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Title: UHMS Position Statement: Topical Oxygen for Chronic Wounds

Abstract:

There is a growing incidence of chronic wounds and recognition from the medical community of the complexity involved in caring for these patients. The prevalence of chronic wounds is estimated to be as high as 2% of the US population [1, 2]. While chronic ulcers and non-healing wounds encompass a wide range of etiologies including trauma, diabetes, venous disease, ischemia, neuropathy and infection, localized ischemia is often a contributing factor [3].

Oxygen is necessary for more than aerobic respiration. It has an essential and well-established role in collagen crosslinking, re-epithelialization, angiogenesis and leukocyte killing of bacteria, as well as reactive oxygen species in cellular signaling [4-6]. In tissues with a deficit of the necessary partial pressure of oxygen these required processes for wound healing are arrested [7]. In addition to localized basic wound care, adjuvant methods are often used to aid the delivery of oxygen to promote healing of chronic wounds.

Hyperbaric oxygen (HBO<sub>2</sub>) therapy is widely recognized and rigorously studied systemic treatment where the patient is entirely enclosed in a pressure-vessel and intermittently breathes oxygen at elevated pressure, typically greater than 1.4 atmospheres absolute (ATA) [8]. One of the indications for HBO<sub>2</sub> therapy is the treatment of selected wounds where localized hypoxia is part of the pathophysiology of failed healing [9]. Systemic mechanisms of HBO<sub>2</sub> therapy which promote healing include increased mobilization of stem cells, improved cellular signaling, and restoration of adequate oxygen content necessary for angiogenesis and collagen formation [7].

An alternative strategy to HBO<sub>2</sub> is to topically deliver oxygen to the wound bed, avoiding systemic delivery. Various methods have been developed to attain this goal. These include localized delivery of oxygen at or near 1 ATA, generating oxygen adjacent to the wound and a multitude of dressings and topical medications designed to provide oxygen directly to the wound surface [10].

With the latter approach, oxygen may be released through the degradation of hydrogen peroxide, or micro/nanobubbles contained within perfluorocarbon or

polyacrylamide polymers, among others. These wound dressings are available in different forms, including hydrogels and films and microfluidic bandages [10]. Topical oxygen emulsions can also be used with dressings to directly deliver oxygen to the wound bed. These dressings all aim to optimize localized wound bed environments and are used as part of an overall wound care strategy.

There are controlled clinical trials using these products, with varying success reported [11]. Synthesizing the results of these trials is impeded by the variability in the type of wounds studied and the outcomes measures used. As they are a local treatment, these strategies need to be distinguished from the administration of HBO<sub>2</sub>, with all its unique systemic effects.

### Conclusions and Recommendations:

1) Devices, wound dressings, and topical medication designed to increase external wound exposure to oxygen should not be termed hyperbaric oxygen therapy. Doing so intentionally or unintentionally suggests that topical oxygen delivery methods are equivalent or identical to hyperbaric oxygen. Any report of methods and devices providing increased topical oxygen delivery to wounds should clearly state that topical oxygen and not hyperbaric oxygen is being delivered.

2) Hyperbaric oxygen therapy provides mechanisms of action and physiological effects which are distinct from those of devices, wound dressings, and topical medication that provide topical oxygen. Study results concerning hyperbaric oxygen should not be used to support topical oxygen therapy.

3) Oxygen containing and oxygen generating wound dressings aim to address localized wound bed environments and are part of overall wound care strategies to optimize local conditions. They are a local treatment and lack the systemic effect of HBO<sub>2</sub> therapy. These treatments are distinct from HBO<sub>2</sub> as they lack the systemic effects of HBO<sub>2</sub> therapy. Hyperbaric oxygen literature should not be used in support of their use and it should be clear that they are not HBO<sub>2</sub>.

4) Topical oxygen may be a promising treatment based on some recent studies, but it cannot be recommended for routine clinical care at this time due to a restricted volume and quality of supporting scientific evidence. More investigation is necessary to determine if topical oxygen can be used in the clinical setting for wound care. In particular, we need better information on precise indications for use, optimal dosing regimens and standardized outcomes. Future clinical studies should address these issues.

5) Before topical oxygen therapy can be recommended for non-healing wounds, its application should be subjected to additional scientific scrutiny to better establish indications for use, dosing and response to treatment.

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