A topical haemoglobin spray for oxygenating pressure ulcers: a pilot study

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Clinical focus

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Abstract

The effect of pressure ulcers on patient quality of life have been recognised as a real problem for many years, and the need for robust and effective management of pressure ulcers is now a prominent national health-care issue. Myriad different interventions exist for the treatment of pressure ulcers, including clinically effective dressings and pressure-relieving devices, yet many pressure ulcers still do not heal and often become a chronic wound. This is the second of a series of articles (Norris, 2014) discussing the clinical evaluation of a topical oxygen therapy in practice. It describes a small evaluation involving 18 patients with pressure ulcers. The study set out to determine the effect of a topical oxygen therapy on wound size. The therapy comprises a canister that sprays pure haemoglobin in a water solution into or onto the wound. The haemoglobin spray needs to be used at least once every 3 days, does not require training on its use and can be used in any care setting. Overall, results identified wound healing progression in all 18 wounds and wound size reduction in 17 of the 18 wounds.

Key words: Chronic wound ▼ Pressure ulceration ▼ Topical oxygen therapy ▼ Wound size reduction

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Recent government initiatives have placed pressure ulcer prevention at the top of the quality agenda (Rossi, 2013), with a reduction in pressure ulcer prevalence and incidence now being used as key quality indicators (Health Information and Quality Authority, 2013). The emphasis on enhancing efficiency while improving care quality outcomes is a key objective in today’s NHS agenda (Department of Health, 2010). Health-care providers will be expected to deliver effective care efficiently with fewer resources by ensuring the implementation of evidence-based practice.

Pressure ulcers have a significant negative impact on a patient’s quality of life, often resulting in pain, risk of infection, loss of dignity and social isolation. Treatment of pressure ulcers and rehabilitation is a challenge for the multidisciplinary team. Pressure ulcers are also complicated wounds brought about by a set of circumstances involving pressure, poor nutrition and often underlying medical problems (Posnett and Franks, 2008). Their treatment involves ensuring that all the contributory causes have been addressed and alleviated. The prevention and management of pressure ulcers involves many different interventions (Moore and Webster, 2013). However, despite the implementation of evidence-based treatments, some pressure ulcers still fail to heal and become chronic wounds. Chronic wounds are defined as wounds that do not follow the well-defined stepwise process of physiological healing but are trapped in an uncoordinated and self-sustaining phase of inflammation (Snyder, 2010).

Despite the different underlying aetiologies, most chronic wounds show a similar behaviour and progress. This uniformity is due to consistent components of the multifactorial pathogenesis of most chronic wounds: local tissue hypoxia, bacterial colonisation, repeated ischemia-reperfusion injury and cellular as well as systemic changes of ageing (Diegelmann and Evans, 2004). Also, as the name suggests, pressure ulcers occur due to high levels of sustained pressure and/or long periods of unrelieved pressure. As a result, there is a reduction in the blood supply to the skin and underlying tissue and potential damage or hypoxia to the underlying microcirculation and tissue.

Oxygen, wound healing and the effects of hypoxia

Physiological wound healing is a well-orchestrated process that ends with wound closure within days or weeks, depending
Hypoxia

Although the role of oxygen in wound healing is not yet completely understood, many experimental and clinical observations have shown wound healing to be impaired during hypoxia (Hopf, 2003). In wound healing, hypoxia can be defined as an insufficient supply of oxygen for the healing process to proceed at a normal rate. However, not all effects of hypoxia are bad. In fact, all wounds initially have areas of hypoxic tissue. Local hypoxia in the micro-environment of the wound causes several wound healing processes to occur, such as leukocyte adherence, angiogenesis, collagen formation and bone formation. However, when the hypoxia is prolonged, deleterious tissue effects can occur (Hopf, 2003).

Using oxygen to facilitate wound healing is important, and studies have demonstrated that treatments such as hyperbaric oxygen therapy (HBOT) improve the healing of chronic venous ulcers in a randomised, controlled clinical trial (Winfield, 2014). However, some patients may not tolerate systemic HBOT side effects; health professionals/patients may find HBOT too expensive; or clinicians may not be able to gain access to a hyperbaric chamber. Sometimes, the cardiovascular system is inadequate for carrying the oxygenated blood to the wounded tissue, or the tissue is so oedematous that the oxygen cannot reach the wound well (Sheffield, 1988).

Topical oxygen therapies are designed to allow oxygen to enter the wound or skin via the external surface of the body rather than from capillaries within. The oxygen is therefore delivered directly to the wound and the systemic side effects are eliminated. Topical oxygen is a powerful and multifunctional source of treatment (Gordillo and Sen, 2009; Winfield, 2014).

Recent technological developments now allow delivery of biologically available dissolved oxygen directly to the wound and skin. The ability to deliver oxygen into areas of tissue hypoxia will lead to increased metabolic support of cellular function, increased reduction of bacterial bioburden, resolution of inflammation, and ultimately quicker healing (Ladizinsky et al, 2010). Clinicians are now able to administer oxygen therapy with increasingly advanced mechanisms and devices.

Despite the fact that pressure ulcers have been in existence in health care for many years, they still remain a significant problem both for the patient and the health-care practitioner. The biggest impact is the negative effect on the patient’s quality of life and it is crucial that innovation in treatment options and evidence-based practice need to continue to be embraced in order not only to prevent the development of pressure ulcers but to ensure a positive impact on the successful treatment of pressure ulcers.

Oxygen is well known to be required for wound healing. Restricted oxygenation is common in chronic wounds and can impair the healing process. Several studies have demonstrated that enhancing wound tissue oxygenation improves wound healing and reduces bacterial colonisation (Gordillo and Sen, 2009; Winfield, 2014).

More evidence-based studies with standardised treatment protocols are required to evaluate the efficacy of oxygen therapy. This pilot study aims to improve the understanding of the role of oxygen in wound healing and to show the outcomes of the evaluation of the use of Granulox in the management of pressure ulcers.

Granulox

Granulox is a haemoglobin spray and is used as a topical oxygen therapy for the treatment of chronic wounds. Haemoglobin is able to bind oxygen and then release it again. When sprayed onto the wound, the water-soluble, red haemoglobin spray is uniformly distributed in the exudate, binding oxygen from the surrounding air and transporting it to the wound base, from which it diffuses into the cells.

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Use, indications and contraindications

The spray is simple to apply and requires no specialist training. It has to be applied at every dressing change or at least every third day. No adverse reactions have been reported to date. However, it is not suitable for use with certain disinfectants and proteolysis or mechanical debridement as these will impair its action. Granulox is contraindicated on infected wounds or pregnant/lactating mothers, as insufficient data is available to evaluate these cases. Debridement of necrotic tissue or slough is advised prior to application in order to enable the spray to be applied to non-devitalised tissue.

Two randomised, controlled trials have been reported on
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Figure 1. Average wound area before and after the evaluation period (cm²)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Granulox</th>
<th>Post-Granulox</th>
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<tbody>
<tr>
<td>0</td>
<td>11.23</td>
<td>3.39</td>
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Granulox. In a first study (n=28), Arenberger et al (2011) showed 93% healing at 6 months with Granulox and 7% without in chronic lower-limb wounds. In a second study over 13 weeks by Arenbergerova et al (2013), the medical efficacy of a combination therapy plus Granulox was compared with therapy without Granulox. It found a 53% size reduction with Granulox versus 21% worsening in the standard care group. Granulox was also examined comparatively with traditional treatment concepts (conventional dry therapy and hydroactive therapy) by Von Eiff (2013). It was found that conventional dry treatment took on average 301 days until wound closure. Hydroactive therapy took 91 days and combination therapy (which included Granulox) took 60 days. No studies have yet been published into pressure ulcers in this area.

Method

A multicentre evaluation was undertaken to examine the efficacy defined as a reduction in wound size/depth after 4 weeks of treatment of Granulox in the treatment of category 2, 3 and 4 pressure ulcers (European Pressure Ulcer Advisory Panel (EPUAP) and National Pressure Ulcer Advisory Panel (NPUAP), 2009). Secondary outcomes addressed patients’ pain, exudate levels and any adverse reactions. The pilot studies took place in both primary and secondary care.

Inclusion and exclusion criteria

Inclusion criteria were patients of 18 years or over with a grade 2, 3 or 4 pressure ulcer based on the EPUAP grading system. Exclusion criteria were grade 1 pressure ulcers, pressure ulcers with clinical signs of infection, pregnant or lactating women, and patients who could not tolerate wound dressings or on whom wound dressings could not be applied.

Treatment and data

Patients who met the inclusion criteria were then treated with Granulox for a 4-week treatment period. They received the same standard care as before the inclusion of the Granulox spray. Standard care included the use of foam adhesive dressings, alginate and hydrofibre dressings and the use of hydrogels.

For the purpose of the evaluations, the same wound assessment protocol, pressure ulcer grading tool and pressure ulcer guidelines were used prior to and during the evaluations.

During the treatment period the test product was applied at each dressing change. Data were collected and collated by completing a detailed evaluation form. Details collected were as follows:

- Number of dressing changes per week
- Wound size (greatest width x greatest length)
- Wound depth (if applicable)
- Wound bed characteristics (these being percentage of slough, granulation tissue and/or epithelial tissue).

Exudate levels were also recorded as either ‘none’, ‘mild’, ‘moderate’ or ‘severe’. Pain levels at dressing change and for ongoing pain were recorded using a visual analogue scale where 0 equals no pain and 10 equals unbearable pain. Data were also collected on the location of the wound, significant comorbidities, wound duration, type of primary dressing, type of redistributing equipment/offloading equipment and any adverse reactions to the use of the Granulox spray. This data collection was standard care in all sites for all patients with
wounds and was collected by the nursing staff at the time of dressing change.

Ethical committee approval was not sought as this was a non-comparative evaluation with a CE-marked product. All patients were provided with product information and gave informed consent.

**Results**

Four sites located in England participated in the evaluation from November 2014 to January 2015. A total of 19 patients were recruited into the study and had Granulox applied to their wounds during the evaluation period. One patient was withdrawn from the evaluation as they did not complete the 4 week treatment period.

**Sample and wound characteristics**

The sample was composed of 7 males and 11 females, with a total of 18 wounds and a mean age of 65 years (range 34–91 years). Some 9 patients had a sacral pressure ulcer, 7 had a heel pressure ulcer, 1 had an elbow pressure ulcer and 1 had a pressure ulcer to the hip. The average wound duration prior to entry to the evaluation was 11 weeks (ranging from 1 week to 52 weeks). The average wound area at week 1 (prior to the first application of Granulox) was 11.23 cm² (range 0.25 cm²–52 cm²). The average wound area at the end of the evaluation period was 3.39 cm² (range 0.15 cm²–12 cm²). A total of 17 of the 18 wounds showed a reduction in size (Figure 1).

A reduction in wound size is evident from one participant's wound images prior to and after the use of Granulox (Figure 2 and Figure 3). The average wound depth prior to the study was 0.97 cm². Following the 4-week treatment period, this decreased to an average depth of 0.37 cm² (Figure 4). Wound depth was measured at the deepest point using a probe and by the same clinician in order to ensure reliability.

All 18 pressure ulcers showed a reduction in sloughy tissue. The average percentage of sloughy tissue decreased from 56% to 11% (Figure 5). The percentage of granulation tissue prior to the use of Granulox ranged from zero to 100%, while the average percentage was 46%. Following the treatment period with the product, the average percentage of granulation tissue increased to 66% (Figure 6).

The average percentage of epithelial tissue prior to the pilot study was zero. Following the 4-week pilot, the average percentage of epithelial tissue was 9%.

![Figure 4. Wound depth (cm)](image1)

![Figure 5. Mean percentages of sloughy tissue](image2)

![Figure 6. Mean percentages of granulation tissue](image3)

![Figure 7. Exudate level pre-Granulox](image4)
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Exudate levels decreased in all 18 wounds following the introduction of the Granulox spray (Figure 7 and Figure 8). All patients reported an improvement in their pain score during the evaluation (Figure 9 and Figure 10). During the 4-week period of Granulox use, the average pain score at dressing change decreased from 6.2 to 2.5 (on a range from zero to 10) and the ongoing pain decreased from 3.7 to 0.9.

The number of dressing changes and, therefore, the number of Granulox applications varied during the evaluation period from 4 to 28 during the 4-week period. The median was 8. This was due to differences in wound size and exudate levels. There were no differences in outcomes between the wounds that had more frequent applications of Granulox. The wound dressing regimens and the type of pressure-relieving devices did not change prior to or during the use of the Granulox spray. Therefore, the results of this pilot study cannot be related to changes in wound regimen or pressure-relieving device.

Discussion

All wounds are reliant on the presence of oxygen to proceed along a successful healing continuum. When oxygen levels become reduced or absent, hypoxia occurs, resulting in a disrupted or halted healing continuum. This hypoxia is also increasingly prevalent in chronic wounds, including pressure ulcers.

This small study utilising a haemoglobin spray to facilitate the diffusion of oxygen into the wound bed of pressure ulcers identified positive results. Some 17 out of the 18 pressure ulcers reduced in size. These results occurred alongside other positive outcomes, such as a decrease in sloughy tissue and an increase in granulation tissue. The results in this study confirm other European studies into the positive effect on wounds of donation of topical oxygen using haemoglobin (Babbadagi-Hardt et al, 2014).

Directions for further research

While the clinical benefits of Granulox are clearly evident from this evaluation and previous evaluations, the continued monitoring of outcomes beyond 4 weeks would strengthen the evidence base on the product’s efficacy. The use of topical oxygen delivery to other wound aetiologies would also be worthy of investigation.

Strengths and limitations

The data available has a restricted informative value owing to the small sample size. However, despite this, withdrawal only occurred in one of the four sites. Data entry was completed for all patients, which meant a full analysis of the pre- and post-application period of Granulox data was available for all patients.

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The differences in frequency of Granulox application varied due to differences in wound size and exudate levels. All sites showed positive outcomes and there was only one patient withdrawal, leaving 18 patients in the study. The inclusion of different patient ages, comorbidities, non-standardised treatment protocols and varying care settings also strengthens the evidence for the efficiency of the product.

One further limitation of the study is the restricted access to the Granulox spray, since it is currently not available to prescribe using an FP10 form. Finally, no health economic analysis took place, which may have strengthened the findings still further.
Declaration of interest: This evaluation was sponsored by Infiest, who provided the product for the study. Infiest did not have any control over the data collection or analysis.


Cardinal M, Eisenbud DE, Phillips CWC


Accelerate wound healing with Granulox

Granulox is a haemoglobin spray which acts to increase oxygen supply to chronic wounds to aid healing.

Case Studies

Start of treatment  | After 15 weeks
---|---
Patient: 43 years, male, venous crural ulcer
Existing for 8 years before Granulox

Start of treatment  | After 8 weeks
---|---
Patient: 65 years, female, amputation wound
Existing for 8 weeks before Granulox

Start of treatment  | After 22 weeks
---|---
Patient: 85 years, female, arterial crural ulcer
Existing for 7 years before Granulox

Adding Granulox to standard care for venous leg ulcers delivered an average 53% reduction in wound size after 13 weeks.

Harnessing the healing powers of oxygen

If you would like to find out more, get in touch with Fredrik Elg, Granulox Product Director UK, to arrange for an evaluation of Granulox as a first step towards formulary inclusion at your Trust or CCG.

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