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REVIEW ARTICLE

# Topical Oxygen for Chronic Wounds: A PRO/CON Debate

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**Abstract** The role of oxygen in wound healing is universally accepted and does not require any further evidence; however the controversy as to whether oxygen delivery systems have the potential to improve wound healing remains to be concluded. Topical oxygen treatment (TOT) involves the delivery of 100% oxygen for a mean of 90 min, once a day at an atmospheric pressure slightly above 1 atm abs. The use of TOT gained increasing interest recently. The current manuscript will summarize the pros and cons of TOT in the view of the available literature.


## Introduction

The use of oxygen in wound healing dates back to the early 60's when hyperbaric oxygen treatment (HBO) started to be used in clinical practice. Topical oxygen treatment (TOT) has followed this introduction toward the end of that decade.[1] Although, the introduction of both treatment modalities roughly coincided with each other, the supporting evidence, obtained either by experimental or clinical studies, did not follow a parallel course. While HBO gained increasing interest throughout the following years, TOT was not as much popular until the recent decade.

Evidence derived from studies conducted on the efficiency of HBO in the treatment of non-healing wounds has erroneously been extrapolated to TOT studies.[2] In 2005 the Undersea and Hyperbaric Medicine Society (UHMS) published a position statement regarding TOT use in chronic wounds and concluded that "*topical oxygen as a therapeutic strategy in wound healing is not adequately supported by scientific data*."[3] A number of studies have been published so far. In an attempt to discuss these latest studies and to contribute to this hot topic, we decided to conduct a pro/con debate session during the VI. National Underwater and Hyperbaric Medicine Conference held in Istanbul, Turkey. The authors of this paper include the two debaters (M.M., A.C.) and the two moderators (G.U., S.A.). It should be noted that the authors did not intend to compare TOT and HBO therapy in any sense, but rather aimed to focus on the efficiency or futility of TOT in the treatment of non-healing wounds.

## Pro: Topical Oxygen for Wounds is Effective

Oxygen supply for chronic non-healing wounds has recently been a focus of interest for many investigators. The

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partial pressure of oxygen ($pO_2$) is a key factor in wound healing and the literature has consistently reported that a transcutaneous $pO_2$ below 40 mm Hg is strongly associated with poor wound healing.[4] While increasing $pO_2$ at the wound edge improves hypoxia, it also promotes several other aspects of wound healing through the production of reactive oxygen species (ROS). Recent evidence, indeed, revealed that oxygen is not merely the primary source of energy, but also generates several ROS which may function as intracellular messengers in normal cell signal transduction and cell cycling. Mechanisms of ROS action are dose dependent and the dose is closely related with $pO_2$. Hydrogen peroxide ($H_2O_2$), for instance, reacts as an intercellular messenger at micro-molar concentrations, causes oxidative stress at milli-molar doses and is used as a disinfectant at a 3% concentrations.[5] Because $H_2O_2$ is more stable than any other ROS and may easily pass across cellular membranes, it is a key messenger in regulating intercellular mechanisms through TGF-β.[6] At μmolar doses, $H_2O_2$ induces neutrophil chemotaxis, endothelial adhesion[7] and matrix metalloproteinase–1 (MMP–1),[8] MMP–2[9] gene expression. Additionally it triggers epidermal growth factor (EGF) dependent signal transduction.[10] $H_2O_2$ also induces vascular endothelial growth factor (VEGF) expression from macrophages and keratinocytes.[11] Several enzymes responsible for collagen synthesis such as prolyl hydroxylase and lysyl hydroxylase and oxidase are known to be oxygen and ROS dependent.[12,13] $H_2O_2$ promotes collagen matrix formation by inducing collagen factor I, III and IV and TGF-β1 mRNA.[14] Finally, fibroblast/myofibroblast transformation is also oxygen and ROS dependent.[15]

The role of ROS in wound healing has been demonstrated in an experimental model, where perfusion was shown to be significantly impaired in the absence of ROS.[16] The majority of chronic wounds are stuck in the inflammatory phase due to impaired oxidative killing, a distinct function of neutrophils that involves ROS generation by NADPH oxidase. Adequate oxygen supply provides normal NADPH oxidase function and regulates cellular motility, angiogenesis and extracellular matrix formation.[17]

While $pO_2$ level and systemic factors are essential in wound perfusion, local factors are as just significant. Accordingly, increasing arterial $pO_2$ levels may not necessarily improve wound oxygenation. Factors such as critical ischemia, inadequate intravascular volume, disrupted vasculature, diffusion barriers, smoking and anxiety may impair wound oxygenation despite elevated arterial $pO_2$ levels. TOT, in this regard, may be an efficient alternate to systemic oxygen treatment modalities.

TOT may be applied in several ways. Conventional TOT involves the delivery of 100% oxygen for a mean of 90 min, once a day at an atmospheric pressure slightly above 1 atm abs.[5] A recently developed technique differs from the conventional one in that it provides continuous oxygenation for 24–72 h.[18] In this modality, an electrochemical oxygen concentrator refines and delivers atmospheric oxygen to the wound site through a cannula at 98%–100% rate.

The diffusion capacity of oxygen is poor; therefore, one may raise concerns regarding TOT and the diffusion distance. Debridement of all devitalized necrotic tissues prior to TOT application accompanied by a high gradient occurring between the source of oxygen and the wound base, however, is theorized to offset this limitation. Even if TOT had provided only a slight increase in $pO_2$ at the tissue level, as Piandatosi noted in his editorial in 2003, this alone would have beneficial effects on wound healing.[4] After almost a decade from this editorial, which raised substantial concerns on the use of TOT, we now finally have supporting evidence both from experimental and clinical studies. In the following section we will initially present evidence from basic science studies supporting the physiological background of TOT and thereafter will report results from recent clinical studies confirming these findings.

Recent experimental studies have, indeed, provided concrete positive evidence on the use of TOT in wound healing. Using the Seldinger method which relies on inserting a prob (OxyLite, Oxford Optronix, Oxford, England) within 2 mm of the wound center,[19] $pO_2$ levels were shown to rise from 5 to 7 mm Hg to above 40 mm Hg following the use of TOT in an ischemic wound model created on the back of a pig. After 6 days of daily 3 h of TOT, the size of the wounds in the TOT group were found to be significantly smaller, VEGF protein expression higher and revascularization more significant than the control wounds. Furthermore, a repeat assessment of $pO_2$ levels at day 22 revealed a persistent increase of $pO_2$ (42 mm Hg) on wounds treated with TOT as opposed to control wounds (11 mm Hg). In an ischemic rabbit ear model, the effects of continuous TOT were assessed on 7 mm circular wounds.[20] Following 8 days of treatment, wounds in the TOT group had significantly more epithelialization on histologic examination as compared with control wounds. Additionally, activator protein-1 (AP-1) levels, a marker for keratinocyte transcription, assessed on PCR were significantly higher in rabbits in the TOT group.

Clinical studies have confirmed the evidence obtained from experimental studies. A large number of observational studies reported successful results with TOT.[21–24] In a recent observational case series study, Gordillo et al, reported promising results with TOT in patients with non-healing chronic wounds who achieved good wound healing, an observation which was confirmed by a significant increase in VEGF expression on biopsy samples obtained from the edge of the wounds.[25] In a more recent non-randomized controlled study conducted by Blackman et al on 28 patients with diabetic foot ulcers (DFUs), the mean healing duration was shown to be significantly shorter with TOT as compared with standard wound care [56 days in 14 of the 17 (82.4%) patients vs. 93 days in 5 of the 11 patients (45.5%)].[26] Finally, Vickie et al, in a randomized controlled trial performed on patients with chronic DFUs, confirmed these findings by demonstrating that patients who received continuous TOT for 4 weeks had significantly higher wound size reduction as compared with patients who received standard wound

care alone [87% (range 55.7%–100%) vs 46% (15%–99%); $p < 0.05$].[27] The difference in the change in cytokine (IL-6, IL-8) and proteinase (MMP-1,-2,-9, TIMP-1) levels between the groups strengthened these results ($p < 0.01$). TOT opponents frequently cite a randomized controlled study conducted by Leslie et al as a clear evidence that TOT is not effective.[28] This study, however, has serious methodological flaws. The most significant of these is that, although TOT does not penetrate to bone, a substantial rate of patients with findings suggestive of osteomyelitis were included in the study [6 (50%) of the patients receiving TOT had abnormal bone scans or x rays and above 70 mm/h sedimentation rate].

In conclusion, current experimental and clinical evidence support the rationale behind the use of TOT in wound healing.

## Con: Topical Oxygen for Wounds is Not Effective

Oxygen plays a central role in wound healing. While, at the early stage of wound healing, low (hypoxia) $pO_2$ is an essential stimulator of growth factors, cytokines, gene activation and angiogenesis,[29] normal (normoxia) or increased (hyperoxia) levels of $pO_2$ are more favorable during the subsequent stages of wound healing.[30] Fibroblast and endothelial cell proliferation, for instance, occurs best at a $pO_2$ of 30–80 mm Hg and collagen synthesis, neovascularization and epithelialization all require a $pO_2$ between 20 and 60 mm Hg.[31] Actually, the role of oxygen in wound healing is universally accepted and does not require any further evidence.[32] The controversy, however, as to which oxygen delivery systems have the potential to restore or increase the rate of oxygen within the wound milieu remains to be concluded.

The literature, hence the evidence, about the use of TOT in chronic wounds is limited and to describe the mechanism of action of TOT, the majority of these reports refer to the evidence obtained from studies related to HBO, which apart from using oxygen does not have much in common. Proponents of TOT claim that it may efficiently deliver oxygen within the wound layers, an assumption which has not gained wide acceptance due to limited evidence. Piantodasi demonstrated that topical oxygen could diffuse through a maximum distance of 50–100 microns and hence claimed that the amount of oxygen absorbed through open wounds would be extremely small.[33] Moreover, given the debris, biofilm layers and devitalized tissues over the wound surface, it would be much assertive to pretend that topical oxygen would efficiently diffuse through all these barriers.

TOT has, let alone its efficacy, several significant pitfalls. First, an increase in the regional pressure of the affected limb may impede circulation, and thereby impair wound healing.[34] Moreover, limb ischemia may occur in case this pressure exceeds the arterial systolic pressure, or vascular congestion if it exceeds arterial diastolic pressure.[4] Second, several experiments demonstrated that a hypoxic tissue gradient, i.e., from the periphery to the center of the wound, is mandatory for angiogenesis and that when this hypoxic gradient is destroyed capillary growth ceases.[29] Therefore, even if TOT had increased wound $pO_2$ levels, it would do this at the center of the wound and would reverse this gradient, eventually resulting in the inhibition of angiogenesis.[34]

Transcutaneous partial oxygen pressure ($TcPO_2$) levels, which has seldom been assessed in TOT studies, were reported not to significantly increase in two studies conducted by Cotto-Cumbo[35] and Mostellar.[36] Mostellar et al,[36] using 6 healthy subjects, compared the influence of HBO and TOT on $TcPO_2$ levels and demonstrated 49% decrease with TOT and 1309% increase with HBOT. Heng et al reported negative influence of TOT on collagen synthesis and fibroblast proliferation.[37,38] Heng et al reproduced these findings in a prospective controlled study where 13 patients treated with TOT displayed decreased collagen synthesis and fibroblast proliferation.[39] Leslie et al, in a randomized controlled study showed that patients receiving TOT ($n = 12$) displayed a longer healing duration as opposed to patients who received standard care alone ($n = 16$).[28] In this study TOT was administered to patients with DFUs in two daily 90-min sessions through a leg chamber that provided humidified 100% oxygen at pressures cycled between 0 and 30 mm Hg (i.e., up to 1.04 atm abs) every 20 s. At day 14 wound size was significantly reduced in all patients, irrespective of which group they were assigned to ($p > 0, 05$). Finally, although fibroblast proliferation and collagen production are widely appreciated as strong indicators of wound healing, several studies, interestingly, have claimed their reduction as a benefit of TOT.[37–39]

To conclude, given the physical properties of oxygen, its limited diffusion distance and poor clinical results obtained from the above mentioned studies, TOT may not currently be recommended for routine use on wounds.

## Conclusion

The pros and cons of TOT are summarized in Table 1. TOT may have a role in wound management and deserves further research however given the fact that TOT does not penetrate to bone and hence would not be efficient for Wagner 3 and higher grade wounds, and that the majority of Wagner grade 1 and 2 wounds already have a big chance of healing with standard measures alone, the use of TOT should currently be restricted to the wounds that fail to show a tendency toward healing for at least 2–4 weeks of treatment with standard wound care. In view of the current

**Table 1** Advantages and Disadvantages of Topical Oxygen.

| Advantages |
|---|
| • Lower cost as opposed to HBO |
| • Home treatment option |
| • No complications such as middle-ear barotrauma as observed in HBOT |
| • No risk of systemic oxygen toxicity |
| • No risk of claustrophobia |
| • Ability to penetrate the wound directly from the surface and not from disrupted vasculature |
| **Disadvantages** |
| • May cause ischemia in case the pressure within the closed medium exceeds systolic pressure |
| • May cause vascular congestion in case the pressure within the closed medium exceeds diastolic pressure |
| • May not allow concurrent negative pressure wound treatment |
| • Does not penetrate to bone |
| • May cause cell toxicity |

poor volume and quality of scientific evidence supporting its use, TOT application should not be recommended outside of a clinical trial. We do not recommend third party pay or reimbursement. Before its routine use, TOT application should be subjected to the same intense scientific scrutiny to which systemic hyperbaric oxygen has been.

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