Oxygen therapies for wound healing: EWMA findings and recommendations

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For wounds to heal, it is essential that macro- and microcirculation is restored in the surrounding tissue (Niinikoski et al, 1991; Gottrup, 2004a). One of the most urgent requirements is oxygen, as it is critically important for the reconstruction of new vessels and connective tissue, and also enables resistance to infection.

Sustained oxygen at the wound site is also vital for patients with non-healing wounds. This has been proven for wounds associated with peripheral arterial occlusive disease and diabetic foot ulcers (DFUs) (Dissemond et al, 2015).

Non-healing wounds are a significant problem in healthcare systems worldwide. In the industrialised world, 1–1.5% of the population will have a non-healing wound at any one time (Gottrup, 2004b). Wound management is expensive and, in Europe, it is expected that wound management accounts for 2–4% of healthcare budgets. Costs are expected to rise as the amount of older people increases, as well as the increase in the number of people with diabetes (Dale et al, 1983; Gottrup, 2004b; Posnett et al, 2009; Hjort and Gottrup, 2010).

Oxygen therapy is a general term that covers hyperbaric oxygen therapy (HBOT) and topical oxygen therapy (TOT). This article, based on the European Wound Management Association (EWMA) document on the use of oxygen therapy (Gottrup et al, 2010), highlights the present knowledge, treatment options and available evidence for the use of oxygen therapies in the care and treatment of non-healing wounds of different aetiologies (Gottrup et al, 2010).

Excluded from this document are animal and cellular models, acute wounds, such as surgical/trauma wounds, and burns. The distribution of supplementary systemic oxygen at barometric pressure in connection with surgery is also not covered.

Role of molecular oxygen in wound healing

Hypoxia acts as an initial physiological signal to promote wound healing, but prolonged hypoxia may maintain pro-inflammatory conditions and prevent wound healing. Thus, ongoing hypoxia induced by chronic infections, including increased oxygen consumption by activated neutrophils, may actually impede wound healing.

It is recommended that measurement of local tissue oxygenation before and during hyperbaric oxygenation may help healthcare professionals identify patients who would benefit from HBOT. However, all oxygen therapies, including local oxygen supply or delivery enhancement by haemoglobin can be improved by knowing the oxygen levels in the proximity of the wound. Measurement of pO_2 near the wound using transcutaneous oximetry (TCOM) is currently approved as the best surrogate for measuring oxygen levels in the wound bed. This measurement strongly depends on several factors, including local perfusion, temperature reactivity, and oxygen outflow through the skin layers (Fife et al, 2002).

The predictive value of TCOM has been mathematically validated for diabetic extremity ulcers with good prediction of the failure to heal rate when a TCOM measurement is made while the patient is breathing oxygen at pressure.

Hyperbaric oxygen therapy

There is evidence that HBOT improves healing by restoring oxygen levels to normal, exerting an anti-infective effect on aerobes and anaerobes, reducing inflammation and oedema, stimulating angiogenesis and vasculogenesis, as well as stem cells. HBOT should be considered for non-healing wounds in order to restore local normoxia or even induce hyperoxia. Efficacy should be monitored, preferably with transcutaneous oximetry measurements and where HBOT is not effective, it should not be continued.

Specific recommendations for different types of non-healing wounds and different populations of patients have been established based on all available clinical evidence and consensus agreements (Mattieu et al, 2016).

In general, HBOT is suggested for the treatment of diabetic foot lesions, ischaemic ulcers and selected non-healing wounds, secondary to standard wound treatment.

More specifically, HBOT is recommended in ischaemic lesions without surgically treatable arterial lesions or after vascular surgery. The use of HBOT is recommended in the presence of chronic critical ischaemia if the patient has diabetes. If the patient has arteriosclerosis, the use of HBOT is recommended in case of

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chronic critical ischaemia, defined as periodical pain, persistent at rest, needing regular analgesic treatment for more than 2 weeks, or ulceration or gangrene of foot or toes with ankle systolic pressure <50mmHg in the non-diabetic or toe systolic pressure <30mmHg in patients with diabetes (European Consensus Document (1991).

HBOT should always be used as part of a multidisciplinary treatment plan with ongoing wound care on a regular basis and not as a stand-alone therapy. Standard wound care should have been provided for at least 4 weeks before the application of HBOT. This would include appropriate debridement, vascular screening for significant peripheral arterial disease and/or local wound hypoxia, adequate offloading and infection therapy. Furthermore, vascular screening, including imaging techniques, should be performed to evaluate if any revascularisation procedure is indicated before HBOT is used. If HBOT is used before an indicated revascularisation (meaning not enough blood perfusion) there would be no effect of HBOT. TCOM is recommended as the best technique to monitor the local pressure of oxygen. For further recommendations refer to the EWMA document (Gottrup et al, 2017).

Topical oxygen therapies

Despite almost 50 years of clinical use, the use of TOT for non-healing wounds remains controversial (Fischer, 1969; Feldmeier et al, 2005; Fife et al, 2007; Fife and Hopf, 2011). TOT can be defined as oxygen that is applied topically over injured tissue by either continuous delivery or pressurised systems. The availability to the wound tissue of topically applied higher pO_2 reverses localised hypoxia (Hopf et al, 2005). This kills anaerobic bacteria and enhances leukocyte function to address all other pathogens (Hunt et al, 1975; Gordillo et al, 2008).

Once the initial inflammatory response subsides, the high availability of oxygen molecules in the wound tissue helps to upregulate angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2) (Gordillo et al, 2008). This results in the prolific structured growth of new blood vessels and the stimulation of collagen synthesis by enhancing fibroblast activity (Gordillo and Sen, 2003; Fries et al, 2005; Tawfich and Sultan, 2009), which improves wound bed granulation, strengthens the formation of collagen tissue and aids wound closure (Gordillo and Sen, 2003; Fries et al, 2005; Sibbald et al, 2007). *Box 1* details the TOT technologies that are available.

The clinical results indicate that using these methods can be better than standard care alone. The clinical evidence for the efficacy of topical oxygen-based treatment ranges from uncontrolled case reports to randomised controlled trials with some limitations. Although most of the published data do not meet the highest standards of evidence, it suggests that adjunctive therapies are easy to handle, safe and may be effective modalities for use in modern wound care strategies in specific sub-populations. Questions about the concomitant action of TOT with other therapeutic procedures, including HBOT, vascular interventions or skin transplantation, still remain.

TOT compared with HBOT generally offers patients increased mobility and ease of adoption within their everyday life.

It is out of the scope of this article to go into specific evaluations of the published literature related to the use of TOT. For more detailed information refer to the EWMA document (Gottrup et al, 2017). More robust data from multicentre prospective placebo-controlled trials affirming clinical efficacy will be required before this therapy can be given a stronger recommendation.

The patient perspective

Many patients view oxygen as a curative therapy (Kelly and Maden, 2014), it is a product they are familiar with and many patients wish to increase their intake of oxygen to assist wound healing.

Despite the paucity of evidence, it seems likely that the patient's perspective will affect the uptake of the therapy — and its perceived success. Healthcare professionals should be able to understand and respond to the patient's perspective in order to encourage a collaborative approach to healing.

The EWMA document recommends that there should be more large-scale, qualitative research that focuses on specific areas of the patient perspective of oxygen treatment. This should focus on patient outcomes associated with oxygen treatment, health-related quality of life for patients receiving oxygen treatment; the advantages of oxygen therapy for the patient from their perspective and the expansion of research into health literacy associated with oxygen treatment.

Cost

There is some evidence on the cost-effectiveness of HBOT for the treatment of acute and chronic wounds. HBOT might reduce overall cost of treating diabetic foot ulcers

Box 1. Technologies available for TOT (Gottrup et al, 2017).

- Continuous delivery of non-pressurised oxygen (CDO)
- Low constant pressure oxygen in a contained chamber
- Higher cyclical pressure oxygen
- Oxygen release through dressing or gel
- Oxygen transfer
- Application of oxygen species.

when the costs of amputation and rehabilitation are taken into consideration. Given the incidence of DFUs, using oxygen therapy to prevent deterioration could result in a cost saving for healthcare services.

There is minor, but increasing, evidence about the effectiveness of TOT due to the relative low cost of its application, at least in specific sub-populations of patients. The evidence of cost savings associated with oxygen-releasing dressings is based on a reduction in the mean number of nurse visits (Moffatt et al, 2014). Furthermore, haemoglobin spray as an adjunct treatment seems to have a positive effect on wound healing and reduce the cost of care (Bateman, 2015).

It is recommended that robust health economic data based on evaluation of large placebo-controlled RCTs should be used to make recommendations on cost-effectiveness. This should be based on providing standard wound care during at least a 4-week period before the implementation of HBOT. Vascular screening is recommended to work out whether a revascularisation procedure is needed before HBOT and TOT or both. The creation of a European wound register that could record the type of oxygen therapy and its outcome in wound care is recommended.

Conclusion

Wounds need oxygen to heal. HBOT has been known for many years; it is well-established for specific indications and there is some evidence that it improves healing.

Due to its relative novelty and the small number of clinical studies involving TOT compared with HBOT, the clinical evidence for the efficacy of TOT ranges from uncontrolled case reports to RCTs with some limitations and the amount of clinical data are growing. TOT adjunct therapies are easy to handle, safe and may, therefore, be effective modalities for specific sub-populations.

The important question about the concomitant action of TOT with other therapeutic procedures, including HBOT, vascular interventions or skin transplantation, has still been unanswered. The patient's perspective seems likely to affect uptake, experience and the perceived success of oxygen therapy for wound management. There is some evidence that HBOT and TOT have been used without extra costs occurring or even with reduced costs in specific clinical settings.

Future perspectives

Diagnostic tools for measuring local hypoxia should be used more regularly to improve oxygen therapies. Further studies should demonstrate which treatment modality would be the best for the patient. In future, smart dressings could incorporate specific sensors and actively modify environmental conditions in the wound.

Well-designed prospective and controlled studies to critically evaluate the efficacy and effectiveness of oxygen therapy for the management of non-healing wounds should also be initiated.

With increasing global antibiotic resistance, the antimicrobial effects of oxygen therapies should be made part of future wound care strategies. WINT

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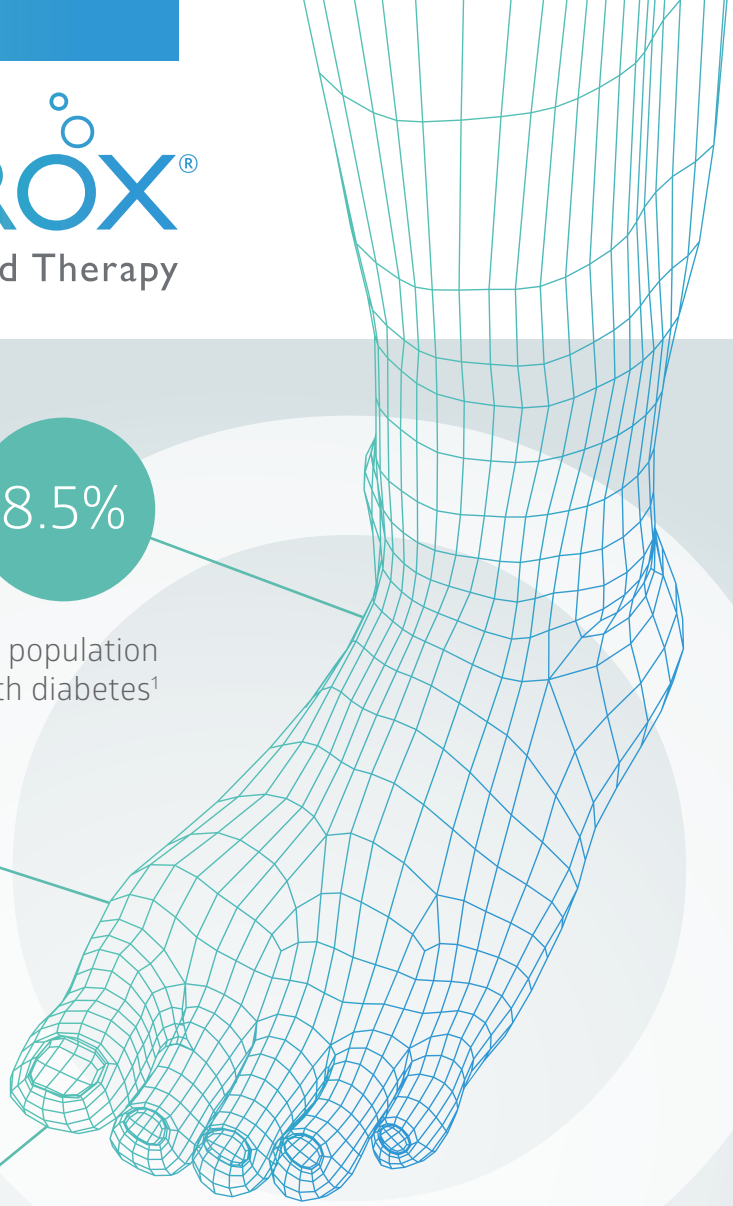

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