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 haemogolobin, 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

Box 1. Assessment of tissue perfusion/ oxygenation (Holtman and Gahtan, 2010; Williams et al, 2003).

Assessment of tissue perfusion and oxygenation status should begin with a thorough, holistic assessment of the patient, health status, conditions, comorbidities, limb and wound. Other components may include:

- Ankle Brachial Pressure Index/Doppler assessment
- Colour duplex imaging
- Waveform analysis (Doppler or pulse volume recording)
- Toe-Brachial Index assessment
- Non-invasive transcutaneous oxygen ($TcPO_2$) measurement
- Photoplethysmography
- Laser Doppler.

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"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 5–10 cm 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. hydropolymer/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

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.

Table 1. Summary of evidence for Granulox.

Reference	Article type	Key points
Babadagi-Hardt et al, 2014	Case study of leg ulcer treatment with compression therapy and Granulox application three times weekly in patient with occlusion of the hepatic veins	▸▸ The wound improved steadily over the study period ▸▸ The wound healed in 16 weeks and had not recurred at follow-up 2 months later ▸▸ Improvement of the hypoxic status of the affected tissue with treatment including topical haemoglobin may be an important factor for wound healing
Arenbergerova et al, 2013	Granulox used in 36 patients with chronic ulcers (2 dropouts), control in 36 patients (5 dropouts); 13-week treatment period	▸▸ Mean reduction in wound surface area for the Granulox group was 53.4%, statistically significantly more than in the control group ▸▸ Mean values of absolute reduction for the Ganulox group were 11.5cm^2 (starting size >25 cm^2), 8.5 cm^2 (15–25 cm^2) and 5.7 cm^2 (5–<15 cm^2) ▸▸ Granulox group had 48% reduction in necrotic tissue (17% in control) and 42% reduction in fibrin tissue (vs 12%) ▸▸ Granulox group had 75% increase in granulation (18% in control) and 78% increase in epithelialisation (vs 7%)
Arenberger P et al, 2011	Overview of results from a clinical trial, therapy observations and single-patient uses of Granulox	▸▸ Clinical trial: 39 of 42 wounds healed ▸▸ Therapy observations: 9 of 9 wounds healed ▸▸ Single-patient uses: 11 of 13 wounds healed ▸▸ In all cases, Granulox was well-tolerated with no product-related adverse events ▸▸ Application of haemoglobin spray may promote chronic wound healing
Wolfgang et al, 2011	Case study of oxygen-opimisation, including daily application of Granulox	▸▸ Wound condition steadily improved over the time Granulox was applied ▸▸ Wound achieved full healing ▸▸ Multiple-channel oxygen-optimisation treatment including Granulox can be used 'practically free of risk' in chronic hypoxic ulceration.

wound area after 2 weeks' treatment (*Table 2*). Standard DFU care (e.g. 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:** achieved full healing in 10 weeks after a year of non-healing status with deep DFU that was clean but static, with no change over the previous 2 months (*Figures 2a–c*).

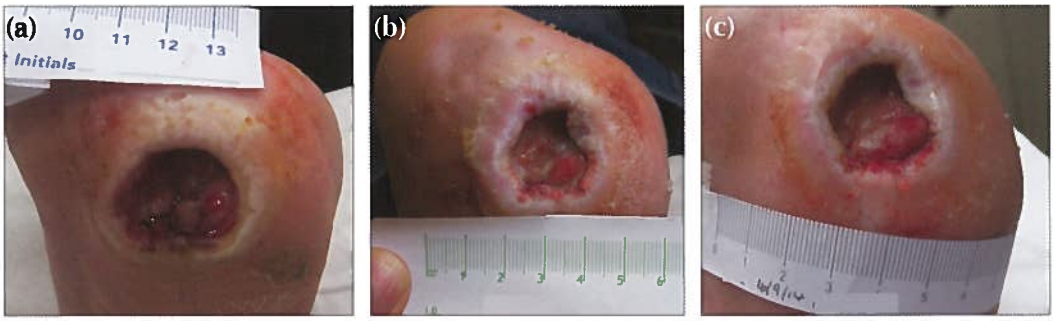
CONCLUSION

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 haemogolobin 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. WUK

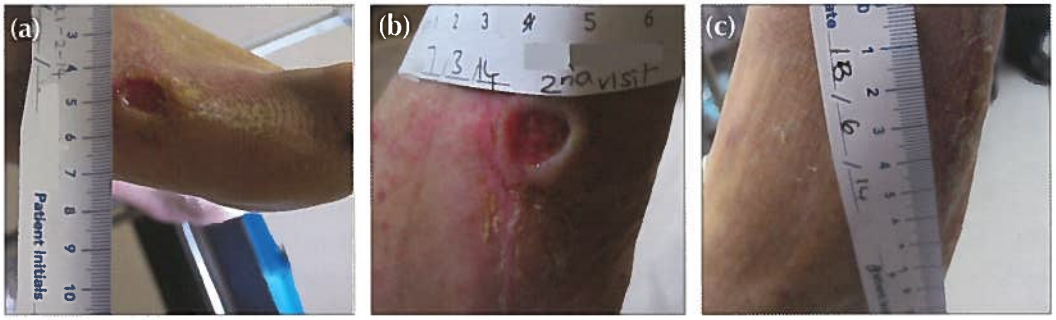
"The pilot study and the evidence show potential for Granulox in the treatment of wounds that show signs of hypoxia."

Table 2. Outcomes from pilot study.

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



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



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

REFERENCES

Arenbergerova M, Engels P, Gkalpakiotis S et al (2013) Effect of topical haemoglobin on venous leg ulcer healing. *EWMA J* 13(2):25–30.

Arenberger P, Engels P, Arenbergerova M, et al (2011) Clinical results of the application of a haemoglobin spray to promote healing of chronic wounds. *GMS Krankenhhyg Interdiszip* 6(1):Doc05

Babadagi-Hardt Z, Engels P, Kanya S (2014) Wound management with compression therapy and topical hemoglobin solution in a patient with Budd-Chiari Syndrome. *J Dermatol Case Rep* 8(1):20–3

Data on file. Plot of Einstein and Smoluchowski equation for diffusion, generated by scientists at University Witten-Herdecke on request from Sanguigmbh

Gottrup F (2004) Oxygen in wound healing and infection. *World J Surg* 28(3):312–5

Holtman D, Gahtan V (2008) Peripheral arterial perfusion: is it adequate for wound healing? *Wounds* 20(8):230–5

International Best Practice Guidelines (2013) Wound management in diabetic foot ulcers. London: Wounds International. Available at: www.woundsinternational.com (accessed 28.10.2014)

Ladizinsky D, Roe D (2010) New insights into oxygen therapy for wound healing. *Wounds* 22(12):294–300

Oyibo SO, Jude EB, Tarawneh I, et al (2001) A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. *Diabetes Care* 24(1):84–8

Schreml S, Szeimies RM, Prantl L, et al (2010) Oxygen in acute and chronic wound healing. *Br J Dermatol* 163(2):257-63.

Sen CK (2009) Wound healing essentials: let there be oxygen. *Wound Repair Regen* 17(1):1–18

Williams DT, Price P, Harding KG (2003) Review: the clinical evaluation of lower limb perfusion in diabetic foot disease. *Br J Diabetes Vasc Dis* 2(6):394–8

Wolfgang KR, Barnikol W KR, Pötzschke P (2011) *Complete Healing of Chronic Wounds of a Lower Leg with Haemoglobin Spray and Regeneration of an Accompanying Severe Dermatolipsosclerosis with Intermittent Normobaric Oxygen Inhalation (INBOI):* Availalble at: http://1.usa.gov/1waisGR (accessed 28.10.2014)