UHMS Position Statement: Topical Oxygen for Chronic Wounds.

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SUMMARY

A small body of literature has been published reporting the application of topical oxygen for chronic non-healing wounds (1-17). Frequently, and erroneously, this form of oxygen administration has been referred to as "topical hyperbaric oxygen therapy" or even more erroneously "hyperbaric oxygen therapy." The advocates of topical oxygen claim several advantages over systemic hyperbaric oxygen including decreased cost, increased safety, decreased complications and putative physiologic effects including decreased free radical formation and more efficient delivery of oxygen to the wound surface. With topical oxygen an airtight chamber or polyethylene bag is sealed around a limb or the trunk by either a constriction/tourniquet device or by tape and high flow (usually 10 liters per minute) oxygen is introduced into the bag and over the wound. Pressures just over 1.0 atmospheres absolute (atm abs) (typically 1.004 to 1.013 atm abs) are recommended because higher pressures could decrease arterial/capillary inflow (13-15). The premise for topical oxygen, the diffusion of oxygen into the wound adequate to enhance healing, is attractive (though not proven) and its delivery is certainly less complex and expensive than hyperbaric oxygen. When discussing the physiology of topical oxygen, its proponents frequently reference studies of systemic hyperbaric oxygen suggesting that mechanisms are equally applicable to both topical and systemic high pressure oxygen delivery. In fact, however, the two are very different. To date, mechanisms of action whereby topical oxygen might be effective have not been defined or substantiated. Conversely, cellular toxicities due to extended courses of topical oxygen have been reported, although, again these data are not conclusive, and no mechanism for toxicity has been examined scientifically (18). Generally, collagen production and fibroblast proliferation are considered evidence of improved healing, and these are both enhanced by hyperbaric oxygen therapy (19). Paradoxically, claims of decreased collagen production and fibroblast inhibition in wounds subjected to topical oxygen have been reported in studies of topical oxygen as a benefit of topical oxygen therapy. The literature on topical oxygen is mostly small case series or small controlled but not randomized trials. Moreover, the studies generally are not aimed at specific ulcer types, but rather at "chronic wounds." This non-specific approach is recognized as a major design flaw in any study of therapies designed to improve impaired wound healing. The only randomized trial for topical oxygen in diabetic foot ulcers actually showed a tendency toward impaired wound healing in the topical oxygen group (17). Contentions that topical oxygen is superior to hyperbaric oxygen are not proven. There are potentially plausible mechanisms that support both possibly beneficial and detrimental effects of topical oxygen therapy, and thus well designed and executed basic science research

and clinical trials are clearly needed. There is some ongoing research in regard to the role of topical oxygen at established wound laboratories (20, 21). Neither CMS nor other third party payors recognize or reimburse for topical oxygen (22, 23).

Therefore, the policy of the Undersea and Hyperbaric Medical Society in regard to topical oxygen is stated as follows:

1. Topical oxygen should not be termed hyperbaric oxygen since doing so either intentionally or unintentionally suggests that topical oxygen treatment is equivalent or even identical to hyperbaric oxygen. Published documents reporting experience with topical oxygen should clearly state that topical oxygen not hyperbaric oxygen is being employed
2. Mechanisms of action or clinical study results for hyperbaric oxygen cannot and should not be co-opted to support topical oxygen since hyperbaric oxygen therapy and topical oxygen have different routes and probably efficiencies of entry into the wound and their physiology and biochemistry are necessarily different.
3. The application of topical oxygen cannot be recommended outside of a clinical trial at this time based on the volume and quality of scientific supporting evidence available, nor does the Society recommend third party payor reimbursement.
4. Before topical oxygen can be recommended as therapy for non-healing wounds, its application should be subjected to the same intense scientific scrutiny to which systemic hyperbaric oxygen has been held.

BACKGROUND

INTRODUCTION

Published reports of topical oxygen date back to the 1960's (1). Several authors have advocated its application as a cheaper and safer alternative to systemic hyperbaric oxygen (1,2,5-8,13-16). In hyperbaric oxygen therapy, the patient's entire body is placed into a pressure vessel and the ambient pressure is increased within the vessel, usually to pressures of 1.5 to 3.0 ATA. The patient breathes oxygen enhanced gas mixtures (usually 100%) either through a mask or head tent device if in a multi-place chamber or some monoplace chambers or by breathing ambient chamber oxygen in most monoplace chambers since usually the monoplace chamber is flooded with and its environment pressurized with 100% oxygen. In this way, it is possible to deliver greatly increased partial pressures of oxygen to the tissues. For example, at 2.0 atm abs patients with reasonable cardiopulmonary function will have an arterial oxygen tension of over 1000 mm Hg and a muscle oxygen tension around 221 mm Hg (24, 25). By comparison, muscle oxygen tension for a subject on air at 1.0 atm abs is about 29 mm Hg and 59 mm Hg if the subject breathes 100% oxygen at 1.0 atm abs. Indeed at 3.0 atm abs for a subject breathing 100% oxygen, there are more than 6 milliliters of oxygen dissolved in every 100 milliliters of plasma, enough to sustain basal metabolic requirements without any oxygen transport by hemoglobin (26-28).

In topical oxygen treatments, either a semi-rigid extremity chamber or a polyethylene bag is placed over an extremity or the patient's trunk and taped in place or sealed with a constriction device to achieve an airtight seal. High flow rates (10 Lpm) of oxygen are directed into the bag and passed over the wound. Pressures achieved within the topical appliance are usually just over ambient pressures (hence the application of the term "hyperbaric"). Heng et al recommend pressures of 1.004 to 1.013 atm abs (13,15). Actually pressures desired would be 0.004 to 0.013 atm abs over ambient pressures with obvious adjustments for altitude

at the administering facility. The proponents of this therapy contend that adequate oxygen to achieve enhanced wound healing diffuses into the wound, although this has not been demonstrated in any published studies. It has also been postulated that reduced harmful free radical formation occurs at the wound oxygen interface with 100% oxygen directly applied to the surface, (15) in part due to the induction of free radical scavenging enzyme systems. This contention is based on references from hyperbaric oxygen, and thus the concept remains hypothetical without supporting evidence (29).

Limitations of Topical Oxygen

Obviously, topical oxygen treatments are not applicable to a number of conditions for which hyperbaric oxygen is indicated. These include air embolism, decompression sickness, gas gangrene, acute anemia, carbon monoxide poisoning, osteoradiation necrosis, or brain abscess. The supporters of this therapy have not made claims for these conditions, but Heng has recommended topical oxygen for osteomyelitis, burns, necrotizing fasciitis, pyoderma gangrenosum, refractory (skin) ulcers and diabetic foot ulcers (13).

The central principle of topical oxygen therapy is that adequate penetration of oxygen can occur through the surface of a wound to enhance the healing process. The process of wound healing is a complex cascade of events involving the coordinated activity of many identifiable steps. These include inflammation, chemotaxis, angiogenesis, fibroblast proliferation, collagen elaboration, epithelial proliferation and finally remodeling (30). Proponents of topical oxygen concede that for its optimal effect wounds must be debrided before each topical oxygen treatment. An exudative or proteinaceous coating on the wound surface will substantially impair oxygen penetration. Certainly, this requirement is an issue in hypoxic wounds such as diabetic ulcers and radiation injuries that characteristically develop a tenacious and gas impenetrable covering in short order after debridement. Heng has proposed and presented diagrammatically that oxygen more readily reaches the wound by diffusion when introduced externally since it has a shorter distance to penetrate (13). However, as indicated by both Piantadosi (31) and Cronje (32), this circumstance reverses the usual oxygen gradient seen in wounds and now provides the highest levels of oxygen at the surface of the wound. In studies of angiogenesis, newly formed blood vessels are always found to move toward hypoxic regions (33). This reversal of the oxygen gradient may well impair angiogenesis rather than promote it. Given the competing effects possible of epithelial enhancement on one hand and angiogenesis suppression on the other, this proposed benefit of topical oxygen must be formally investigated before conclusions can be drawn.

Heng et al (15) reported a controlled trial of topical oxygen versus standard wound care in chronic wounds. The study was not truly randomized since whenever the two available topical oxygen systems were in use, eligible patients were arbitrarily assigned to the control group. Based on the location of these wounds in non-ambulatory patients, it appears that, though frequently complicated by intercurrent pathologies, the primary etiology of these wounds was chronic pressure (13). The treatment of pressure ulcers primarily relates to off-loading the pressure by a permanent change in management and lifestyle. Without such changes these wounds will rapidly recur. In this study capillary density, fibroblast density and collagen deposition were assessed as end points (15). Both fibroblast density and collagen deposition were decreased in the topical oxygen group in biopsies taken from the wounds. Vascular density was reported to be increased. The article concludes that this is a positive outcome stating that this finding

is consistent with decreased wound scarring. Certainly, excess elaboration of collagen, i.e. keloid or hypertrophic scar formation, can be problematic in a healed wound. This conclusion, however, ignores the vital importance of collagen elaboration and fibroblast proliferation in a healing wound, especially where the defect in wound healing in that chronic wound is a disorder of collagen metabolism. Histologic studies have limited usefulness because it is not clear whether the results predict functional status, as measured, for example, by wound tensile strength. In the early phases of wound healing and remodeling as described in this publication, collagen elaboration and deposition by fibroblasts in the wound are essential to successful and durable wound healing. A measured decrease in either at this time point is generally considered indicative of flawed wound healing. On the other hand, plastic surgeons and those interested in fetal healing recognize decreased collagen in a *healed* (distinct from healing) wound as optimal.

Issues of Toxicity

Advocates of topical oxygen therapy claim that it is significantly safer than hyperbaric oxygen. Neurological and respiratory complications are mentioned as comparative limitations of hyperbaric oxygen. Several articles have documented the low incidence of complications as a result of systemic hyperbaric oxygen. In a recent publication, Hampson and Atik (34) have reviewed the experience in regard to oxygen induced convulsions in 20,328 routine patient treatments at Virginia Mason Medical Center. In this report six patients experienced an oxygen convulsion for an incidence of one event per 3,388 treatments. A group from Israel (35) reports an incidence of 2 seizures per 100,000 patient treatments (27). Weaver and Churchill (36) have reported three patients with a history of cardiac disease and reduced left ventricular ejection fractions that experienced pulmonary edema associated with hyperbaric oxygen therapy. One patient died from this complication. The authors advise caution in the use of hyperbaric oxygen in patients with reduced cardiac output because it is likely to increase left ventricular afterload. The authors do indicate that this is a rare complication occurring in 3 of 1028 patients in their experience. Sheffield and Sheffield (37) have published an analysis of complications during a 22 year period of hyperbaric oxygen therapy involving over 170,000 patient treatments in a multi-place hyperbaric chamber. They report an incidence of 36 seizures over this time period (1.7 per 10,000 exposures requiring removal from the chamber and 0.4 seizures per 10,000 exposures addressed by removal from oxygen only). This group includes not only those treated for routine indications at lower pressures but also includes emergency patients treated at 3.0 atm abs on 100% oxygen. The review included 25 patients taken initially to 6.0 atm abs for air embolism, but these patients did not breathe 100% oxygen at this pressure. Additional complications involving several other organ systems are reported in this extensive experience, and these are exceedingly low and for the most part minor in their severity. Otic barotraumas amounted to just over one half of all complications. The total complication rate was 83.4 events per 10,000 patient exposures. Perhaps the most telling statistic is that only 39 patients refused to complete their treatment during this 22 year period. Notably, in this report no patient fatalities have occurred. Pott and associates (38) have reported a study which followed 18 systemic hyperbaric oxygen patients over 6 weeks with weekly pulmonary function studies. This study failed to demonstrate any decrement in pulmonary function. Clark (39) has published another summary of complications reported in the literature due to hyperbaric oxygen that confirms the previously cited work (37).

Based on these reviews, it can be stated that the incidence and severity of complications in commonly used hyperbaric oxygen protocols is very low.

While systemic complications of topical oxygen therapy would not be expected, Heng et al (18) have published a paper documenting endothelial cellular toxicity of topical oxygen. Gross changes in wounds were reported with prolonged treatment, consisting of depressed whitened areas granulation tissue beds. These were observed after 8 weeks of treatment and resolved with the cessation of topical oxygen treatment. This report potentially represents a significant contradiction of claims of decreased free radical damage with topical oxygen, although the mechanism and significance of the findings in this study are not clear. Sufficient data are not available to draw conclusions, and the effect may not relate to free radicals, but to other factors such as cooling or drying of the wound. No such observation, however, has been made with the continuation of hyperbaric oxygen, where the amount of granulation tissue continues to increase over time. One would also expect that free radical damage visible grossly after 8 weeks of treatment would actually be ongoing at a cellular level for some time before visually evident. It seems reasonable that directly bathing an open wound with high flow rates of oxygen could cause oxidative damage to fragile budding capillaries and their endothelial cell linings, which could negate potential benefits of increased oxygen availability (both oxygen and oxidants are required for wound healing) on the surface of the wound. Direct oxygen application is well known to have drying effects on open wounds and mucous membranes. In some series of topical oxygen, humidification of the oxygen is accomplished. The whole subject of free radical effects in wound healing is extremely complex and beyond the scope of this discussion. Two recent papers from investigators at Ohio State University contain a discussion of these issues, (40, 41) as does the Piantadosi editorial (31).

Published Results of Topical Oxygen

Several papers by additional authors have reported largely anecdotal results in applying topical oxygen with a presumptive beneficial outcome (1-16). A summary of these papers is included in tabular form below. Table 1 first delineates the AHA (American Heart Association) criteria for evidence evaluation and grading by which these papers are evaluated (42, 43). Table 2 lists the publications reporting topical oxygen as a strategy for wound healing enhancement, gives results and assigns a level of evidence represented by each paper. The inclusion of papers in this group is restricted to reports wherein topical oxygen was the only modality offered (other than standard wound care). The authors recognize that there are additional publications where topical oxygen was combined with other modalities such as electrical stimulation or laser application. These are excluded from further discussion because those results reported cannot be clearly attributed to the topical oxygen. The only truly randomized trial of topical oxygen was published by Leslie et al (17). Patients with diabetic foot ulcers were randomized to topical oxygen vs. standard care. No improvement in wound healing was seen in the topical oxygen group. In fact, there was a trend toward delayed healing in the topical oxygen group. A recent case series by Kalliainen et al (16) concluded that "topical oxygen had no detrimental effects on wounds." The authors also stated that based on their small case series "it does not appear that topical oxygen alone is adequate for management of lower extremity wounds and decubitus ulcers." Based on the published results of this paper, topical oxygen should be considered to have no better than mixed results. to separate it from the other entries because it is the only truly randomized study.

Table 1.

AHA Emergency Cardiovascular Care Levels of Evidence

Level 1: Statistically significant randomized controlled trials (RCT's).

- **1A:** Meta-analysis of multiple positive RCT's.
- **1B:** One or more positive RCT's with statistically positive results
- **1C:** Meta-analysis with inconsistent but significant results

Level 2: Statistically insignificant RCT's

- **2A:** Meta-analysis of positive RCT's but not statistically significant
- **2B:** One or more positive RCT's; not statistically significant
- **2C:** Meta-analysis of inconsistent RCT's; not statistically significant

Level 3: Prospective, controlled, but not randomized cohort studies

Level 4: Historic, non-randomized cohort or case-control studies

Level 5: Human case series

Level 6: Animal or mechanical model studies

Level 7: Reasonable extrapolations from existing data; quasi-experimental designs

Level 8: Rational conjecture (common sense); historical acceptance as standard practice

Table 2. Summary of Clinical Topical Oxygen Publications

First Author	Title	Date of Publication	Study Design	Etiology of Wounds Treated	Results	AHA Level of Evidence
Fischer BH[1]	Topical hyperbaric oxygen treatment of pressure sores and skin ulcers	1969	58 patient case series	Mix of pressure diabetic, venous stasis ulcers and osteomyelitis-most pressure sores	52/58 Healed	5
Fischer BH[2]	Treatment of ulcers on legs with hyperbaric oxygen	1975	30 patient case series	Mix of burns, pressure,venous stasis, collagen vascular, postop wounds-most pressure sores	28/30 Healed	5
Morgan SE[3]	Topical therapy of pressure ulcers	1975	Review article; no new cases presented	No original cases	N/A	5 (since it does cite 4 other case series)
Diamond E[4]	The effect of hyperbaric oxygen on lower extremity ulcerations	1982	11 Patient Case Series	Diabetic, arterial, traumatic-most venous	11/11 Healed	5
Heng MCY[5]	Local hyperbaric oxygen administration for leg ulcers	1983	Commentary with no new patient data	No original cases	N/A	8 (paper represents discussion of need for oxygen in wound healing and includes discussion of collagen synthesis and hyperbaric physiology)
Heng MCY[6]	Hyperbaric oxygen for a foot ulcer in a patient with polyarteritis nodosa	1983	Single case report	Polyarteritis Nodosa	Wound resolved	5 (cases series of 1)

Heng MCY[7]	Hyperbaric oxygen therapy for pyoderma gangrenosum	1984	2 patients Case series of	Pyoderma Gangrenosum	Wounds healed in both patients	5
Heng MCY[8]	A simplified hyperbaric oxygen technique for leg ulcers	1984	Prospective controlled but non-randomized study of 6 patients with 27 ulcers compared to 5 control patient with 10 wounds	Trauma, diabetes, most arterial insufficiency	18/27 wounds healed in O2 group vs. none healed in control group	3
Ignacio, D[9]	Topical oxygen therapy treatment of extensive leg and foot ulcers	1985	15 patient Case series	Arterial, venous, most with osteomyelitis and/or diabetes	11/15 patient healed; 3 amputations and 1 death	5
Lehman WL[10]	Human bite infections of the hand: adjunct treatment with hyperbaric oxygen	1985	Prospective controlled trial:16 patients with O2; 27 No O2	Human bites	Topical O2 of no value in superficially or moderately infected group; hospital stay was shortened in severely infected (P‹ .05)	3 (Though prospective not randomized since assignment to control group occurred when limb chamber was not available)
Upson AV[11]	Topical hyperbaric oxygenation in the treatment of recalcitrant open wounds	1986	2 patient Case series	Arterial ulcers	Both healed	5
Kwiecinski MG[12]	Therapeutic value of hyperbaric oxygen in lower extremity ulcerations	1987	Comment; no new patient data	No new patient data	N/A	8
Heng MCY[13]	Topical hyperbaric oxygen for problem skin wounds	1993	Comment and description of techniques; no new patient data	No original patient data	N/A	8

Heng MCY[14]	Enhanced healing and cost-effectiveness of low pressure oxygen therapy: a feasibility study of technology transfer	2000	15 patient case series with 24 wounds	Pressure, diabetic, arterial ulcers, 4 complicated by osteomyelitis	22/24 wounds healed	5
Heng MCY[15]	Angiogenesis in necrotic ulcers treated with hyperbaric oxygen	2000	40 patients in prospective but not randomized trial	Virtually all pressure sores with many complicated by diabetes or osteomyelitis	90% healed in O2 group; only 20% in control group	3 (patients were not truly randomized since patients were assigned to control group when O2 delivery devices were in use)
Kalliainen G[16]	Topical oxygen as an adjunct to wound healing: a clinical case series	2002	32 patient Case series (58 wounds)	Malnutrition, pressure, radiation, PVD-most diabetic)	38/58 healed; 10 no effect by O2; 2 amputations	5
Leslie CA[17]	***Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers***	***1988***	***Randomized controlled trial of 28 patients***	***All Diabetic***	***No difference between groups; trend toward delayed healing in O2 Group***	***2***

The table shows that the vast majority of publications (10/17 publications) represent Level 5 evidence (Case Studies).

Three papers represent Level 3 evidence (controlled but not randomized). The study by Leslie presents Level 2 evidence (randomized, controlled but not statistically significant).

Hyperbaric oxygen therapy has received approval for reimbursement from CMS (the Center for Medicare and Medicaid Services) for application of hyperbaric oxygen to diabetic wounds of the lower extremity (44). This approval is conditional upon three criteria:

1. The wound must be a Wagner's Class III or higher.
2. The patient is diabetic and the sequelae of diabetes have contributed to the development of the wound.
3. The patient has failed an adequate course of standard wound care.

In order to achieve this approval for reimbursement, an intensive assessment of the supporting literature was accomplished. This review involved a contract with the New England Medical Center to independently examine the scientific merit of hyperbaric oxygen intervention (45). Warriner and Hopf (46) discuss this process and the supporting literature which includes four randomized controlled trials in the current Oxygen Therapy Committee Report. Before topical oxygen can be accepted for application in wound healing, it should be submitted to a similar scrutiny and formal review.

Comparative Effects of Hyperbaric Oxygen

Most wounds that are chronic and appropriate for hyperbaric oxygen involve a systemic disorder (such as diabetes) or a regional insult (such as radiation injury or irreversible large vessel flow impairment). It seems counterintuitive that a local therapy would have major application under these conditions. The anti-inflammatory and vasoconstrictive impact of systemic oxygen can lead to reduced edema while increasing tissue oxygen, which is likely to be a benefit in wounds with a major component of inflammation and edema. A systemic therapy such as hyperbaric oxygen would more likely be appropriate to address these disorders. The sum total of wound care biochemistry and physiology does not occur at the wound surface. Macrophages and neutrophils need to be mobilized and migrate into the wound. All the needed nutrients and catalysts required for wound healing must be delivered by the circulation. The use of a topical therapy in lieu of a systemic therapy for a regional or systemic pathology which includes a chronic wound is analogous to the application of a topical antibiotic in lieu of a systemic antibiotic for a regional or systemic infection. Piantadosi (31) in his recent editorial discusses many issues related to the advantages of hyperbaric oxygen in wound healing enhancement efforts. He also discusses some positive implications of enhanced oxygen including the need for certain free radical oxygen species as a necessary component of the complex interplay of many factors and biochemical reactions in wound healing. Marx (47) has emphasized the importance of hyperbaric oxygen in changing the entire microvascular milieu in the setting of radiation soft tissue and bony necrosis.

Hyperbaric oxygen therapy has been shown to enhance angiogenesis in hypoxic wounds and radiation injuries (48, 49). A study of transcutaneous oxygenation done by Cotto-Cuombo and associates (50) failed to demonstrate an increase in oxygen tensions in the periwound environment with topical oxygen while the enhanced tissue oxygen delivery with systemic hyperbaric oxygen has been well documented (51).

Future and Current Studies of Topical Oxygen

In at least two well respected and established wound laboratories (The University of California at San Francisco and Ohio State University), there is ongoing research and interest in topical oxygen as a possible therapeutic strategy for wound healing in chronic wounds. Hopf (20) thinks that topical oxygen may support epithelial proliferation and coverage of the superficial wound. Virtually none of the research to date has specifically addressed this particular type of wound. Results in most published studies appear to be best in venous ulcers, which generally fall into this category. The Ohio State group (16,40,41) continues to investigate topical oxygen as one of many potential interventions in chronic wound management. It is possible that further study will establish a role for topical oxygen in the management of some wounds. To date, this information is not conclusive and routine application of topical oxygen to chronic open wounds is not supported. The Undersea and Hyperbaric Medical Society encourages such research efforts.

While the FDA has approved medical devices for the administration of topical oxygen, there has been no approval by CMS for reimbursement of oxygen delivery to wounds by these devices. In clinical practice, the use of these devices should be held to the same rigorous standards as have been applied to systemic hyperbaric oxygen treatment.

SUMMARY

Topical oxygen is not hyperbaric oxygen, and it is inaccurate and misleading to conflate the terms. Results of hyperbaric oxygen studies cannot be extrapolated to support topical oxygen treatments. To date, topical oxygen as a therapeutic strategy in wound healing is not adequately supported by scientific data. Those publications supporting its use are few in number and of a low level of scientific evidence. There are also reports, including the only randomized prospective trial, that show no benefit from topical oxygen. One study also documents toxicity to the healing wound with continued application. CMS and other third party carriers do not reimburse for its use. Before topical oxygen can be recommended as standard therapy for chronic wounds, it should undergo the same intensive review to which hyperbaric oxygen was subjected.

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