Pilot study: haemoglobin spray in the treatment of chronic diabetic foot ulcers

**KEY WORDS**
- Chronic wound healing
- Diabetic foot ulcers
- Wound oxygenation

Wounds cannot heal without oxygen. In fact, healing wounds demand more oxygen than healthy tissue — yet chronic wounds are often at least partly due to vascular insufficiency. A novel spray aims to make use of haemoglobin, the transport molecule for oxygen in the bloodstream, to bind atmospheric oxygen and deliver it to the hypoxic wound bed. The product, Granulox® (Infirst Healthcare), may be of particular interest in patients with impaired levels of tissue perfusion/oxygenation, which may be impeding wound healing.

Without the presence of oxygen, wounds cannot heal. Extreme hypoxia has often been noted in wounds that fail to heal, because a lack of oxygen is "not compatible with life or tissue repair" (Sen, 2009). Reactive oxygen species (ROS) thrive in a hypoxic environment, leading to the tissue damage and other cellular processes that stall wounds in the inflammatory phase (Schreml et al, 2010).

Oxygen is required at the cellular level to minimise ROS and generate the extra energy damaged tissue needs for healing (Sen, 2009). In a wound bed, oxygen is a key nutrition component for the development of granulation tissue and resistance against infection (Gottrup, 2004). Wounds thus have high oxygen demands, so the extent to which a wound is adequately oxygenated may determine healing (Sen, 2009).

**IMPEDIMENTS TO WOUND OXYGENATION**

Because wounds cannot absorb oxygen from the air, it is important that oxygen be delivered internally via the vascular system. Haemoglobin is the molecule in the blood that acts as oxygen's transport system through the circulatory system and into tissue. This is why, if tissue does not bleed, it cannot heal — the microcirculation of oxygen via blood flow is vital for wound healing (Gottrup, 2004).

In general, the amount of oxygen is reduced as it diffuses from the bloodstream to the peripheral tissues (Ladizinsky and Roe, 2010). In patients with peripheral arterial disease, oxygen transport is compromised, and the resulting lack of tissue perfusion to the wound bed and periwound area is a risk factor for non-healing (Sen, 2009). This is particularly true in diabetic foot ulcers (DFUs) and leg ulcers of all aetiologies, which develop as a result of compromised vascularity in the extremity (Holtman and Gahtan, 2008).

Tissue perfusion should therefore be evaluated in patients with wounds, to address issues surrounding compromised circulation (Gottrup, 2004) (Box 1). If a patient has significant arterial disease, referral to a vascular specialist for further evaluation and revascularisation is warranted (Holtman and Gahtan, 2010). However, if referral...
**Product Focus**

“*It is important to evaluate tissue perfusion in patients with wounds and address issues surrounding compromised circulation.*

is not indicated per local protocols, the care plan should seek to manage the wound indications, and restore oxygenation and nutrition to the wound bed (Gottrup, 2004).

In addition to vascular compromise, the presence of exudate impedes oxygenation of the wound. Even a thin film of liquid blocks 95% of unaided oxygen diffusion; the higher the exudate level, the lower the likelihood adequate oxygen will be delivered to the wound bed (Data on file).

**How Granulox Can Increase Oxygen Supply**

Supplementary oxygen has been shown to decrease wound complications (Gottrup, 2004), but such therapies (e.g. hyperbaric oxygen therapy) are limited by expense and poor access and, therefore, often rendered impractical for standard wound care. Haemoglobin-mediated facilitated oxygen diffusion can be achieved by applying haemoglobin to the wound bed as an aqueous solution (Arenbergerova, 2013).

Granulox® (Infirst Healthcare) is a novel haemoglobin spray to support the healing of chronic wounds. Produced from porcine blood products, the haemoglobin binds atmospheric oxygen and carries it to the wound bed, where it is then released. Based on the principle of facilitated diffusion, because haemoglobin does not get used up or dissipate, it can create a cycle of continuous oxygen transport (Arenbergerova et al, 2013).

A randomised, controlled trial found that aiding oxygen supply to the wound bed of VLUs via treatment with Granulox ‘is an important add-on procedure for successful wound treatment’ (Arenbergerova et al, 2013). This product may therefore be of particular interest in patients with impaired levels of tissue perfusion/oxygenation that may be impeding wound healing (Table 1).

**Granulox in Practice**

Every patient with a wound needs to be assessed holistically to identify intrinsic and extrinsic factors. This should encompass a full patient history including medication, comorbidities and factors likely to reduce wound oxygenation. It should also take into consideration the history of the wound, and previous wounds and how healing progressed in them.

A thorough of assessment of this nature should be carried out before treatment with Granulox (Box 2). Granulox should be considered for wounds that are stuck or slow to heal, particularly if it is felt that poor perfusion is a factor in non-healing. It should not be used on wounds that are infected.

Before Granulox application, cleanse the wound with saline. If using octenidine dihydrochloride, rinse thoroughly afterwards with saline. Spray Granulox uniformly from about 5–10cm from the wound. There are up to 30 applications in a can of Granulox (each application costs about £4.30).

After application, Granulox may be used with any dressing that is ‘wet’ and ‘air-permeable’ (e.g. hydrocolloid/foam dressings, superabsorbents/hydrofibers, hydrogels). Film dressings and alginates are less desirable. Granulox should not be used with hydrocolloid or occlusive film dressings, or negative pressure wound therapy systems.

**Pilot Study**

In a pilot study with four patients with non-healing DFUs, positive results were seen. Two wounds healed, and one saw a significant reduction in wound area after 2 weeks’ treatment (Table 2).

**Box 2. Advice for using Granulox.**

**Pharmacy**

➤ It is expected that Granulox will be available over the counter in the future in the UK; in the meantime, it must be obtained on formulary through the pharmacy

**After application**

➤ To avoid surface drying, clean the spray head after application with an alcohol-soaked cleaning cloth

➤ If the spray has become clogged, remove and replace

**Storage**

➤ Granulox is best stored refrigerated (2°C–8°C) for daily use up to 6 weeks

➤ On the day of treatment, the can may be allowed to warm to room temperature (up to 25°C)

**Patient considerations**

➤ With the right level of education and concordance, it is possible patients could self-apply at home

➤ Because Granulox is produced from porcine origin, patients should be informed in case they cannot be concordant for religious or moral reasons.
Standard DFU care (e.g., offloading, infection management) was implemented before treatment with daily Granulox application was started (International Best Practice Guidelines, 2013). Two of the cases are highlighted here:

**Patient 1:** A deep DFU, including bone and articulation, of more than 12 months’ duration reduced in area by 20% in 2 weeks (*Figures 1a–c*).

**Patient 2:** A deep DFU that was clean but static, with no change over the previous 2 months (*Figures 2a–c*).

## CONCLUSION

The pilot study and evidence show potential for Granulox in the treatment of wounds that show signs of hypoxia. As haemoglobin is the blood’s transport molecule for oxygen, this porcine-based haemoglobin spray could be a solution for delivering vital oxygen to the wound bed where lack of perfusion may be impeding healing. However, further randomised, controlled trials must be conducted with larger numbers of patients to continue to build the evidence regarding this innovative product.

**REFERENCES**


Table 2. Outcomes from pilot study.

<table>
<thead>
<tr>
<th>Wound type/location</th>
<th>Wound severity (Oyibo et al, 2001)</th>
<th>Non-healing status</th>
<th>Treatment duration</th>
<th>Treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1 Neuropathic diabetic foot ulcer</td>
<td>Texas A3</td>
<td>12 months</td>
<td>2 weeks</td>
<td>20% reduction</td>
</tr>
<tr>
<td>Patient 2 Neuropathic foot ulcer, patient with spina bifida</td>
<td>Texas A1</td>
<td>12 months</td>
<td>10 weeks</td>
<td>Healed</td>
</tr>
<tr>
<td>Patient 3 Neuropathic diabetic foot ulcer after amputation</td>
<td>Texas A2</td>
<td>9 months</td>
<td>12 weeks</td>
<td>Healed</td>
</tr>
<tr>
<td>Patient 4 Neuropathic foot ulcer</td>
<td>Texas A3</td>
<td>12 months</td>
<td>12 weeks</td>
<td>Improved, then stopped after patient missed appointment, and wound worsened and became infected</td>
</tr>
</tbody>
</table>

Figures 1a–c. (a) baseline; (b) week 1; (c) week 2.

Figures 2a–c. (a) baseline; (b) week 2; (c) after healing.