Oxygen has a crucial role in wound healing; 97% of chronic, non-healing wounds have been shown to have low oxygen levels (Hauser, 1987). Topical oxygen therapy has been shown to be effective in treating non-healing wounds, but is still underutilised. A working group of key opinion leaders met in February 2015 to determine the potential role of topical haemoglobin in non-healing wounds and to develop a clear decision-making pathway for clinical practice, as well as sharing practical tips for use. The group’s consensus recommendations on appropriate use are presented here.

Wounds cannot heal without adequate oxygen. Oxygen is needed to generate the extra energy required for healing damaged tissue, driving tissue granulation and resistance against infection (Sen, 2009; Gottrup, 2004). Thus, the process of wound healing demands increased levels of oxygen and other metabolites.

Mild hypoxia is a normal biological response following an injury; along with a series of initial responses, this causes oxygenated plasma to diffuse from the surrounding intact tissue to the hypoxic wound area, in order to aid healing (Bishop, 2008). However, extreme hypoxia and local ischaemia mean that insufficient oxygen reaches the wound; this is a common feature of wounds that fail to heal (Sen, 2009). Reactive oxygen species (ROS) thrive in this hypoxic environment, which leads to tissue damage and other cellular processes that stall wounds in the inflammatory phase and further delay healing (Schreml et al, 2010).

A chronic wound is defined as a wound that fails to progress towards healing following 2–4 weeks of standard care and requires further intervention (van Rijswijk and Polansky, 1994; Sheehan et al, 2003; Margolis et al, 2004). However, the working group felt that use of the terms ‘acute’ or ‘chronic’ wounds is outdated, and proposed that these should be replaced with the terms ‘healing’ and ‘non-healing’ wounds.

Non-healing wounds due to a lack of oxygen may signal underlying vascular problems, which can be micro cellular level, local ischaemia or macro level, which would include peripheral arterial or cardiac disease, resulting in tissue oedema that can further reduce local perfusion (Sen, 2009). Evidence shows that poorly oxygenated wounds almost never heal, while oxygenated wounds do – in one study, 97% of non-healing wounds were found to have low oxygen levels (Hauser, 1987); see Figure 1. Measurement of tissue oxygenation by transcutaneous oximetry (TcPO₂) can serve as a useful clinical tool for wound management (Ruangsetakit et al, 2010; Arsenaut et al, 2012; Zulec, 2014).

The working group agreed that it is likely that most non-healing wounds have a level of hypoxia and this is well supported by the evidence. However, wound ischaemia can often go unnoticed and this may be due to difficulty in measuring tissue oxygenation (TcPO₂), absence of cardinal signs and symptoms, or lack of nursing/podiatry time and resources. The panel recommend that clinicians recognise the role of hypoxia in non-healing wounds and that further work should be done to raise awareness about the role of oxygen in non-healing wounds and the potential for interventions that can aid healing.

**USING SUPPLEMENTARY OXYGEN IN NON-HEALING WOUNDS**

It is extremely difficult for wounds to absorb oxygen directly from the air; it is therefore important that oxygen be delivered via blood circulation. In
patients with vascular problems, oxygen transport is even more compromised and the resulting lack of tissue perfusion to the wound area is a major risk factor for non-healing (Sen, 2009). This particularly applies in diabetic foot ulcers (DFUs) and leg ulcers, as these often develop as a result of compromised vascularity (Holtman and Gahtan, 2008).

If the vascular system cannot deliver sufficient oxygen naturally, supplemental oxygen has been shown to aid healing and decrease wound complications (Gottrup, 2004). However, therapies such as hyperbaric oxygen therapy are of limited use in standard wound care due to equipment requirements and a lack of clinical and cost efficacy (NHS England, 2013). Therefore, supplemental oxygen through topical haemoglobin is a more practical solution, which creates a cycle of continuous oxygen transport to the wound bed (Arenbergerova et al, 2013), binding atmospheric oxygen and transporting it to the wound bed, where it is released.

Granulox® (infirst Healthcare, London, UK) is a topical haemoglobin spray produced from sterile porcine products, which is designed for the treatment of slow-healing and non-healing wounds. Topical haemoglobin has been studied in randomised clinical trials (RCTs) versus standard care, and has shown superior short-term (≤6 months) efficacy in patients with chronic venous insufficiency (Arenberger et al, 2011; Arenbergerova et al, 2013). Short-term (≤7 months) case and pilot studies in the UK have also demonstrated reduced slough, pain and wound area, as well as increased granulation of epithelial tissue and improvement in patient quality of life following treatment with Granulox in non-healing and slow-healing ulcers (Chadwick, 2014a; Chadwick, 2014b; Green et al, 2014; Green and Mohamud, 2014; Norris, 2014; Tickle, 2015). The research on topical haemoglobin is growing and findings to date have been positive. Further studies are required to assess its long-term efficacy and optimum frequency of application in order to inform clinical practice (Healthcare Improvement Scotland, 2014).

**GRANULOX: INDICATIONS**

Granulox can be used to optimise the wound environment in slow-healing and non-healing wounds that have not responded to standard care. Prior to any treatment, it is important to make a full holistic assessment of both the patient and the wound (see proposed treatment pathway for topical haemoglobin, Figure 2). Before using Granulox, all wounds showing signs of delayed healing should be optimised using the principles of wound bed preparation (Dowsett and Newton, 2005) to decrease bacterial load, manage exudate levels and remove non-viable tissue. Underlying contributory factors should be addressed and appropriate measures taken to support wound healing (e.g. provide offloading/compression therapy/refer for vascular surgery) and control other contributory factors (e.g. diabetes/cardiac disease management, nutritional support).

According to the instructions for use, Granulox should not be used on infected wounds or wounds with clinical signs of infection, as there is not currently sufficient evidence in this area. The working group discussed this issue and agreed that more research is required regarding this contraindication, as this will currently exclude a large number of potential patients who could otherwise benefit from topical haemoglobin.

**IMPLEMENTATION IN WOUND CARE**

The working group recommended that topical haemoglobin should be considered after 2–4 weeks of best practice standard care, if the wound fails to respond substantially to treatment (Figure 2). For patients at high risk of delayed wound healing at initial assessment (e.g. immunosuppressed patients), topical haemoglobin may be considered earlier. For patients with poorly perfused wounds, correction of the underlying cause should be identified as the primary part of treatment; once perfusion is optimised, if oxygenation is still required then supplemental oxygen should be considered. It was
Clinical experience using Granulox highlighted some useful tips for use:

- Rinse the nozzle with warm water or saline directly after use to prevent the nozzle from becoming blocked.
- Inform patients of the red appearance of the product in advance of use.
- Take appropriate action to avoid staining of clothes, using appropriate secondary dressing to prevent strikethrough and leakage.
- Exudate levels should be managed prior to application of the product — high exudate levels may flush the product out of the wound bed, with the potential to lose some of its beneficial oxygen-giving properties.
- Cleanse the wound at each dressing change to reassess the wound.
- Debride the wound as appropriate.
- Ideally Granulox should be stored in the fridge. If this is not possible, non-refrigerated products will last at least 6 weeks (from the time the product is received). It was advised that for patients at home (where it is applied twice per week), the product should last approximately 18 weeks when it is taken out in the mornings (on the days when it is being used) and refrigerated the remainder of the time. In the clinic environment, where it is used numerous times throughout the day and week, refrigeration overnight will extend the lifecycle 6–12 weeks.
- The recommendation for optimal use of Granulox was to reapply at every dressing change, with a maximum wear time of 3 days.

### TREATMENT MILESTONES

The group recommended that informal reassessment of the wound occur at every visit, while formal review of treatment should occur every 4 weeks, as improvement is expected to occur within this timeframe (see treatment pathway in Figure 2). If there are signs of improvement, the treatment can be continued for a further 4 weeks. If no improvement is seen at 4 weeks, clinicians should consider alternative treatment options. Expected markers of healing would be: reduction in size of wound; improvements to appearance, wound bed, tissue, range of movement, exudate volume.

There are currently no guidelines regarding when to stop treatment, thus the group recommended that where there are no adverse reactions, clinicians should stick to the 4-week review intervals and use their clinical judgement as to when to stop.
The working group stressed the importance of patient and staff education in informing patient choice. Some patients may be concerned by the porcine component of Granulox — e.g. due to religious beliefs — so the clinician will need to discuss this with these patients before use. The product information emphasises that ‘each production lot is tested for sterility by an accredited laboratory; the high level of quality ensures that only sterile products will be shipped.’

FUTURE RESEARCH

Evidence for the use of topical haemoglobin is building; however, the working group raised a number of areas for future research, to extend product use and help provide further support for formulary applications. The group’s discussions led to the following research suggestions:

- Well conducted clinical RCTs to obtain robust evidence for the product, particularly with regard to long-term efficacy
- Studies on its mode of action (in vivo and in vitro evidence) to optimise indications for use.
- Information on the impact of facilitating oxygen diffusion on matrix metalloproteinase levels may also be of use, as this could mean both ischaemia and inflammation is being treated
- Studies in which oxygen levels are sequentially evaluated clinically (i.e. before, during and at the end of the study treatment period, or until healing/discontinuation) would be beneficial in determining the stages at which the product can be initiated and stopped. Information on the decreased need for oxygen in the wound as it heals may lead to further guidance on optimal treatment period and frequency of application
- Post-marketing surveillance to provide standardised data collection, which may allow true comparisons to be made
- Structured case studies with strict criteria, designed specifically for different types of wounds, may be useful
- More information on the role of topical haemoglobin in the paediatric population — in particular, management of epidermolysis bullosa
- Further research on cost-effectiveness of product and impact on patients’ quality of life
- Further information on what is the optimal secondary dressing.

SUMMARY

Topical haemoglobin should be considered after 4 weeks of standard care in patients with a non-healing wound, and could be considered earlier for patients at high risk of delayed wound healing. The working group devised a treatment pathway to provide guidance on assessment and management, with practical tips for application and review. Full holistic assessment of both the patient and wound is vital, and any underlying causes for non-healing wounds should be treated as priority. Patient education is key, as is support of non-specialist staff. While evidence for short-term use is building, further research is needed to determine long-term use and cost-effectiveness to support practising clinicians.

REFERENCES


Bishop A (2008) Role of oxygen in wound healing. J Wound Care 17(9):399–402


