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Topical oxygen as an adjunct to wound healing: a clinical case series

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Abstract

Background: Disrupted vasculature and high energy-demand to support processing and regeneration of wounded tissue are typical characteristics of a wound site. Oxygen delivery is a critical element for the healing of wounds. Clinical experience with adjunctive hyperbaric oxygen therapy in the treatment of chronic wounds have shown that wound hyperoxia increases wound granulation tissue formation and accelerates wound contraction and secondary closure. Nevertheless, the physiologic basis for this modality remains largely unknown. Also, systemic hyperbaric oxygen therapy is associated with risks related to oxygen toxicity. Topical oxygen therapy represents a less explored modality in wound care. The advantages of topical oxygen therapy include low cost, lack of systemic oxygen toxicity, and the ability to receive treatment at home, making the benefits of oxygen therapy available to a much larger population of patients. *Materials and methods:* Over 9 months, seven surgeons treated 58 wounds in 32 patients with topical oxygen with follow-up ranging from 1 to 8 months. The data presented herein is a retrospective analysis of the results we have achieved using topical oxygen on complex wounds. *Results:* Thirty-eight wounds in 15 patients healed while on topical oxygen. An additional five wounds in five patients had preoperative oxygen therapy; all wounds initially healed postoperatively. In two patients, wounds recurred post-healing. In ten wounds, topical oxygen had no effect; and two of those patients went on to require limb amputation. There were no complications attributable to topical oxygen. Three patients died during therapy and one died in the first postoperative month from underlying medical problems. Two patients were lost to follow-up. *Conclusions:* In this case series, topical oxygen had no detrimental effects on wounds and showed beneficial indications in promoting wound healing.
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Keywords: Acute and chronic wounds; Oxygen therapy; Diabetes

1. Introduction

Disrupted vasculature and high energy-demand to support processing and regeneration of wounded tissue are typical characteristics of a wound site. Low supply and high demand of oxygen results in hypoxia. Oxygen delivery is a critical element for the healing of wounds [1–3]. In the presence of poor blood flow, the availability of oxygen to the wound site is thought to be a rate-limiting step in early wound repair. Indeed, transcutaneous oxygen measurement (TcPO2) alone helps to reliably estimate probability of healing in the ischemic extremity [4].

Factors that can increase oxygen delivery to the regional tissue, such as supplemental oxygen, warmth, and sympathetic blockade, can accelerate the time line of healing [5,6]. Intermittent oxygen therapy has been shown to promote collagen synthesis and is beneficial for producing the extracellular matrices that support wound healing [7].

Wound repair can often be facilitated by increasing the partial pressure at which oxygen is supplied to wounds [1]. Clinical experience with adjunctive hyperbaric oxygen therapy in the treatment of chronic wounds [8] have shown that wound hyperoxia increases wound granulation tissue formation and accelerates wound contraction and secondary closure [9,10]. Nevertheless, the physiologic basis for this modality remains largely unknown. Recent studies show that both molecular oxygen as well as its reactive derivatives have the potential to promote wound healing [11,12,20].

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Topical oxygen therapy represents a less explored modality in wound care [13]. Pure oxygen is locally administered to an affected region of the body at 1.03 atmospheres of pressure, and this can be done in the patient's own home (Fig. 1). It is indicated for the treatment of open wounds. The advantages of topical oxygen therapy include low cost and the lack of systemic oxygen toxicity. Systemic hyperbaric therapy requires that patients be placed in special chambers in the presence of trained physician specialists with the delivery of oxygen in the chamber at 2–3 atmospheres of pressure. Whether topical oxygen therapy has similar efficacy as systemic hyperbaric oxygen therapy remains to be established. A few brief studies have reported the effects of topical oxygen therapy on wound healing. These studies are mostly observational and do not address underlying mechanisms [14–16]. Based on prospective randomized clinical studies it has been inferred that topical oxygen therapy represents a cost-effective approach [17] to promote wound angiogenesis [18].

Thus, there is sufficient rationale to justify the use of oxygen therapy delivered topically. Because this is a relatively new method for treating wounds, it is incumbent upon us to determine the conditions under which it should be applied. The objective of this analysis was to evaluate the efficacy of topical oxygen as an adjunct to wound healing and determine which wounds are most responsive to this type of intervention. This retrospective, non-randomized report is one of the largest case series to date of patients treated with topical oxygen to promote wound healing.

2. Case series

2.1. Materials and methods

2.1.1. Patient selection

All patients in this retrospective study cover the results at a single institution and were managed either by plastic surgeons or physicians at the multidisciplinary Wound Healing Center. The patients selected for data analysis represent all the patients who have completed topical oxygen therapy over a 9-month-period of time, beginning in February, 2001, when this modality was introduced in our institution. There were no specific predetermined exclusion or inclusion criteria when considering patients for treatment with this modality other than the contraindications for the use of topical oxygen. These include: (1) inadequate perfusion to support wound healing, (2) wound completely covered with eschar, (3) wounds with fistulae or deep sinus tracts where the end can not be probed, and (4) patients who will not agree to refrain from smoking during oxygen administration. Prescribing patterns were sensitive to the cost of this modality, and it was not used for small acute wounds expected to heal by secondary intent. If the wound had failed management by traditional means or was at high risk of developing healing problems

Fig. 1. Patient shown wearing boot form of topical oxygen device on the arm. Note adhesive strip on the upper arm to permit insufflation with 100% oxygen to 1.03 atmospheres of pressure. These devices have a pressure relief valve to prevent excess pressure buildup during use.

postoperatively, topical oxygen was considered as an adjunct to standard wound care. The system is latex-free, making it safe for use on latex-sensitive patients.

2.1.2. Topical oxygen therapy

Topical oxygen was administered to the wound(s) as directed by a protocol similar to that used previously [17–19]. A sterile, single-use, disposable, gas-impermeable chamber with adhesive edges (GWR Medical, Chadds Ford, PA) applied as either a boot or a bag was secured around the affected limb or wound (Fig. 1), and 100% oxygen was administered at one atmospheres of pressure for 90 min for 4 days consecutively. This was followed by a 3 day rest period. The cycle was repeated as long as the wound appeared to be healing, until surgery was performed, or until it became evident that the treatment was having no success (as evidenced by wound growth or no change in size over a several week period). Aside from the cycling of oxygen treatments, wound care was not standardized. Petroleum-based products were not used as per the manufacturer's recommendations because of the potential for topical residue to limit oxygen diffusion into the wound. Treatment with topical oxygen was performed in the hospital, in patients' homes, and in extended care facilities. Patients or their caregivers were taught to apply the device, and a representative of the company providing the device (GWR Medical) visited the patients approximately every 3 weeks during the course of their treatment to document wound response.

2.1.3. Documentation of wound status

Photographs were taken before, during, and at the completion of therapy with a digital camera; and images were processed with the Wound*Imager*™ 2.0 medical database (MED-DATA Systems, Inc., Cherry Hill, NJ) [20]. Wound area was recorded, and depth was measured if feasible. In this series, wound measurements were recorded in cm^2 with the absolute change in size and percent change in size calculated to document changes during treatment. Wounds were considered healed when completely covered with epithelium.

2.1.4. Analysis parameters

Patients' records were reviewed for the presence of significant co-morbid conditions, duration of wound presence prior to initiating oxygen therapy, wound etiology, location, and size, length of follow-up, and final disposition of the wound.

2.1.5. Statistics

This case analysis is descriptive; statistics comparing healing within the group were not calculated. Values are noted as means ± standard deviation (S.D.).

3. Results

Over 9 months, seven surgeons treated 58 wounds in 32 patients with topical oxygen with follow-up ranging from 1 to 8 months. There were no complications associated with use of topical oxygen. Topical oxygen therapy was used to treat post-surgical wounds, pressure ulcers, venous stasis ulcers, neuropathic foot ulcers, diabetic hand ulcers, and acute trauma-induced wounds. The largest subgroup was the post-surgical category. Most post-surgical wounds were in the extremities. Most patients had at least one co-morbid condition (Table 1). The most common conditions were diabetes mellitus ($n = 10$), malnutrition as defined by total protein, serum albumin, and pre-albumin below reference values ($n = 6$), paraplegia ($n = 6$), cancer ($n = 6$), and active infection ($n = 4$).

3.1. Patient outcome

Of the 58 wounds, 38 (65.5%) healed during treatment with topical oxygen (Fig. 2). Of the remaining 20 wounds, four healed after undergoing surgical flaps or grafts; 11 did not heal; three patients (with three wounds) died during treatment; and two patients (with two wounds) were lost to follow-up. When post-surgical healing is included, 72.4% of all wounds ultimately healed in response to oxygen therapy (Fig. 2). The observed rate of healing increases to 75.0% (42/56), when the patients that were lost to follow-up are not included because the final disposition of their wounds could not be determined. Patients who were lost to follow-up were not included in any analyses depicted in subsequent figures.

Two of the eleven unhealed wounds went on to require limb amputation. These patients were categorized as topical oxygen treatment failures in our analyses. One patient died within a month of amputation from a pulmonary embolus, the amputation site healed in the second patient. This patient was categorized as a

Table 1
Co-morbid conditions present in wound patients

Condition	Number of patients[a]
Diabetes	10
Malnutrition	6
Paraplegia	6
Cancer	6
Active infection	4
Peripheral vascular disease	3
Morbid obesity	3
Immunosuppressives	2
Radiation therapy	2
Lymphedema	1
Klippel trenauny weber disease	1

[a] Several patients had multiple co-morbidities.

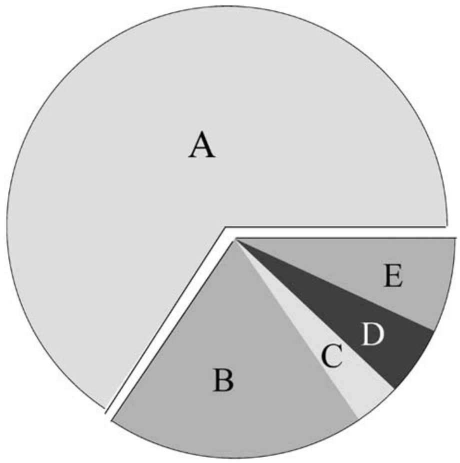

Fig. 2. Outcomes for all patients ($n = 32$) whose wounds ($n = 58$) were treated with topical oxygen and had completed their therapy during the 9 month study period. A, healed with topical oxygen only ($n = 38$); B, did not heal even when subjected to topical oxygen treatment ($n = 11$); C, lost to follow up; D, died during treatment for reasons unrelated to oxygen therapy ($n = 3$); E, healed when topical oxygen therapy was combined with graft or flap ($n = 4$). Complete healing was achieved in 72.4% (42/58), inability to achieve complete healing was noted in 18.9% (11/58) of wounds with the final disposition of 3.4% (2/58) of the wounds not evaluable because patients were lost to follow-up.

treatment failure and not a death, since she was not receiving topical oxygen at the time of her demise. The three patient deaths occurring during treatment were not related to the topical oxygen and were included in our analyses as wounds that failed to heal. All three patients had diabetes mellitus. One developed intra-abdominal sepsis, one had a post-operative myocardial infarction, one was morbidly obese and had respiratory failure. Wounds recurred in two patients. One patient had 11 lower extremity venous stasis ulcers that healed, but developed a new venous stasis ulcer within a month of stopping topical oxygen. In the second patient, a neuropathic foot wound was treated with preoperative oxygen followed by surgical closure. Initially the wound appeared to heal, but the surgical wound partially dehisced. Two patients with poorly controlled diabetes mellitus on immunosuppression for renal transplantation had progression of osteomyelitis while being treated with topical oxygen. After undergoing a metacarpal ray amputation, one healed without difficulty. The other required two additional metatarsal ray amputations before healing.

3.2. Treatment duration and wound response

Treatment duration ranged from 24 to 233 days. The mean treatment time was 80.6 ± 54 days. The duration of treatment for wounds that healed was 71.1 ± 50.1 days and for wounds that did not heal it was 101.2 ± 59.5 days. Initial wound sizes ranged from 0.29 to 92.2 cm^2 with a mean of 13.5 ± 21.4 cm^2. For wounds that healed the initial size was 8.1 ± 11.1 cm^2 and for wounds that did not heal the mean initial size was 25.3 ± 32 cm^2. Among wounds that did not heal, the average decrease in size was 6.5 ± 15.9 cm^2, and the average percent decrease in size was $71 \pm 63.3\%$ (Fig. 3). Four wounds increased in size during therapy. One patient was not included in calculation of wound sizes because his large wound made him a statistical outlier (1000 cm^2 compared with the range of 0.29–92.2 cm^2 in the other patients).

3.3. Wound acuity

Prior to instituting topical oxygen therapy, wound duration ranged from 1 day to approximately 4 years with a median time of 4 months (Fig. 4). Patients with acute wounds had a 69% healing rate as compared with 83% healing in wounds present in 7–16 weeks and 73% healing in wounds present for more than 16 weeks. With chronic wounds (> 16 weeks), surgical therapy was used in combination with topical oxygen in approximately 20% of patients that achieved a healed wound.

3.4. Wound location

Wound location impacted healing and the effect of location was analyzed in the context of wound acuity and etiology. In acute post-surgical or post-traumatic wounds, analysis focused on wound location as a having a significant impact on the patients' response to oxygen treatment. For chronic wounds analysis focused on etiology, as being a significant determinant of the patients' response to oxygen therapy. In many instances the etiology of chronic wounds also indirectly indicates

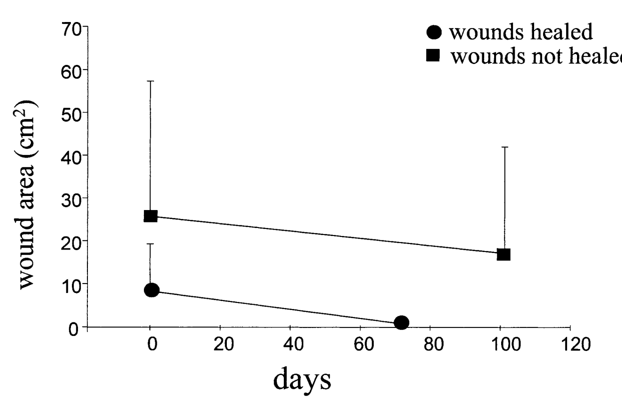

Fig. 3. Wounds treated with topical oxygen therapy decreased in size over time. In this case series 51/55 wounds became smaller in size when treated with topical oxygen. The three patients not included in the analysis include those two lost to follow-up and one patient with an extremely large wound (see text for details). Note that the average size of non-healing wounds was substantially larger than those that healed. Size may be an important variable in determining whether to use topical oxygen as an adjunctive versus primary therapy for wounds.

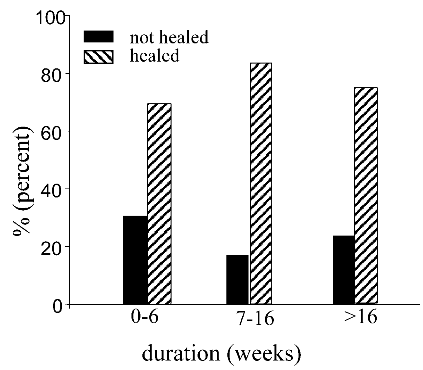

Fig. 4. Wound healing versus wound duration prior to initiating topical oxygen therapy. The acute wound subgroup appears to have the poorest healing rate, with 69% (9/13) of all wounds healed. However, this subgroup also includes the three wounds from patients that died, an important indicator of their health status while trying to heal wounds. Without this patient population the healing rate in the acute wound group would have been 90% (9/10).

location, e.g. venous stasis ulcers. For acute traumatic or post-surgical injuries, wounds involving the trunk and upper extremities responded well to topical oxygen with a 75 and 100% healing rate seen for those two locations, respectively (Fig. 5). The two acute trunk wounds that did not heal were in the same patient, a morbidly obese diabetic male who died of respiratory failure. Acute lower extremity wounds had a less reliable wound healing response at 50% (Fig. 5). Among chronic wounds a good response to topical oxygen therapy was noted in patients with venous stasis ulcers and diabetic hand ulcers as respective healing rates of 92 and 91% were observed (Fig. 6). However, neither of the two neuropathic foot wounds healed in response to topical oxygen therapy and only 44% of decubitus ulcers healed with this modality (Fig. 6). Fig. 6 is also noteworthy because it links co-morbid conditions with outcome, which has a significant impact on response. Comparing decubitus wounds with a 44% healing response to acute trunk wounds with a 75% healing rate illustrates this point well. Overall, the wounds least responsive to topical oxygen were post-surgical lower extremity wounds, pressure ulcers, and neuropathic foot ulcers.

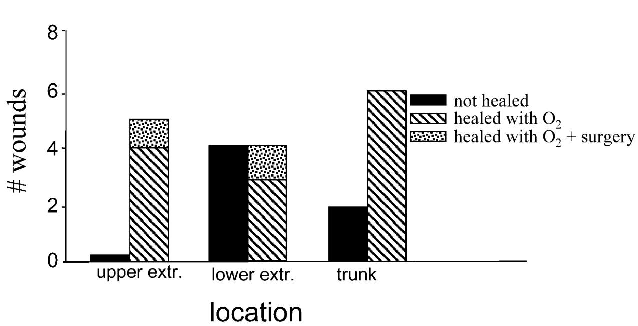

Fig. 5. Location of wound appears to influence response of acute wounds to oxygen therapy. Wounds on the trunk and upper extremity had healing rates of 75% (6/8) and 100% (5/5), respectively, and thus had much greater success when compared with lower extremity wounds, which completely healed 50% (4/8) of the time.

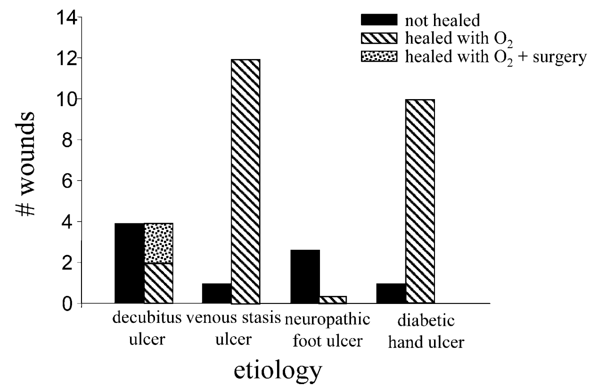

Fig. 6. Etiology of wound appears to influence response of chronic wounds to oxygen therapy. Neuropathic foot ulcers may be resistant to the effects of oxygen therapy as none (0/2) of these wounds healed. Decubitus ulcers also faired poorly when treated with topical oxygen alone indicating that patients with neuropathic disorders may be less responsive oxygen therapy. The size of the decubitus ulcers may have also contributed to the lack of complete healing seen in some of these patients.

4. Discussion

This case series analysis looked at topical oxygen as a therapeutic option for wounds which were chronic or which had a high chance of poor healing. We did not limit our indications because we hoped to establish which, if any, wounds responded to topical oxygen treatment. Given that we saw progression of osteomyelitis in two patients with diabetes, this indication should be very carefully considered. There have been no reports of side effects from the topical oxygen, and this analysis showed that the majority of chronic wounds and all acute wounds decreased in size during therapy. In this non-randomized analysis, it appears that topical oxygen is a useful adjunct to healing.

Upper extremity wounds and wounds of the trunk were most responsive to topical oxygen. In this relatively limited analysis, it does not appear that topical oxygen alone is adequate for management of lower extremity wounds and decubitus ulcers. However, for lower extremity wounds correlation with transcutaneous oxygen levels may help identify candidates more likely to respond to this type of therapy [4,21], which was not done routinely in this case series.

Complete healing was achieved in 38/42 healed wounds with topical oxygen alone, but surgery was required with four of the chronic wounds to achieve closure. For lower extremity wounds and decubiti, topical oxygen may be helpful as an adjunct to surgery, similar to HBO therapy for flap or graft preparation, but this has yet to be established. This also reflects the need to determine appropriate endpoints of therapy. The prescribing physician has much greater discretion with this modality as opposed to HBO. Achieving the appropriate balance between using topical oxygen to complete healing versus an adjunctive therapy in preparation for surgical wound coverage/closure is important to optimize the cost effective use of the device. Pursuing this type of data will help to refine the patient selection and improve the wound healing rates.

In comparing topical oxygen to other, more-standard, wound care regimes, it is helpful to look at the time-to-healing as an endpoint. Expected wound healing rates using hyperbaric oxygen are difficult to determine. In the past 10 years, three randomized controlled trials have been reported and only one of those studies reported complete healing as an endpoint [22–24]. In the randomized double-blind placebo controlled study by Bouachour et al. comparing the efficacy of HBO versus standardized therapy for acute crush injuries, they reported a 94.4% healing rate in HBO (100% O_2 @ 2.5 atm) treated patients versus a 55.5% healing rate in patients receiving placebo (21% O_2 @ 1.1 atm). It is important to note that this study evaluated only acute wounds. A more representative cohort might be obtained by comparing wound healing rates at the Wound Care Center at our institution, which is managed by the National Healing Corporation (NHC). A review of their 6 month data show an overall wound healing rate of 91% by 16 weeks (unpublished data), which includes, but is not limited to the use of hyperbaric oxygen therapy. Sixteen weeks is a frequently used time-point at which a therapeutic plan is re-evaluated. Our average treatment time with topical oxygen alone was 11 weeks with a healing rate of 65.5%. If we include those patients treated with adjunctive surgical procedures our healing rate increases to 75%. At a similar time-span for NHC, their healing rate was 79% (unpublished data). In this study, there were 28 wounds in ten patients with diabetes. Three of the patients died, one was lost to follow-up and 23 of the remaining 24 wounds healed (96%). The only wound that failed to heal was a foot wound. The wounds that did heal consisted of ten venous stasis ulcers, one abdominal wound, 11 hand ulcers and an acute post-operative leg wound. With greater refinement of our patient selection process, we hope to achieve similar or better wound healing rates with topical oxygen therapy.

The successful results that have been reported with HBO indicate that benefits to wound healing can be derived from the use of oxygen therapy. However, the limited number of indications recognized by third party payers and the broad range of contraindications for HBO therapy combined with limited availability of chambers means that many patients cannot receive these treatments. Recently, the commercial availability of a topical oxygen delivery device has made the concept of oxygen therapy feasible for application to a larger population of patients. The advantages of topical oxygen include the ability for the patients to receive treatment in their own homes and minimal risks associated with use of the device. Topical oxygen provides another tool in the armamentarium of physicians treating complex wounds and makes the potential benefits of oxygen therapy available to a broader range of patients than HBO. However, it suffers from the same reliance on empiricism as HBO to determine how it is best utilized. The data presented here represents one of the largest reported case series of patients using topical oxygen therapy for wound healing. Until the mechanisms for oxygen therapy are better understood we are forced to rely upon critical analysis of our experiences through retrospective case series, such as this one, and randomized clinical trials to optimize the use of this new modality.

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