REVIEW ARTICLE

The Role of Oxygen in Wound Healing: A Review of the Literature

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BACKGROUND The presence of oxygen is necessary for normal wound healing. Oxygen has been given as a therapeutic modality to assist and speed wound healing.

OBJECTIVE The objective was to summarize the role of oxygen in wound healing.

MATERIALS AND METHODS A literature review of clinical and basic science studies regarding oxygen and wound healing was conducted.

RESULTS Hypoxia appears to jump start wound healing via hypoxia-inducible factor 1α and reepithelialization. Nonetheless, oxygen is often required to start or sustain other wound healing processes.

CONCLUSION Both the absence and the presence of oxygen have effects on wound healing; however, its role is not completely understood. Although hyperbaric oxygen and topical oxygen therapy have been described in aiding wound healing, case-controlled prospective studies are lacking and evidence for their efficacy is inconsistent.

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Numerous experimental and clinical reports have suggested that oxygen plays a crucial role in wound healing. Oxygen is involved in multiple wound healing processes including oxidative killing of bacteria, reepithelialization, angiogenesis, and collagen synthesis.[1] Therefore, oxygen has been explored as a therapeutic modality to aid wound healing. However, evidence exists both in support of and against the use of hyperbaric and topical oxygen therapy to improve wound healing.[2–5] This review will summarize what is known about the role of oxygen in wound healing, discuss the effects of external factors that influence oxygen (such as smoking or dressing materials), and explore the evidence for the use of oxygen as therapy in managing patients with acute or chronic wounds.

Normal Wound Healing

Normal wound healing is characterized by four phases: inflammation, proliferation, granulation tissue formation, and tissue remodeling.[6] Each step is not considered distinct from the others, but rather there is a continuum. The first step after acute injury is clot formation, in which platelets initiate the clotting cascade as well as release chemotaxic factors such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) for recruitment of more platelets, inflammatory cells, and fibroblasts.[6] At first leukocytes and monocytes dominate the inflammatory cell population, but later on Day 4, macrophages dominate.[7,8] The main role of these latter cells in the inflammatory phase is to debride the wound site and prevent infection.[6]

Keratinocytes begin reepithelialization about 24 hours after wounding.[6] Although at this time it is unclear what exact signals allow the keratinocyte to phenotypically change into a migratory cell, the main factor in human serum that promotes keratinocyte migration is tumor necrosis factor-α (TNF-α).[9]

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Following this, the fibroblasts and endothelial cells undergo fibroplasia and angiogenesis, respectively. These two processes are interconnected as they are both stimulated by the growth factors that are present in the extracellular matrix at this stage.[6]

The final step in wound healing is tissue remodeling, which increases the tensile strength of the skin and eventuates into a mature scar.[10] Eventually Type III collagen is converted to Type I collagen via extracellular matrix-degrading metalloproteinases.[6] Matrix metalloproteinases (MMPs) are collagenases needed for this process as well as for reepithelialization.

Oxygen and Cellular Activity

To understand the role of oxygen in wound healing, it is helpful to understand the central role oxygen plays in cellular activity (see Table 1). One of the most significant cellular processes oxygen is involved in is oxidative phosphorylation in mitochondria. This results in adenosine triphosphate (ATP) production.[2,11,12] Oxygen homeostasis is necessary to produce and maintain ATP levels in cells, providing energy critical for proper cellular function and protein synthesis.[12]

TABLE 1. Potential Benefits of Oxygen on Wound Healing

Inflammation	• Prevention of infection via: ☐ Increased ROS activity in oxidative killing of bacteria[15,25] ☐ ROS role in inducing neutrophil chemotaxis[23,25,26] ☐ Optimal production of ROS by NADPH-linked oxygenase[15,25] ☐ Synergism with antibiotics[29]
Proliferation	• Increased reepithelialization via ROS role in the function of growth factors, such as EGF[2] • Increased keratinocyte differentiation and keratinocyte migration[80-83] • Increased production of fibroblasts and endothelial cells[79]
Collagen synthesis	• Induction of basic fibroblast growth factor via ROS production[13,43] • Optimal function of enzymes for proper posttranslational hydroxylation and cross-linking of collagen[44-47] • Enhanced wound contraction by triggering myofibroblast differentiation[49]
Angiogenesis	• Induction of VEGF via destabilization of normoxia[20,51,52]
Other	• Affects ATP production[12]

In addition, recent studies have suggested that reactive oxygen species (ROS), such as H_2O_2 and superoxide (O^{2-}), may have an important role in wound healing beyond oxidative killing of bacteria.[12,13] Both hypoxia and hyperoxia increase ROS production, which cannot occur in an oxygen-free system.[14] ROS at low concentrations are thought to act as cellular messengers to stimulate key processes associated with wound healing, including cell motility, cytokine action (including PDGF signal transduction), and angiogenesis.[15,16] More specifically, it has been shown that hypoxia induces hypoxia-inducible transcription factor 1α (HIF-1). HIF-1α is the regulated part of the transcription factor heterodimer HIF-1α/β, which complexes inside cells with another endogenous form of HIF. Together they act as a transcription factor and enter the cell nucleus. There, under hypoxic conditions, HIF-1 binds to hypoxia response elements in gene promoter regions. HIF-1α up-regulates genes involved in glucose metabolism, erythropoiesis, iron transport, control of vessel tone, and angiogenesis.[12,17] Therefore, HIF-1 also regulates oxygen homeostasis in the wound.[18] Hypoxia can also decrease the production of interleukin (IL)-2 and IL-8, which play a role in activating neutrophils, macrophages, T cells, and perhaps even endothelial cells.[19]

Oxygen and the Inflammatory Phase

Coagulation

Initially, a wound undergoes disrupted vasculature and increased oxygen consumption and thus has a hypoxic environment.[11] Wound oxygen tensions have been described as approximately 0–10 mmHg in the center, 60 mmHg at the periphery, and

100 mmHg in arteries.[20] Oxygen delivery in wounds depends on oxygenation and perfusion of blood and the diffusion distance from blood to tissue, which is related to the partial pressure of oxygen.[19,21]

As mentioned above, recent work has revealed that in the coagulative phase of wound healing, the clotting cascade and the function of PDGF rely on ROS activity. This ROS activity is initiated by wound hypoxia.[22,23] Hypoxia is also necessary in the beginning phase of wound healing for induction of other cytokines released from activated platelets and monocytes, such as TGF-β, vascular endothelial growth factor (VEGF), TNF-α, and endothelin-1. These cytokines have effects on cell proliferation, chemotaxis, and vascular permeability, among other roles important in wound healing.[6]

Although hypoxia acts as the initial stimulant to begin the process of wound healing, chronic hypoxia cannot sustain the process. Hypoxia leads to anaerobic metabolism that creates acidosis and inadequate ATP production to maintain normal cellular function, especially since the wound site is so metabolically active.[24]

Prevention of Infection

While hypoxia may be important in the coagulation process, the presence of oxygen is critical for infection prevention in the inflammatory phase. ROS play a central role to the prevention of wound infection. After coagulation begins, neutrophils and monocytes infiltrate the wound site and produce ROS in the process of the respiratory burst—the main defense against wound infection. ROS, such as H_2O_2 and O^{2-}, are produced by neutrophils and macrophages via nicotinamide adenine dinucleotide phosphate-oxidase (NADPH)-linked oxygenase.[15] This key enzyme requires oxygen to work optimally, and thus hypoxia blunts oxidative killing activity.[25] Studies have established that the K_m or half-maximal ROS production is 45 to 80 mmHg of oxygen, with maximal production at >300 mmHg.[11,25] In addition, not only are ROS central to the respiratory burst, but they also induce neutrophil chemotaxis.[23,25,26]

Clinically, several scenarios have illustrated the effects of oxygen on wound infection rates. In a study of guinea pig wounds inoculated by *Escherichia coli*, increased exposure to ambient oxygen decreased the extent of necrosis.[27] Moreover, anal wounds seem to have fewer infections than expected for such a contaminated environment. Some authors believe that increased perfusion and oxygenation in this anatomic site may be the reason for this observation.[28] Furthermore, supplemental oxygen has been found to work synergistically with antibiotics, specifically aminoglycosides.[29]

Oxygen levels have also been shown to have predictive value in preventing surgical wound infections. In a prospective human study, 500 patients with colorectal resection were split into two groups. One group received 80% oxygen supplementation perioperatively and 2 hours postoperatively, while the other received 30% oxygen in the same manner. Wound infection rates were inversely correlated to subcutaneous oxygen tension. There was half the rate of infection in the 80% oxygen group (5.2% [13/250] vs. 11.2% [28/250]). If the oxygen tension was 90 mmHg or more, there were no infections.[30] Another prospective study of 130 general surgery patients showed that the oxygen tension of the subcutaneous wound ($PsqO_2$) was a predictor of wound infection. The infection rate was inversely proportional to the maximum $PsqO_2$.[31] Gottrup[19] also notes that oxygen should have a preventative effect against anaerobic wound infection.

Oxygen and the Proliferative Phase

Reepithelialization

Older studies suggested that oxygen stimulates reepithelialization. However, these studies did not clearly distinguish between reepithelialization, the formation of granulation tissue, and overall wound

closure.[32,33] Initially in the wound healing process, wound hypoxia may play a critical role in jump-starting reepithelialization. O'Toole and coworkers[34] have demonstrated that under in vitro conditions, hypoxia increases keratinocyte motility. These keratinocytes had increased expression of lamellipodia proteins (ezrin, radixin, and moesin), which are cytoskeletal proteins involved in cell motility. In addition, hypoxia stimulated expression of Type IV collagenase and decreased expression of laminin-5, which inhibits keratinocyte motility. The same authors also demonstrated that low levels of ROS, as with hydrogen peroxide solution, inhibited the migration and proliferation of keratinocytes.[35] Nevertheless, ROS and other oxygen metabolites are necessary for the function of growth factors, such as EGF, which also affect reepithelialization.[2]

Moreover, wound healing in aged patients may also be related to oxygenation. Aged human keratinocytes (from persons greater than 60 years old) show slower keratinocyte motility in response to hypoxia than young keratinocytes (20–39 years old).[36] This may be due to the effects of oxygen on MMPs. MMP-1 is an interstitial collagenase required for keratinocyte migration on Type I collagen, while MMP-9 is a Type IV collagenase.[37] In young keratinocytes, hypoxia induces MMPs 1 and 9, tissue inhibitor of metalloproteinase, and TGF-β1 receptors. All of these factors promote keratinocyte motility and reepithelialization.[34,36,38]

Collagen Synthesis

Both the presence and the absence of oxygen have been shown to influence collagen synthesis. TGF-β1 is a growth factor responsible for the transcription of the procollagen gene. TGF-β1 activity has also been shown to increase the migration of young cultured human fibroblasts.[11,39] Falanga and coworkers[40,41] showed that hypoxia up-regulates TGF-β1 synthesis and secretion by fibroblasts in vitro and increases expression of the procollagen 1 gene COLA1. Siddiqui and colleagues[42] also demonstrated that acute hypoxia increases fibroblast proliferation, collagen synthesis, and expression of TGF-β1 mRNA. Chronic hypoxic conditions (six passes in hypoxia) decreased this activity; however, it was reversible once the cells were put back into higher oxygen environments.[42] In addition, ROS produced from oxidative stress also induces basic fibroblast growth factor.[13,43]

Nonetheless, oxygen is needed for the latter steps of collagen synthesis including posttranslational proline and lysine hydroxylation and cross-linking.[44] Fibroblasts need oxygen tensions of 30 to 40 mmHg to deposit collagen properly and the production of collagen is proportional to oxygen tensions.[15] Oxygen is needed for lysine and proline hydroxylation—the step required for collagen release from cells.[45] The major enzymes involved in the posttranslational steps of collagen synthesis, namely, prolyl hydroxylase, lysyl hydroxylase, and lysyl oxidase require oxygen as a cofactor.[45–47] Prolyl hydroxylase, which is required for hydroxyproline synthesis, is essential for triple helix formation. Without oxygen, the underhydroxylated pro-alpha peptide chains fail to form a triple helix. If exported out of the endoplasmic reticulum of the fibroblast, it is a nonfunctional protein.[48]

Oxygen is also required for collagen cross-linking and maturation. Lysyl hydroxylase and lysyl oxidase allow for proper collagen cross-linking.[46] Oxygen may even play a role in wound contraction by triggering the differentiation of fibroblasts into myofibroblasts; however, this phenomenon has only been demonstrated in cardiac tissue thus far.[49]

Angiogenesis

As with collagen synthesis, hypoxia seems to initiate neovascularization, but cannot sustain the process.[3,44] Of all the angiogenic growth factors in wounds, VEGF is considered the most influential.[22] Hypoxia and ROS stimulate fibroblasts, keratinocytes, and macrophages to release VEGF though the mechanism is not fully known.[1,22,44]

Hypoxia also induces a VEGF receptor, FLT-1.[12,50] Experimentally, VEGF has been shown to increase its expression in both hypoxic and hyperoxic environments.[51] One explanation of this apparent paradox is that VEGF is induced when normoxia is destabilized.[20] Angiogenesis, though, proceeds more efficiently and can only be maintained with sufficient oxygen. VEGF reestablishes higher oxygen tensions no matter which way VEGF is initially induced.[20,52] However, experiments have shown that the inhibition of neovascularization induced by chronic hypoxia cannot be overcome by added VEGF.[44]

Smoking, Stress, and Diabetes

Factors causing vasoconstriction or damage to the microvasculature, such as smoking, psychological stress, and diabetes, result in poor wound healing.[10] Smoking introduces substances such as nicotine, carbon monoxide, and hydrogen cyanide, which significantly decrease oxygen delivery and impair the immune response. Smoking also induces arteriolar vasoconstriction and ischemia, decreases fibroblast activity, and increases platelet adhesiveness, which increases clotting and decreases perfusion.[53,54] In one study, smoking two cigarettes caused a 9% to 55% (average, 22%) reduction of blood flow to the foot.[55] It also demonstrated decreased tissue oxygen levels for up to 50 minutes, and this seemed to correlate with nicotine blood levels. Nicotine is thought to be the central cause of vasoconstriction because nicotine stimulates catecholamine release.[56]

However, interestingly, the nicotine patch did not produce the same results, and tobacco smoke contains hundreds of other compounds.[57] Carbon monoxide competitively inhibits oxygen binding to hemoglobin by displacing oxygen from hemoglobin and decreasing oxygen transport, while hydrogen cyanide inhibits cytochrome oxidase which prevents cells from utilizing oxygen.[53,54,58]

Studies have also shown that smoking also has implications for wound infection. Smokers have higher rates of wound infection than nonsmokers.[59] However, using the nicotine patch does not increase infection rates. In a prospective study of 78 patients (48 smokers of at least 20 cigarettes a day and 30 nonsmokers), sacral punch biopsy wounds were followed for 15 weeks. The smoking group was randomized into smoking continuously or smoking for 1 week and then abstinence with a nicotine patch or abstinence with a placebo patch over the remaining weeks. Smokers had a higher rate of infections—12% versus a 2% rate in nonsmokers. Abstinence from smoking for 4 weeks reduced wound infection rates, and nicotine patch use did not worsen infection rates.[59] Another study supported these findings and suggested that smoking intervention, involving reduction of smoking 6 to 8 weeks prior to surgery, may be enough to decrease postoperative infections and overall morbidity in orthopedic joint replacement surgeries.[60] Finally, smoking over 10 years has been found to be associated with decreased immunoglobulins, CD16 + /natural killer cells and CD4/CD8 ratio due to increases in CD8 + cells.[61]

In addition, smoking has other detrimental effects on wound healing. Smoking causes emphysema and bronchitis, disease processes that decrease arterial oxygenation, lung fibroblast proliferation, and migration.[62–64] Collagen contraction and wound contraction are decreased in smokers, probably due to decreased fibronectin production.[65] Smoking decreases granulation tissue formation and wound healing in mice.[64]

Patients under high-stress situations, such as hospitalized and surgical patients, may have compromised wound healing. By activation of the sympathetic nervous system and vasoconstriction, stress may increase oxygen demand and decrease oxygen delivery. Therefore, one can increase oxygen delivery and accelerate wound healing with factors like warmth, sympathetic blockade, and supplemental oxygen.[7]

Diabetes is a disease that affects the microvasculature. High intracellular levels of glucose and glycolysis lead to the formation of products that are

toxic to endothelial cells. The vasculature becomes functionally abnormal, leukocyte–endothelial cell interactions increase, and perfusion decreases, which all lead to decreased oxygen and nutrient delivery to the wound.[66] Healing in diabetic wounds is further compromised because neutrophils have function poorly in a hyperglycemic environment.[67]

Wound Dressings

Wound dressings can play a role in the rate and quality of healing. First, wound dressings provide a moist environment. Dressings have been shown to increase epithelialization by a factor of two in pigs, decrease necrosis of ischemic skin flaps and decrease scar formation.[68–70] To improve reepithelialization, Eaglstein and colleagues[71] concluded that polyurethane (PUD) dressings (e.g., OpSite, Smith & Nephew, London, UK) need to be used within 24 hours (preferably 6 hours) and left on for 24 hours. In another report, after 3 days, hydrocolloid dressings (e.g., DuoDERM, Convatec, Skillman, NJ) and PUD improved epithelialization and collagen synthesis compared to air-exposed wounds. Hydrocolloid dressed wounds fared better than those with PUD.[72] Covered wounds may prolong exposure of the wound to growth factors in the extracellular matrix.[73]

Dressings may also increase hypoxia to the wound which may stimulate wound healing processes such as reepithelialization. Both oxygen-permeable PUD and oxygen-nonpermeable hydrocolloid wound dressings can create an almost negligible oxygen wound tension (4.5 mmHg O_2 vs. 0 mmHg O_2).[74] Petrolatum-impregnated dressings also impede oxygen delivery.[3] However, more viable neutrophils were found in the oxygen-permeable PUD, which may prevent more infections.[74]

On the other hand, dressed ischemic wounds have been shown to have decreased tensile strength compared to undressed wounds after 14 days.[70] In theory, dressings provide the ability to protect the wound from bacterial contamination. However, this was not supported by a study that found that leaving clean or clean contaminated wounds undressed does not lead to higher risk for infection.[75] In fact, certain occlusive dressings can increase the numbers of anaerobes in a wound. Specifically, in one study, DuoDERM and Vigilon (Bard Medical, Covington, GA) showed higher levels of *Clostridium perfringes* and *Bacteroides fragilis* versus OpSite and air-exposed wounds, while OpSite and Vigilon showed higher levels of *Pseudomonas aeruginosa* compared to air-exposed wounds.[76] Therefore, the effects of dressings on oxygen tension, moisture, and contamination and the timing of dressing wounds may be significant and need to be further investigated.

Hyperbaric Oxygen Therapy

Based on experimental evidence, it would appear that increasing oxygen tension at the wound site may result in a faster, more efficient healing process. Therefore, oxygen therapy has been initiated to aid healing of acute and chronic wounds. Hyperbaric oxygen therapy (HBOT) is one method of supplemental oxygen delivery and is used mainly for chronic wounds. HBOT is defined as the administration of 100% oxygen at a pressure of greater than 1 ATM.[24]

HBOT is a US Food and Drug Administration (FDA)-approved treatment with some established indications. These include chronic, nonhealing wounds, necrotizing soft tissue infections, clostridial gas gangrene, crush injuries, thermal burns, graft preparation, refractory mycoses, refractory osteomyelitis, osteoradionecrosis, intracranial abscess, blood loss anemia, carbon monoxide poisoning, cyanide poisoning, air embolism, and decompression sickness.[77] Contraindications include recent ear or sinus surgery, seizure disorders, febrile disorders, certain chemotherapies due to increased pulmonary toxicity, upper respiratory infections, emphysema, a history of thoracic surgery or pneumothorax, pacemakers, optic neuritis or otosclerosis, viral infections, congenital spherocytosis, hyperthermia, claustrophobia, and pregnancy.[24,78]

As far as the evidence for efficacy in chronic wounds, studies of animals and cultured cells show that HBOT does indeed increase the proliferation of fibroblasts and endothelial cells, thereby aiding granulation tissue and wound contraction.[79] HBOT also increases the differentiation of keratinocytes and keratinocyte migration on a human skin equivalent model.[80–83] Sheikh and coworkers[52] demonstrated increased VEGF levels in the wound fluid of rats undergoing HBOT. Clinical evidence includes a pooled analysis of randomized, controlled studies of HBOT and diabetic lower extremity ulcers, which concluded that HBOT decreases amputations in diabetic foot ulcers and reduces the size of venous ulcers at 6 weeks, but not at 18 weeks.[4,84] A controlled study of diabetic leg ulcers found HBOT to result in significantly decreased ulcer size on Day 15, but not after 30 days of treatment, while a smaller review found that HBOT did increase the trend toward decreased ulcer size.[85,86] A controlled study found that HBOT decreased the incidence of bacterial colonization in diabetic ulcers, but did not shorten the length of hospital stays.[87]

Transcutaneous oximetry is a recent technique providing an objective way to measure tissue oxygenation near a wound. A transcutaneous oxygen pressure monitor determines oxygen perfusion in tissue ($TcPO_2$). Serial recordings of $TcPO_2$ are usually made with the patient breathing room air and 100% oxygen at 1 ATM and during HBOT.[88] $TcPO_2$ is thought to be more indicative of both impaired microvascular and microvascular blood flow compared to an ankle-brachial systolic blood pressure index which may only measure macrovascular disease.[89] $TcPO_2$ measurements have been shown in several studies to determine patients who have a better chance of succeeding or failing at HBOT. The $TcPO_2$ of diabetic patients with foot ulcers have been studied. Those patients with an in-chamber $TcPO_2$ of 200 to 400 mmHg had a greater chance of success with HBOT.[89,90]

However, HBOT studies have been criticized, and this may explain the mixed results. Often these studies have very small sample sizes, unstandardized treatment protocols beyond the HBOT, and/or poor evaluation of the patients' comorbidities.[3] A randomized, controlled study of diabetic foot ulcers with populations well selected for age, sex, and comorbidities did not show that HBOT accelerated wound ulcer healing.[91] Thus, the clinical action of HBOT is yet to be established, and additional studies will be necessary to determine efficacy.

Stress-impaired wound healing is another complication that could potentially be reversed with HBOT. In a mouse study where the mice were restrained for 3 days and then wounded, HBOT was able to relieve the effects of stress and thus allow wounds to heal as efficiently as the control group. However, HBOT did not show significant improvement in wound healing in the control group, which was not under stress.[18]

On the other hand, HBOT can also have disadvantages to wound healing due to the potential stress it can induce both psychologically and physiologically. Not only can HBOT cause stress in the claustrophobic patient, but also there are numerous risks, including middle ear barotrauma and hypoglycemia.[24] The most serious reported adverse effect of HBOT is generalized seizures, although it is reported to be rare (1/3388 or 0.03%).[77] Other theoretical risks have been brought on by studies showing that HBOT shifts the body to an oxidative state. HBOT causes free radical generation in leukocytes in vitro, although evidence exists that it may not be as concerning with intermittent HBOT, and has not been demonstrated in vivo in healthy volunteers.[20,79,92] Oxidative stress from HBOT can impair red blood cell function in vitro.[20] HBOT has been associated with mutations in human blood DNA, apoptosis and arrested cell growth in fibroblasts, and hematopoietic cells.[81,93,94] Considering the potential complications of HBOT and lack of large retrospective or case-control studies, it becomes critical to determine whether or not the benefits outweigh the risks.

Topical Oxygen Therapy

Some have suggested topical oxygen is a better alternative for HBOT. Not only is it potentially less

toxic, but topical oxygen is also much more convenient in that it can be done at home, is less expensive, and has fewer complications (see Table 2).[5] The method of topical oxygen treatment is the administration of pure oxygen to a localized region of the body via a plastic inflatable device.

In support of its efficacy, one retrospective observational study of 58 complex surgical wounds in 32 patients determined that 65% (38 of 58 in 15 patients) healed completely on topical oxygen.[5] In this clinical case series, the average wound duration was 4 months (range, 1 day to 4 years). Most patients had at least one comorbidity. The wounds selected were those that either failed routine wound care or were expected to fail due to higher risk, although this was not defined. Wounds were exposed to a sterile single-use disposable boot or bag with 100% oxygen at 1 ATM for 90 minutes, 4 days consecutively. Mean treatment time was 80 $\pm$ 54 days (range, 24 to 233 days) and the follow-up period ranged from 1 to 8 months. In both the healed and the nonhealed groups, 51 of 55 treated wounds decreased in size.

TABLE 2. Contrasting Hyperbaric Oxygen with Topical Oxygen Delivery for Wound Care*[2]

Systemic Hyperbaric Oxygenation	*Topical Delivery of Oxygen*
■ Systemically oxygenates blood at 2–3 ATM	■ Topically oxygenates wound tissue at 1 ATM
■ Requires specialized facilities and personnel	■ Portable devices available bedside and in field
■ Relatively expensive	■ Inexpensive
■ Relies on vascular system to deliver O_2 to wound	■ Can deliver oxygen directly to superficial wounded tissue severed from circulation
■ Poor vascularity of wound tissue limits O_2 diffusion	■ Oxygenation not dependent on vascular bed
■ Risk of multiorgan oxygen toxicity	■ No risk of multiorgan oxygen toxicity
■ Relatively well studied for outcome, limited studies addressing underlying mechanisms	■ More limited research literature on outcome and mechanism

*Reproduced, with permission, from Gordillo and Sen.[2]

Wounds least responsive were neuropathic ulcers, postsurgical lower extremity wounds, and pressure ulcers. There were no complications.

Fries and colleagues[3] used topical oxygen (3–6 L/min 3 hours a day for 7 days via a mask) to open dermal wounds in pigs. Each of the four pigs had 10 wounds created on the back, half exposed to topical oxygen and half not treated. Topical oxygen accelerated wound closure as measured by histology, and increased keratin 14, VEGF expression and tissue pO_2 to 2 mm of depth. Of note, all wounds were also dressed with PUD dressings, which may have obscured the differences.

Studies of topical oxygen, though, have been criticized. These studies included different types of wounds (surgical, diabetic, pressure, and stasis ulcers, acute and chronic), comorbidities (malnutrition, paraplegia, cancer, and infection), wound care regimens, and age of patient populations. Topical oxygen therapy would not be able to be used in smokers for safety reasons.[5] Most importantly, there are few studies on this subject, and none have been case-controlled in humans. Larger series of patients in case-controlled trials would need to be studied to prove its benefits.

The effects of supplemental oxygen therapy are less understood except for its beneficial effects on wound infection as previously discussed. Little is known about how supplemental oxygen affects wound healing through its systemic effects or through local perfusion near wounds. Raising arterial oxygen levels by 100 mmHg only elevates wound PO_2 by 3 mmHg according to one study.[95,96] However, another study showed optimal growth of in vitro keratinocyte cultures with low ambient oxygen tensions, beginning at 2% O_2 (13 mmHg). Clearly, determining the exact role oxygen plays in wound healing is complex and not fully understood.

Conclusion

Supplemental oxygen as a treatment for wound healing appears promising, but many questions

remain. Although studies on wound healing and supplemental oxygen are lacking, there are numerous other reports of encouraging results from the clinical use of both topical and hyperbaric oxygen therapy. When scrutinized though, many studies lack power or contain a mixed population of wounds and the results are somewhat inconsistent. In addition, these studies were largely on patients with abnormal wound healing. Without large, randomized, case-controlled trials, the benefits of oxygen therapy for enhanced wound healing remain anecdotal. Our current understanding is that both the presence and the absence of oxygen play a role in wound healing. As our understanding of how the different states of oxygenation (hypoxia, normoxia, and hyperoxia) affect wounds at different stages of wound healing increases, hopefully the role of supplemental oxygen as a therapy in wound healing will also be clarified. In addition, the relationship between oxygen and moisture in wound healing and the use of wound dressing materials needs to be further examined. Therefore, since oxygen has a key role in wound healing, further investigation remains warranted.

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