridement.

At first glance, stimulation of angiogenesis by oxygen appears paradoxical considering that hypoxia is a well-established stimulus of neovascularization. Hypoxia activates the transcription factor HIF1α, which in turn activates the synthesis of VEGF, a major proangiogenic factor.[18] However, it is important to note that only acute hypoxia stimulates neovascularization, whereas chronic hypoxia inhibits new vessel formation.[19,20] Delivering oxygen to the chronically hypoxic wound not only restores mitochondrial respiration and ATP synthesis, but also enables ROS production, which is a major stimulus of VEGF synthesis[13,18,19] and provides a substantial role in the immune defense in wounds.[21]

Supplying chronic wounds with oxygen, even at supraphysiological levels, is therefore likely to promote, not inhibit, neovascularization. This hypothesis is supported by clinical observations that delivery of oxygen to chronic wounds leads to excessive exudates generation and the rapid formation of granulation tissue in these treated wounds.[22] Research has shown that many of the wound repair processes involving oxygen are accelerated at pO$_2$ levels higher than those found in healthy tissue. Mean subcutaneous pO$_2$ levels in normal skin at 3–4 mm depth are in the range of 45–65 mmHg,[23–25] significantly lower than ambient pO$_2$. However, fibroblast proliferation and protein production have been reported to be optimal at 160 mmHg, i.e., at pO$_2$ levels 2-fold to 3-fold higher than those found in healthy tissues.[26] In addition, the optimum pO$_2$ for angiogenesis and fibroblast and endothelial cell replacement is also estimated at 50–100 mmHg, i.e., significantly above the pO$_2$ of normal tissue exposed to room air.[27] Leukocyte killing is likely maximized at pO2 of 250 mmHg and is rapidly reduced at levels below 40 mmHg.[28] In addition, the rate of angiogenesis has been shown to be directly proportional to oxygen levels in injured tissues and rates of collagen deposition have been shown to increase proportionally with pO$_2$ levels to more than 250 mmHg.[19] In addition, raising oxygen above normal physiologic levels has also been shown to enhance collagen synthesis and tensile strength in both animal and human subjects[15,29,30] and can increase the level of collagen organization (better appearance and tensile strength).[31] Simply correcting vasoconstriction and hypoxia has been shown to result in as much as a 10-fold increase in collagen deposition in wound repair.[15,32–34]

While oxygen toxicity of the alveoli and retina in neonates is well-recognized, it remains rarely reported in wound healing. The only reports of oxygen toxicity in wound healing stem from the use high pressures, as in the case of HBO, which can supersaturate tissues[35–37] and in a single observation of the effect of topical hyperbaric oxygen on wounds. Prolonged exposure (>8 weeks) led to reversible changes in the endothelial cells.[38] These data support the notion that supplementing O$_2$ directly to wounds should improve tissue repair, particularly in metabolically compromised wounds or wounds with insufficient blood supply. Because tissues continuously utilize O$_2$ and are unable to store O$_2$, an effective O$_2$–based wound therapy would provide continuous O$_2$ supply, tissue pO$_2$ levels should be maintained above the pO$_2$ of healthy tissue, and closer to pO$_2$ required for optimal cell functions. It is therefore not surprising that the underlying therapeutic benefit of continuous therapy would therefore be significantly greater than that seen with therapy modalities that only provide intermittent, supra-physiologic oxygen.

THERAPEUTIC OXYGEN MODALITIES

Until recently, the two primary methods of oxygen-based therapies used to treat wounds were Hyperbaric Oxygen (HBO) and Topical Hyperbaric Oxygen (THO), the term used initially in the literature and more recently shortened to "Topical Oxygen" (TO). A distinct, third class of oxygen generation and delivery wound care devices has recently emerged that requires further clarification of, and distinction from the generic term "topical oxygen." This new class provides continuous treatment of wounds with oxygen and, may be referred to as Continuous Diffusion of Oxygen (CDO) therapy or "transdermal oxygen therapy." While all three technologies (Figure 1) are similar in that they use oxygen as an aid to affect wound healing, there are several major technological and therapeutic differences. HBO therapy treats with 100% oxygen, systemically, at high pressures. THO therapy treats directly at the wound site by surrounding a patient's wound using oxygen at pressures slightly above atmospheric. ("Hyperbaric" in this context will be discussed later in this paper.) Both HBO and THO treat for 90 minutes per day, 4 or 5 days per week based on developed protocols.[39] In contrast, the CDO class of devices is portable and use oxygen, delivered continuously at normospheric pressure, directly to the wound site covered with an occlusive moist wound dressing. A comparison of the features between the various oxygen therapies is shown in Table 1.

SYSTEMIC OXYGEN THERAPY: HYPERBARIC OXYGEN (HBO)

Oxygen delivered under high pressure, known as Hyperbaric Oxygen (HBO) therapy, has been used therapeutically since the 1600s. Increased oxygen delivery to tissues may be achieved with simple physical gas law relationships. Henry's Law states that the amount of an ideal gas dissolved in solution is directly proportional to its partial pressure. At sea level (1.0 atm, 760 mmHg), the plasma concentration of oxygen is 0.3 mL/dL. This increases to 1.5 ml/dL when breathing 100% oxygen. Hyperbaric oxygen, at 3.0 ATM, increases plasma levels to 27 vol%. At this concentration, arterial oxygen tensions may reach 2000 mmHg and tissue oxygen tensions of up to 500 mmHg.[40] Delivery of oxygen to areas of hypoxia is ultimately achieved by diffusion along this gradient.
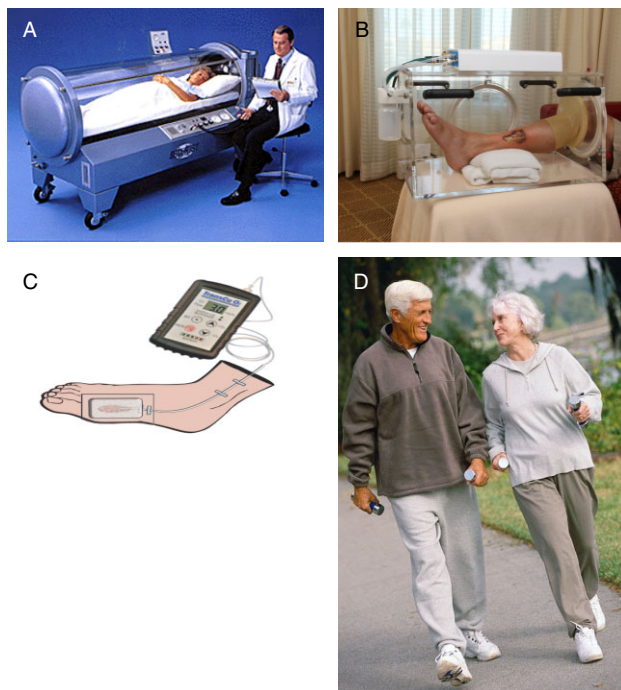
Figure 1. Oxygen therapeutic modalities: (A) Hyperbaric oxygen (with permission, Sechrist Industries, Inc, Anaheim, CA). (B) Topical wound oxygen (with permission, AOTI, Inc, Oceanside, CA). (C) Continuous oxygen diffusion (with permission, EO2 Concepts, Inc, San Antonio, TX). (D) Active treatment with continuous oxygen diffusion (with permission, EO2 Concepts, Inc, San Antonio, TX).

The principal effect of HBO is to increase the oxygen concentration in tissues by increasing the oxygen dissolved in circulating blood plasma and especially into areas of relative hypoxia. On a cellular level, HBO obviates the detrimental effects of ischemia-reperfusion injury by inducing a control over the level of circulating reactive oxygen species.[37,41]

Recent reports also suggest that HBO therapy mobilizes stem/progenitor cells through Nitric Oxide (NO) dependent pathways, which may enhance ischemic limb perfusion and wound healing.[42–44] Hyperoxia, through a vascular endothelial growth factor-mediated pathway, induces the production of bone marrow NO, which in turn triggers the mobilization of Endothelial Progenitor Cells (EPC) into the circulation.[44] Further research is needed to elucidate the underlying molecular mechanisms.

An HBO treatment typically consists of systemic exposures to 100% oxygen at pressures of between 2.0 to 2.4 atmospheres in a mono- or multi-place chamber. Treatment sessions last approximately 90 minutes and are repeated daily until treatment regimens or results are achieved. For treatment of wounds, transcutaneous oximetry (TCOMS) can aid in treatment timing and diagnosing hypoxic wounds that will respond to HBO treatment.[45–47]

HBO therapy may be beneficial for use in several clinical indications (Table 2). Clear evidence exists for the efficacy of HBO treatment following carbon monoxide poisoning because HBO reduces half-life of carboxyhemoglobin and it aids in reducing the damaging effects of ischemia-reperfusion injury.[48,49] Treatment of decompression sickness or air embolism with HBO has few supporting clinical trials, but vast clinical experience strongly supports its efficacy for these indications. In accordance with Boyle's Law (the pressure and volume of a gas are inversely proportional), HBO reduces nitrogen bubbles in vessels as well as decreasing the

Table 1. Comparison of oxygen-based wound therapies

Modality	Hyperbaric oxygen	Topical oxygen*	Continuous diffusion of oxygen (CDO)
Application	Systemic	Regional	Localized
Direct wound treatment	Sometimes	Yes	Yes
Treatment mode	Intermittent	Intermittent	Continuous
Therapy days per week	5–7	5–7	7
Therapy time per day	90 minutes	90 minutes	24 hours
Treatment location	Patient in pressurized chamber	Limb or wound in chamber or bag	Occluded, moist wound dressing
Treatment at home?	No	Maybe[†]	Yes
Patient mobility	No	No	Yes
Maintain moist wound environment	Possible	Possible	Yes
Pressure	High 2-2.4 ATA	Low[‡] <1.07 ATA	Low (<20 mmHg)
Flow rate	Very high Up to 600 L/minute	High 5–60 L/minute	Low 3–10 ml/hour

Notes:
*Known as Topical Hyperbaric Oxygen therapy in early literature.
[†]Can be treated at home, yet patient immobile during treatment.
[‡]Treatment typically applied to extremity: limb may be constricted for therapy.

Table 2. HBO: Medicare approved indications for HBO therapy with ICD-9 diagnosis[74]

1. Acute carbon monoxide intoxication, (ICD-9-CM diagnosis 986).
2. Decompression illness, (ICD-9-CM diagnosis 993.2, 993.3).
3. Gas embolism, (ICD-9-CM diagnosis 958.0, 999.1).
4. Gas gangrene, (ICD-9-CM diagnosis 0400).
5. Acute traumatic peripheral ischemia. (ICD-9-CM diagnosis 902.53, 903.01, 903.1, 904.0, 904.41.)
6. Crush injuries and suturing of severed limbs. (ICD-9- CM diagnosis 927.00- 927.03, 927.09–927.11, 927.20–927.21, 927.8–927.9, 928.00–928.01, 928.10–928.11, 928.20–928.21, 928.3, 928.8–928.9, 929.0, 929.9, 996.90- 996.99.)
7. Progressive necrotizing infections (necrotizing fasciitis), (ICD-9-CM diagnosis 728.86).
8. Acute peripheral arterial insufficiency, (ICD-9-CM diagnosis 444.21, 444.22, 444.81).
9. Preparation and preservation of compromised skin grafts. (ICD-9CM diagnosis 996.52; excludes artificial skin graft).
10. Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management, (ICD-9-CM diagnosis 730.10–730.19).
11. Osteoradionecrosis as an adjunct to conventional treatment, (ICD-9-CM diagnosis 526.89)
12. Soft tissue radionecrosis as an adjunct to conventional treatment, (ICD-9-CM diagnosis 990).
13. Cyanide poisoning, (ICD-9-CM diagnosis 987.7, 989.0).
14. Actinomycosis, only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment, (ICD-9-CM diagnosis 039.0–039.4, 039.8, 039.9).

harmful effects of ischemia-reperfusion effects as discussed previously.[50,51]

HBO may be also used in acute crush, burn situations, chronic wounds and infections to increase oxygen delivery to ischemic tissue. Added benefits may include reduced edema through hyperoxia-induced vasospasm and reduced inflammation.[52] While evidence for use following thermal injury is mixed,[53] at least one study has shown that HBO shortens healing times in thermal burns and may help halt the conversion of second degree to third degree burns.[54] In addition, HBO also appears beneficial in the treatment of radiation injury,[55] necrotizing Infections,[56] and diabetic foot wounds.[57,58]

There is also evidence that the use of HBO can decrease the major amputation rate and is more cost effective than standard wound and healthcare in diabetic patients.[59] Recent evidence has also suggested that hyperbaric oxygen may treat radiation defects including radiated wounds, mandibular osteoradionecrosis and radiation proctitis.[60,61] In addition, in certain cases of anaerobic infections such as gas gangrene or infections caused by *Clostridium perfringes*, HBO can improve mortality and morbidity.[62] Compromised skin flaps, both pedicled as well as free flaps, and skin grafts can be treated with HBO with promising results.[63]

Systemic pressurization of 2–3 times normal atmospheric pressure does have potential side effects and complications. The most serious, and life-threatening, condition is unrecognized/untreated tension pneumothorax as the chamber pressure would further exacerbate the condition. Commonly, one may experience progressive, reversible myopia during the course of treatment, occurring due to pressure-induced lens deformation. Ear and sinus barotraumas is also a common side effect of HBO, occurring between 2% and 17% in elderly wound care populations. In addition, oxygen in very high concentrations has toxic effects on the body, including pulmonary edema, exacerbation of congestive heart failure, seizures and retinal damage.[37] Fortunately,

serious complications with HBO are not common and may be further reduced in frequency by proper patient selection, recognizing that this may reduce the availability of HBO for some patients.

HBO therapy also has several practical limitations. The delivery of this therapy requires substantial infrastructure including the chambers, chamber operators and "oxygen farms." Geographically, patients may not have ready access to an HBO treatment facility and logistical challenges may hinder or prevent patients from obtaining services. Also, patients may not be able to tolerate therapy due to medical reasons. The use of HBO also poses a rare, yet real, devastating fire risk.

REGIONAL OXYGEN THERAPY

Systemically delivered O_2 may not effectively reach the center of the most hypoxic portion of a wound because the microcirculation of ulcerated tissue is impaired and the diffusion distance is too great. As such, there is growing interest to deliver oxygen therapy locally, directly at the hypoxic portion of the wound, to achieve improved outcomes in wound care.

Evidence is growing that in humans, a substantial amount of oxygen may be absorbed, systemically, by the transcutaneous route and that this route may supply the outer 250–400 um of human skin in vivo.[64] Roe et al. in an in vitro setting, used varying thicknesses of viable human skin both with and without intact epidermis to determine the quantity of, and distance that oxygen may diffuse by this route.[65] Using both topically dissolved and topical gaseous oxygen sources, they demonstrated effective transcutaneous penetration of topically applied oxygen through skin thicknesses of >700 μm. There was no significance difference in the rate of oxygen penetration between the dermal-only and intact epidermis groups. Similar to oxygen in inspired air at the alveolar surface of the lung, oxygen diffusion occurs across a moist wound surface into solution within the tissue. According to

Table 3. Summary of published clinical results using regional oxygen therapy

Reference	# Patients (oxygen)	Wound age	Mean closure time	% Full closure	% Full closure (control)	Adverse events?
Fischer, 1969[75]	52	3 months–24 years	16 days	88.5	n/a	No
Ignacio et al., 1985[76]	15	—	—	73.3	n/a	No
Landau, 1998[77]	50 (15)	9 ± 6.6 months	3 ± 1.8 months	86	n/a	No
Heng et al., March 2000[78]	15	3.65 ± 4.4 mo	—	83.3	n/a	No
Heng et al., Sept 2000[79]	40 (13)	NR	NR	90	22	No
Kalliainen et al., 2003[80]	32	4 months median	71.1 ± 54 days	75	n/a	No
Bakri et al., 2008[81]	25 (14)	0 (acute)	n/a	n/a	n/a	No
Banks and Ho, 2008[72]	3	3–6 months	n/a	n/a	n/a	No
Gordillo et al., 2008[67]	57 (25)	54.7 ± 8.9	—	—	—	No
Hirsh et al., 2009[82]	6	32 months	9.8 wks	83.3	n/a	No
Tawfick and Sultan, 2009[83]	83 (46)	2–20 years	45 days	89	35	No
Blackman et al., 2010[68]	28 (17)	6.1 months	56 days	82.4	45.5	No

physical properties of gases, explained by Henry's law, the amount of an ideal gas dissolved in solution is proportional to the partial pressure of that gas in contact with the liquid or tissue. Air at sea level has a total pressure of 760 mmHg (1 atm) with a partial pressure of oxygen of 159 mmHg (21% O_2). By increasing the partial pressure of oxygen at a wound surface (i.e., converting environment to 100% O_2, pO_2 = 760 mmHg), the amount of oxygen diffusing into the tissue will increase up to 5-fold and even greater "wound oxygenation" will occur. Evidence suggests that the atmosphere above a wound surface exposed to 100% O_2 raises the resulting O_2 levels in the tissue up to as high as 250 mmHg pO_2.[65]

TOPICAL OXYGEN THERAPY

Originally termed "Topical Hyperbaric Oxygen"(THO) and more recently referred to simply and generically as "Topical Oxygen" (TO) has been in use since the 1960s. This modality places a bag, boot or extremity chamber around the limb or affected area and seals it tightly to prevent leak. The device is then filled with O_2 from an external tank to pressures slightly above atmospheric (typically less than 1.07 atmospheres) but high flow rates (5–60 L/min), creating an O_2-rich environment at the wound surface. Treatment typically mirrors that of HBO therapy protocols with sessions lasting from 90 minutes to 4 hours a day, three to five days a week[39] (see Figure 1B).

While TO devices evolved from HBO therapy, involve the use of oxygen applied to a wound under theoretically slightly elevated pressure and utilize similar treatment protocols, these devices have been met with more skepticism than their predecessors. Presently, there is little Level 1 and 2 evidence supporting TO therapy. Furthermore, in a 2005 position paper released by the Undersea and Hyperbaric Medicine Society (UHMS), the authors highlighted differences between hyperbaric and topical hyperbaric oxygen therapy, concluding that these two modality classes work by different mechanisms. Based on this mechanistic difference the authors recommend that TO should not be considered hyperbaric therapy and called for additional research on this modality.[66]

Topical oxygen therapy does offer several advantages when compared to HBO, including potentially a more diverse therapeutic patient population at a lower risk profile by avoiding the potential side effects of high pressure and systemic oxygen. TO may be offered in more diverse settings such as home and remote clinics at a lower cost threshold, however the patient is still required to be immobilized and attached to an external oxygen delivery device.

Conversely, TO has the disadvantage of not creating as large of an oxygen potential because it does not use the higher pressures associated with HBO and is not applicable for CO poisoning, decompression sickness and necrotizing fasciitis. TO may also not be applicable in wounds covered with eschar, fistulae or deep sinus tracts. Topical oxygen also requires an open, exposed wound surface during treatment, which may be subject to desiccation during therapy sessions.

Because HBO and TO require an external O_2 source, both therapies have the disadvantage of severely restricting patient mobility during treatment.

TOPICAL OXYGEN CLINICAL DATA

Following the UHMS paper, several publications began to explore the mechanistic differences and report clinical results (Table 3). Fries et al. using a porcine wound model, demonstrated a rapid increase in tissue O_2 levels after the topical application of 100% O_2 with a TO device (GWR Medical).[20] Within four minutes of application, the oxygen level 2 mm below the surface was found to rise from 5–7 mmHg to 40 mmHg. In this experiment, by day five, TO treated wounds showed a statistically significant reduction in wound size and rate of wound healing as compared to control (room air) wounds. TO treated wounds also had higher levels of VEGF protein expression and greater blood vessel density than control wounds. Interestingly, in TO treated wounds, the pO_2 elevation (42 mmHg vs. 11 mmHg for room air wounds) persisted for over 2 weeks after treatment completion, suggesting durability of the vascularization that was induced during treatment.

In one of the first prospective studies to report oxygen-induced gene expression in wound tissue, Gordillo et al.[67]

compared the effect of HBO to TO on wound closure and VEGF expression in chronic wounds. The authors screened 1854 consecutive patients, enrolling 57 into the study. Thirty-two patients, qualified based on CMS guidelines for treatment with HBO; 25 were offered treatment with TO. The wound edges were biopsied at three time points in the study to evaluate for O_2-sensitive gene expression. The authors found that TO resulted in statistically significant reduction in wound size as compared to HBO. Similarly, direct wound oxygenation treatment showed a statistically significant increase in VEGF expression in the wound tissue, whereas HBO did not. No adverse or toxic effects were reported from using direct wound oxygenation. While this prospective, nonrandomized series (Level 3 evidence) shows that TO benefits wound healing and appears to induce VEGF expression at the wound edge during treatment, the comparison of outcomes is difficult.

The effect of direct wound oxygen therapy was compared to the standard, conventional compression therapy in the treatment of refractory venous ulcers. In nonhealing venous wounds present for over two years, showing no healing for greater than one year, Tawfick and Sultan found that 89% of the TO treatment group ($n = 46$) achieved wound closure by 12 weeks as compared to 35% healing in conventional moist dressing ($n = 37$) therapy ($p < 0.0001$).[58] The median time to full closure was 45 days in the TO group and 182 days in the standard therapy arm. Further, TO showed reduction in percentage of MRSA colonization rates and associated wound pain scores. And, at one year, wound recurrence rates were 0% in the TO group and 38.5% in the conventional therapy group.

In 2010, Blackman et al. published a prospective, controlled study of the treatment of diabetic foot ulcers with direct wound oxygenation.[68] Patients presenting to their wound center were assigned or self-selected to either treatment with topical oxygen ($n = 17$) or standard silver/moist wound therapy ($n = 11$). While the study results may be criticized for randomization methods, the oxygen treated wounds were present for longer duration on presentation (mean 6.1 months vs. 3.2 months) and were of greater size (4.1 cm^2 vs. 1.4 cm^2) than the standard therapy wound group. The patients treated with oxygen were noted to have significantly higher proportion of wounds that successfully healed (82% vs. 45%, $p = 0.013$) and a shorter median time to healing (56 days vs. 93 days, $p = 0.04$). No adverse events or evidence of oxygen toxicity were noted during the study.

In summary, the aforementioned studies have shown the following positive effects of using intermittent topical wound oxygen therapy:

- Oxygen delivery to the tissue during therapy
- Increased VEGF expression and angiogenesis
- Improved wound healing,
- Improved wound closure rate
- Reduction in MRSA infection
- Pain reduction
- Reduced venous stasis ulcer recurrence

CONTINUOUS DIFFUSION OF OXYGEN THERAPY (CDO)

In order to further advance wound care treatment options and mitigate the challenges associated with HBO and TO thera-

pies, a new class of devices has emerged. In general, these devices provide continuous oxygen delivery to the wound site at much lower flow rates than HBO or TO. The therapeutic devices tend to be portable and much smaller than TO extremity or HBO chambers, potentially allowing improved access to care, patient mobility and lower cost.

Individual devices in this therapeutic class have been referred to as transcutaneous O_2, low-flow oxygen, topical oxygen emulsion and transdermal continuous oxygen therapy. For purposes of this discussion and future device classification, Continuous Diffusion of Oxygen Therapy (CDO) provides a general mechanistic description and recognizes that this class of devices may be utilized across a wide spectrum of wounds (including those without cutaneous or dermal structures).

Initially, CDO was classified with the topical hyperbaric devices as both share the common feature of delivering O_2 directly (i.e., "topically") to a wound surfaces. However, there are several distinctions to note: CDO provides a continuous, low flow (3–12 ml/hr) delivery of O_2 to an occluded, moist wound environment. The devices are used in adjunct to existing dressings and do not limit patient mobility. TO devices provide intermittent therapy (i.e., 90 minutes/day, 5 days a week) at high flow rates (40 L/min). Without adjunctive humidification systems, this high flow rate may cause desiccation, which would prevent O_2 solubilization in the wound fluid and dramatically reduce O_2 transport into the tissue. Many of the TO devices require immobilization during treatment and/or a constrictive device to enclose the treatment site.

CDO devices do not provide supra-physiologic, systemic oxygen delivery like HBO, therefore is not applicable for CO poisoning, decompression sickness, osteoradionecrosis and necrotizing fasciitis. CDO may also not be applicable in wounds covered with eschar or deep sinus tracts as this modality requires a moist, open, exposed wound surface during treatment, to allow for oxygen diffusion.

Recent work in animal models shows improved wound healing with CDO devices. Said et al. utilized an ischemic rabbit ear model to study the effect of continuous delivery of oxygen to a wound surface.[69] Histological analysis of the wounds showed a significant increase in epithelial coverage of the O_2-treated wounds as compared to controls. The authors noted a 91% greater coverage at day 5 ($p = 0.02$) and 156% greater coverage at day 8 ($p = 0.01$). Their findings also suggested that sustained O_2 therapy may improve granulation tissue formation, provisional matrix deposition and cellular metabolism.

In a subsequent study using a diabetic mouse model, Asmis et al. randomized dorsal punch wounds to CDO or a sham device.[31] Oxygen therapy resulted in a mean reduction of wound size by 60.2% vs. 45.2% in the sham group ($p = 0.022$). At day 10, the O_2-treated wounds were 83.1% closed compared to 71.2% in sham wounds ($p = 0.008$). On H&E evaluation, the O_2-treated wounds were noted to have increased collagen deposition as compared to sham treatment wounds.

Davis et al. looked at the continuous delivery of oxygen to a porcine burn model, utilizing a supersaturated oxygen suspension in a perflurocarbon dressing.[70] In this double-blind study, use of the topical oxygen emulsion on second degree burns and partial thickness wounds showed a statistically significant increase in the rate of epithelialization compared to untreated wounds ($p = 0.001$).

Several human clinical trials utilizing CDO therapy suggest efficacy and benefit with use of this therapeutic modality. Kemp and Hermans reported use of CDO in recalcitrant diabetic foot ulcers.[71] CDO devices were utilized in eleven patients with 14 wounds that failed to heal with standard therapies, including HBO, negative pressure and low intensity laser. Twelve wounds (86%) achieved healing in an average of 46 days (range: 13–119 days). The two remaining ulcers achieved 90% reepithelialization, despite patient non-compliance with off-loading guidelines.[71]

Additional reports of CDO use in decubitus ulcers,[72] painful wounds[73] and DFUs[72] suggest CDO may be efficacious in these conditions as well.

Additional studies (Clinicaltrials.gov Identifier: NCT01645891 and NCT01291160) are currently underway to investigate the biologic basis for this therapeutic modality, explain the mechanism and measure the degree of efficacy compared to standard wound therapy.

SUMMARY

In conclusion, the growing understanding of the importance of oxygen in wound healing is driving the development of new therapeutic devices designed to deliver oxygen to wounds and improve wound therapies. It is clear that one must distinguish between systemic and regional therapy and intermittent and continuous oxygen delivery as there are clear physiologic and mechanistic differences between these classifications.

Today, three very distinct modes of oxygen delivery exist: Hyperbaric oxygen, Topical (intermittent) oxygen and Continuous oxygen, each with intrinsic advantages and disadvantages:

- HBO is a widely used and well-accepted form of oxygen therapy, though is limited by its infrastructure and mechanical requirements. HBO delivers oxygen systemically, on an intermittent basis, using high pressure and high flow rates.
- Topical oxygen, while less utilized than HBO, does have supporting literature as to physiologic effect and clinical outcomes. This therapy delivers oxygen locally, under slightly elevated pressure, but only on an intermittent basis, and using high flow rates.
- Continuous diffusion of oxygen, a newer therapeutic approach, is a distinct therapy with growing experimental evidence. It has fewer reported risks and side effects than previous modalities and offers therapeutic ease of delivery. It is the only therapy class capable of continuous oxygen delivery, without pressure, and at very low flow rates.

Future evolution in the field of oxygen-based wound therapies will continue to optimize and focus therapy, minimize risk or side effects and reducing the impact on the patient during therapy.

ACKNOWLEDGMENTS

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