Evaluating the effect of a haemoglobin spray on size reduction in chronic DFUs

ABSTRACT

Aim: The aim of this multi-centre observational evaluation was to assess the percentage reduction in wound area of non-healing diabetic foot ulcers (DFUs), treated with Granulox haemoglobin spray over a 4-week period. Secondary outcome parameters—for example, adverse events, patient acceptability and ease of use—were also recorded. Method: After a run-in-period (2 weeks for existing patients and 4 weeks for new patients) to determine if the wounds were non-healing despite receiving local best practice, patients whose foot ulcers had decreased in size by < 20% were then entered into the evaluation. A sample of 17 patients (4 females and 13 males), comprising 4 with type 1 and 13 with type 2 diabetes, with a total of 20 DFUs, met the inclusion criteria. These data were collected from six sites across the UK. Results: There was an overall positive reduction in size in 14 of the wounds, equating to a mean reduction of 53.8% (standard deviation (SD): 26.6; range: 11.9–100%). One participant, with two ulcers, had to be withdrawn due to infection. All clinicians and participants found the product easy to use. Conclusion: The addition of a topical oxygenation therapy in this cohort of non-healing DFUs showed reduction in wound surface area and progression to healing. The product was also found to be acceptable and very easy to use by both participants and clinicians.

Key words: Diabetic foot ulcer ■ Topical oxygen therapy ■ Wound healing ■ Hypoxia ■ Non-healing wounds ■ Haemoglobin

Introduction and background

Diabetes UK (2016) reports that the number of people diagnosed with diabetes is over 4 million and the prevalence of foot ulceration in this population is around 4–10% (Alexiadou and Doupis, 2014). A DFU is usually considered a deleterious marker of diabetes complication status, signifying peripheral neuropathy and/or peripheral arterial disease in the lower limb (Boulton et al, 2004). In addition, within the diabetic population there is often increased microvascular pressure and the resultant injury to the microvascular endothelium can cause adaptive microvascular sclerosis (Diehm et al, 2009), which is a loss of vasodilatory reserve and autoregulatory capacity accompanying increased diabetes disease duration, which usually results in microangiopathy and hypoxia within the wound/peri-wound milieu (Tooke, 1995; Young et al, 2008). This is likely to impair healing and result in chronic, non-healing DFUs that are extremely difficult to manage. There are around 135 diabetes-related amputations performed each week in England and Wales, the majority of which are preceded by chronic non-healing ulceration (Boulton et al, 2004; Diabetes UK, 2012; Martins-Mendes et al, 2014; Diabetes UK, 2015). Nevertheless, there still remains considerable variation within clinical practices and rates of amputation across different NHS settings (National Institute for Health and Care Excellence (NICE), 2015).

Peripheral arterial disease and associated local tissue hypoxia dramatically affects patient outcomes and a tissue oxygen concentration below 40% drastically reduces healing rates (Hauser, 1987) (Figure 1). Hypoxic conditions also reduce the body’s immune cells’ ability to generate energy, and changes their inflammatory behaviour: neutrophils persist and impair macrophage activity. Macrophages are essential for wound repair as they clear debris, control inflammation and coordinate cellular growth. If oxygen can be introduced to a hypoxic wound then this will remove persistent neutrophils, improve macrophage activity and help mediate cellular repair. Absorption of oxygen by wound tissue from the atmosphere by simple diffusion is not particularly successful, therefore it is essential to use a carrier in order to increase available oxygen (Chadwick et al, 2015). A way of improving oxygen saturation at the wound bed is by using hyperbaric medicine, also known as hyperbaric oxygen therapy (HBOT), which is the medical use of oxygen at a level higher than atmospheric pressure (Kranke et al, 2015). However, NICE guidelines NG19 state that due to its poor cost effectiveness, poor availability and the lack of supporting evidence, this should not be offered for diabetic foot ulcerations, unless as part of a clinical trial (NICE, 2015).

This multi-centre evaluation aimed to develop the ideas of previous work by Bateman (2015), correlating data from six centres across both primary and secondary care settings in the UK. The aim of this evaluation was to assess the percentage reduction in wound area of non-healing diabetic foot ulcers (DFUs), treated with haemoglobin spray over a 4-week period. Secondary outcomes such as adverse events, patient acceptability and ease of use were also recorded.

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Haemoglobin is the body’s natural oxygen transporter and it is able to undergo a reversible binding with oxygen molecules. Haemoglobin has the ability to directly bind to oxygen if the partial pressure is high but will then release this oxygen if the partial pressure of oxygen is low, such as that found in the hypoxic wound bed.

Oxygen therapy aims to redress the oxygen saturation within the tissues to above 40% and thus facilitate an environment conducive to healing and repair (Arenbergerova et al, 2013). Topical haemoglobin therapy does this by allowing oxygen from a greater concentration (when compared with that of hypoxic wound tissue) such as that available atmospherically (PO₂=160 mmHg at sea level), to be conveyed into the hypoxic wound bed through a process known as ‘facilitated diffusion’ using the haemoglobin as its carrier. There is an increasing body of evidence to support the use of haemoglobin spray as a topical wound therapy in non-healing wounds (Table 1).

Its use is supported primarily by a randomised, single-blind, single-centre study versus placebo that investigated the effect of haemoglobin spray on healing of venous leg ulcers (Arenbergerova et al, 2013). Supporting this work is a single acute centre descriptive evaluation undertaken to explore the efficacy of haemoglobin spray in DFUs (Bateman, 2015). Healthcare Improvement Scotland (2014) gave a cautiously optimistic innovative technology overview in which it advocated more research to help inform clinical practice, specifically on frequency and duration of use. The aforementioned randomised controlled trial has shown that haemoglobin spray reduces wound size in the short term (Arenbergerova et al, 2013). Some significant additional benefits were noted in a study with the use of haemoglobin spray, which includes a reduction in slough and a significant reduction in pain levels (Hunt, 2015).

Granulox topical oxygen therapy comprises haemoglobin in the form of a non-aerosol-based wound spray (approximately £4.25 per application) and is a ‘class 3’ medical device. A consensus statement by a working group (Chadwick et al, 2015) provides a comprehensive algorithm for determining appropriate use (Figure 2). The product requires very little specialist training, so patients find it easy to administer to their wounds between treatment visits, during dressing changes (Bateman, 2015); however, the decision to use the haemoglobin spray should be made by an appropriately skilled practitioner. The spray is not indicated for infected wounds or carrier. There is an increasing body of evidence to support the use of Granulox as a topical wound therapy in non-healing wounds (Table 1).

Method

This clinical evaluation aimed to treat suitable patients with haemoglobin spray over a 4-week period. This follow-up period was chosen as the percentage change in foot ulcer area after 4 weeks can be considered a robust predictor of healing at 12 weeks (Sheehan et al, 2003). After a run-in-period (2 weeks for existing patients and 4 weeks for new patients) to determine if the wounds were non-healing despite receiving local best practice, patients whose foot ulcers had decreased by less than 20% were entered into the evaluation.

The clinicians received training on the use of the

Figure 1. Reduced oxygen levels lead to delayed or failed healing and poorly oxygenated wounds almost never heal (Hauser, 1987)

* Regional perfusion index: oxygen levels in wound versus oxygen levels in upper-body skin.
All 18 showed a reduction in slough and exudate levels in all wounds. Mean values of absolute reduction for the treatment group were 11.5 cm². Wound condition steadily improved over the time the spray was applied. Single-patient uses: 11 of 13 wounds healed.

Exclusion criteria:
- Complete healing of one ulcer at 12 weeks
- 2 patients were excluded due to non-compliance and 2 due to infection.

Clinical trial: 39 of 42 wounds healed. Mean reduction in wound surface area for the treatment group was 53.4%, 25% completely healed at 4 weeks, 54% of patients slough free at week 2. Ankle brachial pressure index below 0.5 or toe pressure of <70 mmHg ischaemia and are candidates for immediate surgical revascularisation. The mean age was 59.2 years (standard deviation ±10.5). Application of haemoglobin spray may promote chronic wound healing.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Article type</th>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arenberger et al, 2011</td>
<td>Overview of results from a clinical trial, therapy observations and single-patient uses of haemoglobin spray</td>
<td>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, spray was well tolerated with no product-related adverse events. Application of haemoglobin spray may promote chronic wound healing.</td>
</tr>
<tr>
<td>Barnikol and Pöttschke, 2011</td>
<td>Case study of oxygen optimisation, including daily application of haemoglobin spray</td>
<td>Wound condition steadily improved over the time the spray was applied, Wound achieved full healing, Multiple-channel oxygen-optimisation treatment including haemoglobin spray can be used ‘practically free of risk’ in chronic hypoxic ulceration.</td>
</tr>
<tr>
<td>Arenbergerova et al, 2013</td>
<td>Haemoglobin spray used in 36 patients with chronic ulcers (2 dropouts), control in 36 patients (5 dropouts); 13-week treatment period</td>
<td>Mean reduction in wound surface area for the treatment group was 53.4%, statistically significantly more than in the control group, Mean values of absolute reduction for the treatment group were 11.5 cm² (starting size &gt;25 cm²), 8.5 cm² (15–25 cm²) and 5.7 cm² (5–15 cm²)</td>
</tr>
<tr>
<td>Babadagi-Hardt et al, 2014</td>
<td>Case study of leg ulcer treatment with compression therapy and haemoglobin spray application three times weekly in patient with occlusion of the hepatic veins</td>
<td>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</td>
</tr>
<tr>
<td>Chadwick, 2014</td>
<td>Observational pilot study of 4 patients with non-healing DFUs</td>
<td>20% wound reduction in a recalcitrant non-healing ulcer of &gt;12 months duration, Complete healing of one ulcer at 10 weeks, Complete healing of one ulcer at 12 weeks, One patient’s wound deteriorated due to non-compliance/non-attendance</td>
</tr>
<tr>
<td>Norris, 2014</td>
<td>A multi-centre observational pilot study in non-healing venous leg ulcers; 17 patients recruited and a 4-week endpoint</td>
<td>Three patients withdrawn due to protocol violation need for biopsy and non-completion of run-in, Nine out of the remaining 14 reported improved pain levels, Wound area reduced from 52 cm² to 45 cm² and all the wounds of the remaining 14 patients improved</td>
</tr>
<tr>
<td>Bateman, 2015</td>
<td>To evaluate % reduction in wound surface area after 4 weeks of haemoglobin spray application, in 20 patients with non-healing DFUs (mean wound duration 10 months). All patients had Sinbad scores of ≤2</td>
<td>All wounds demonstrated a significant reduction in exudate levels at 4 weeks, 25% completely healed at 4 weeks, Mean 62.3% wound size reduction at 4 weeks</td>
</tr>
<tr>
<td>Hunt, 2015</td>
<td>Evaluated the effectiveness of haemoglobin spray in 100 patients who presented with sloughy wounds</td>
<td>100% of patients slough free at week 5, 96% of patients slough free at week 4, 54% of patients slough free at week 2, 23% of patients slough free after just 2 treatments</td>
</tr>
<tr>
<td>Tickle, 2015</td>
<td>A multi-centre observational evaluation of 19 patients with pressure ulcers, with a 4-week endpoint</td>
<td>One patient was withdrawn due to non-compliance, All 18 showed a reduction in slough and exudate levels in all wounds, All patients reported improvement in pain</td>
</tr>
<tr>
<td>Wakenshaw and Roper, 2015</td>
<td>10 wounds with different aetiologies treated with haemoglobin spray for 8–10 weeks</td>
<td>75% of patients progressed towards healing, 2 patients were excluded due to non-compliance and 2 due to infection</td>
</tr>
</tbody>
</table>

Source: Adapted from Chadwick, 2014

Table 2: Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age over 18 years</td>
<td>Presenting with infection (use of systemic antibiotics)</td>
</tr>
<tr>
<td>DFU located below the ankle</td>
<td>Pregnancy or actively lactating</td>
</tr>
<tr>
<td></td>
<td>Ankle brachial pressure index below 0.5 or toe pressure &lt;70 mmHg</td>
</tr>
<tr>
<td></td>
<td>HbA1c &gt;10% or 86 mmol/litre</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressed or using corticosteroids</td>
</tr>
</tbody>
</table>

A sample of 17 patients (4 females and 13 males), comprising 4 with type 1 and 13 with type 2 diabetes, with a total of 20 DFUs met the inclusion criteria (Table 2) after the run-in-period and were enrolled (Table 3). A low ankle brachial pressure index of 0.5 or toe pressure of <70 mmHg was chosen because these patients are likely to have acute ischaemia and are candidates for immediate surgical revascularisation. The mean age was 59.2 years (standard deviation ±10.5). Application of haemoglobin spray may promote chronic wound healing.
Table 3. Patient demographics

<table>
<thead>
<tr>
<th>Participant no.</th>
<th>Gender</th>
<th>Age</th>
<th>SINBAD score*</th>
<th>DM1/DM2</th>
<th>Significant comorbidities</th>
<th>Wound duration</th>
<th>Peripheral neuropathy</th>
<th>Peripheral ischaemia</th>
<th>Offloading used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>55</td>
<td>2</td>
<td>DM2</td>
<td>Obesity, smoker, reduced mobility</td>
<td>5 months</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>67</td>
<td>3</td>
<td>DM2</td>
<td>Obesity, smoker, reduced mobility, Parkinson’s</td>
<td>6 months</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>47</td>
<td>1</td>
<td>DM2</td>
<td>Smoker</td>
<td>4 months</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>48</td>
<td>4</td>
<td>DM2</td>
<td>Obesity, hypertension</td>
<td>8 weeks</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>52</td>
<td>3</td>
<td>DM1</td>
<td>Obesity</td>
<td>3 months</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>35</td>
<td>2</td>
<td>DM2</td>
<td>Hypertension</td>
<td>24 months</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>48</td>
<td>2</td>
<td>DM1</td>
<td>Charcot ankle, hypothyroidism</td>
<td>12 months</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>57</td>
<td>3</td>
<td>DM1</td>
<td>Previous foot amputation due to osteomyelitis and cellulitis. Excess alcohol</td>
<td>24 months</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>80</td>
<td>3</td>
<td>DM1</td>
<td>Lymphoid leukaemia, hypertension</td>
<td>8 months</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>61</td>
<td>2</td>
<td>DM2</td>
<td>Atrial fibrillation, MI</td>
<td>3 months</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>75</td>
<td>3</td>
<td>DM2</td>
<td>Multiple sclerosis</td>
<td>12 months</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>68</td>
<td>3</td>
<td>DM2</td>
<td>Hypertension and high cholesterol</td>
<td>5 months</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>51</td>
<td>1</td>
<td>DM2</td>
<td>Hypertension, hypercholesterolaemia, neuropathy</td>
<td>6 months</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>72</td>
<td>3</td>
<td>DM2</td>
<td>Hypertension, retinopathy, neuropathy. History of falls but no diagnosed cause</td>
<td>9 weeks</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>53</td>
<td>2</td>
<td>DM2</td>
<td>Rheumatoid arthritis</td>
<td>10 weeks</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>Male</td>
<td>65</td>
<td>1</td>
<td>DM2</td>
<td>ED, peripheral neuropathy, hypertension</td>
<td>48 months</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>17</td>
<td>Male</td>
<td>72</td>
<td>2</td>
<td>DM2</td>
<td>CKD stage 4, PVD, hypertension, CVD, detrusor instability, atypical pituitary lesion, hypogonadotropic hypogonadism, previous CVA</td>
<td>24 months</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

† During Granulox evaluation period only
CKD: chronic kidney disease; CVA: cerebrovascular accident; CVD: cardiovascular disease; DM1: diabetes mellitus type 1; DM2 diabetes mellitus type 2; ED: erectile dysfunction; MI: myocardial infarction; PVD: peripheral vascular disease

deviation (SD): 12.1; range: 5-80 years). The average wound duration was 10.6 months (SD: 12.5; range: 2-48 months). The ulcers were classified using the SINBAD system (Ince et al, 2008). This foot ulcer classification system evaluates site, ischaemia, neuropathy, bacterial infection, area and depth using a scoring system to help predict outcomes and enable comparison between patients and centres. In all six sites, neuropathy was diagnosed using a 10g monofilament. SINBAD scores for the sample ranged from 1 to 4, with 7 having a score of 3, which correlates with a poor outcome (Ince et al, 2008). Patient 15 was withdrawn at week 3 due to a wound infection in the DFU (upper foot ulcer). The standard of care dressings used during the run-in period and subsequent evaluation were adhesive and non-adhesive foams, Hydrofiber, superabsorbents and antimicrobials.

As this was a non-comparative evaluation with a CE-marked product and the haemoglobin spray was used as an adjunct to gold standard care and best practice, ethics approval was not required or sought. For all investigators, this was in accordance with their trust’s policy. All participants were provided with written and verbal information on the product and all gave written consent. Each participant was treated according to the same local clinical practice guidelines received in the run-in period with the addition of haemoglobin spray applied at each dressing change. Wound progress was monitored and evaluated over a 4-week treatment period or until the ulcer healed, whichever occurred first. A photographic record of the wound’s progress was kept together with the number of dressing changes per week; data on wound bed characteristics—wound size measurements, percentage of epithelial, granulation, slough and necrotic tissues present; and exudate levels (assessed as none, mild, moderate or severe)—were collected weekly. Participants and clinicians were asked to report on their experience of the ease of application of the haemoglobin spray, using scoring on a nominated scale of 1 (extremely difficult) to 5 (extremely easy); this feedback was recorded using free text comments. Details of any adverse events were recorded through the treatment period. The...
### Table 4. Results: primary outcome measures

<table>
<thead>
<tr>
<th>Participant no. (ulcer)</th>
<th>W1</th>
<th>W4</th>
<th>% change</th>
<th>Slough (%) W1</th>
<th>W4</th>
<th>Granulation tissue (%) W1</th>
<th>W4</th>
<th>Epithelial tissue (%) W1</th>
<th>W4</th>
<th>Exudate level</th>
<th>Primary dressing used</th>
<th>Total no. of primary dressing changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.84</td>
<td>4.40</td>
<td>-43.9</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>50</td>
<td>70</td>
<td>Moderate</td>
<td>Mepilex Border, changed every 72 hours</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>12.16</td>
<td>7.50</td>
<td>-38.3</td>
<td>60</td>
<td>0</td>
<td>40</td>
<td>60</td>
<td>10</td>
<td>40</td>
<td>Severe</td>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>2.70</td>
<td>1.00</td>
<td>-63.0</td>
<td>40</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>50</td>
<td>80</td>
<td>Moderate</td>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>8.96</td>
<td>5.75</td>
<td>-35.8</td>
<td>50</td>
<td>0</td>
<td>50</td>
<td>60</td>
<td>0</td>
<td>40</td>
<td>Severe</td>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>8.40</td>
<td>4.00</td>
<td>-52.4</td>
<td>60</td>
<td>0</td>
<td>30</td>
<td>40</td>
<td>10</td>
<td>60</td>
<td>Severe</td>
<td>Mild</td>
<td>8</td>
</tr>
<tr>
<td>6 (right)</td>
<td>2.25</td>
<td>2.25</td>
<td>0.0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Melolin</td>
</tr>
<tr>
<td>6 (left)</td>
<td>3.30</td>
<td>1.96</td>
<td>-40.6</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Melolin</td>
</tr>
<tr>
<td>7</td>
<td>0.55</td>
<td>2.55</td>
<td>363.6</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Mild</td>
<td>Mild</td>
<td>Allevyn Adhesive</td>
</tr>
<tr>
<td>8</td>
<td>2.00</td>
<td>1.62</td>
<td>-19.0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Severe</td>
<td>Moderate</td>
<td>Durafiber; KerraMax Care</td>
</tr>
<tr>
<td>9</td>
<td>70.00</td>
<td>12.00</td>
<td>-82.9</td>
<td>100</td>
<td>0</td>
<td>70</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>Severe</td>
<td>Moderate</td>
<td>Aquacel Ag; Mepilex Heel</td>
</tr>
<tr>
<td>10</td>
<td>57.00</td>
<td>18.60</td>
<td>-67.4</td>
<td>65</td>
<td>0</td>
<td>35</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Mild</td>
<td>Granugel and Aquacel Foam (W1–W2); Aquacel Foam (W3–W4)</td>
</tr>
<tr>
<td>11 (1)</td>
<td>6.60</td>
<td>0.06</td>
<td>-99.1</td>
<td>65</td>
<td>0</td>
<td>35</td>
<td>10</td>
<td>0</td>
<td>90</td>
<td>Mild</td>
<td>Mild</td>
<td>Flaminal and Mepilex Border to both for W1–W2; Mepilex Border to just wound 1 for W3–W4; Flaminal and Mepilex Border to wound 2 for W3–W4</td>
</tr>
<tr>
<td>11 (2)</td>
<td>10.88</td>
<td>4.75</td>
<td>-56.3</td>
<td>80</td>
<td>15</td>
<td>20</td>
<td>85</td>
<td>0</td>
<td>0</td>
<td>Mild</td>
<td>Mild</td>
<td>ActivHeal Foam</td>
</tr>
<tr>
<td>12</td>
<td>13.11</td>
<td>11.55</td>
<td>-11.9</td>
<td>100</td>
<td>50</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>Severe</td>
<td>Severe</td>
<td>ActivHeal Foam</td>
</tr>
<tr>
<td>13</td>
<td>0.12</td>
<td>0.00</td>
<td>-100.0</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Mild</td>
<td>None</td>
<td>Allevyn Adhesive</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>4.83</td>
<td>4.83</td>
<td>0.0</td>
<td>60</td>
<td>&lt;10</td>
<td>40</td>
<td>≥90</td>
<td>0</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Zetuvit and Aquacel for W1–W2; Aquacel and sterile gauze for W3; Aquacel and Biatain for W4</td>
<td>4</td>
</tr>
<tr>
<td>15 (lower)</td>
<td>1.53</td>
<td>0.40*</td>
<td>-73.9</td>
<td>20</td>
<td>80</td>
<td>0</td>
<td>80</td>
<td>0</td>
<td>Moderate</td>
<td>Biatain and Zetuvit for W1–W3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>15 (upper)</td>
<td>0.30</td>
<td>1.20*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0.21</td>
<td>0.12</td>
<td>-42.9</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Moderate</td>
<td>Mild</td>
<td>Mepilex</td>
</tr>
<tr>
<td>17</td>
<td>0.18</td>
<td>0.28</td>
<td>55.6</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Mild</td>
<td>Mild</td>
<td>Mepilex</td>
</tr>
</tbody>
</table>

*Stopped trial at week 3 due to wound becoming infected
Table 5. Results: patient and clinician experience

<table>
<thead>
<tr>
<th>Participant no.</th>
<th>Adverse events?</th>
<th>Did participant or nurse stop using Granulox?</th>
<th>Give comments on ease of use of Granulox and its acceptability to participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>No</td>
<td>Participant happy to use independently under supervision. No issues expressed</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>No</td>
<td>Participant happy to use independently</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>No</td>
<td>Participant said ‘it dried my wound up’. ‘Comfortable and no pain’</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>No</td>
<td>Participant found it easy to use once foot positioned</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>No</td>
<td>Participant found it easy to use independently. ‘Less wet exudate. And reduced dressing changes’</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>No</td>
<td>Extremely easy to use. No adverse reactions</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>No</td>
<td>Some issues with the nozzle blocking up but otherwise easy to apply. Participant continued until June 15, wound healed 19/8/15</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>No</td>
<td>Easy to apply. No adverse events</td>
</tr>
<tr>
<td>9</td>
<td>None</td>
<td>No</td>
<td>Excellent ease of use. Participant extremely pleased with ulcer progress during this period</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
<td>No</td>
<td>Wound progression good. Extremely simple to understand and use</td>
</tr>
<tr>
<td>11</td>
<td>None</td>
<td>No</td>
<td>So simple to use</td>
</tr>
<tr>
<td>12</td>
<td>None</td>
<td>No</td>
<td>(Blank)</td>
</tr>
<tr>
<td>13</td>
<td>None</td>
<td>No</td>
<td>The participant was happy with the product and using it. It is difficult to determine its impact as at the same time participant increased his use of insoles as he had been advised</td>
</tr>
<tr>
<td>14</td>
<td>None</td>
<td>The nurse, who worked with the participating clinician, refused to use Granulox for the entire trial, resulting in the patient receiving it only once a week. She did not want to use something she did not understand; despite being given all the relevant paperwork. She is now happy to use Granulox</td>
<td>Participant happy as long as you warn them it’s very red and resembles blood. Problem with vegetarian participants due to animal product</td>
</tr>
<tr>
<td>15</td>
<td>Yes</td>
<td>Stopped trial at week 3 due to (upper) wound becoming infected</td>
<td>Difficult if participant has an issue with porcine ingredient</td>
</tr>
<tr>
<td>16</td>
<td>None</td>
<td>No</td>
<td>Easy to use. Participant dresses wound themselves</td>
</tr>
<tr>
<td>17</td>
<td>None</td>
<td>Participant forgot to use Granulox but was advised to apply it when they went back home</td>
<td>Participant reported clogging and difficulty spraying Granulox, despite changing the nozzle</td>
</tr>
</tbody>
</table>

The primary outcome of this observational evaluation was assessed by percentage wound reduction achieved over the 4-week treatment period; wound size reduction was calculated from the wound surface area (cross-sectional width and length measured in centimetres).

These data were collected from six sites across the UK (four community and two acute settings), which participated in the evaluation from May 2015 to December 2015.

Results

There was an overall positive reduction in wound size in 14 of the wounds that completed the evaluation (Table 4), with a mean reduction of 53.8% (SD: 26.6; range: 11.9–100%) over the 4-week application period.

Participant 15 (who had two wounds) was withdrawn from the final analysis due to a significant infection in one of the wounds (reported as the upper wound) at week 3; this wound also increased significantly in size (300%). This adverse event, which occurred during the 4-week treatment period, comprised an episode of soft tissue infection, which is not unexpected in the diabetic foot as more than half of DFUs become infected (Lavery et al, 2003); participant 15’s other wound (the lower wound) had a substantial reduction of 73%.

One wound of participant 6 (reported as right foot) and participant 14 showed no reduction in size over the time period of this trial. Participant 14 had the application of the haemoglobin spray stopped for a period of time due to the clinician refusing to apply the product as they said they ‘did not want to use a dressing they did not understand’ despite being provided with full written information (Table 5).

Participant 7 showed some initial reduction in size between week 1 (0.55 cm²) and week 2 (0.4 cm²), a reduction of...
27.3%, but then there was a substantial increase in wound surface area of 363.6%. This deterioration was thought to be as a result of a broken removable cast.

All clinicians involved were satisfied with the ease of use of the product and 13 of the 16 participants included in the final analysis (81%) scored the ease of applying this product as 5 ‘extremely easy to use’ and were happy to use it independently between treatment visits (Table 5 and Figure 3). All participants had positive comments on the acceptability of the haemoglobin spray. One participant commented that participants should be warned before use ‘as it is very red and resembles blood’.

The frequencies of dressing changes and haemoglobin spray applications for the 16 patients included in the final analysis were 50% three times a week, 37.5% twice weekly and 12.5% daily changes; all dressing regimes were the same as during the run-in period.

Although not one of the pre-set objectives, it was interesting to note that the 11 wounds that had slough present at the start of the trial showed at least a 50% reduction (or a complete resolution) of slough at week 4, and exudate levels also improved in the majority of cases (Table 4 and Figure 3).

Discussion

Peripheral arterial disease or local tissue hypoxia dramatically affects participant outcomes and a tissue oxygen concentration below 40% is said to drastically reduce healing rates (Hauser et al, 1987). This small multi-centre observational evaluation explored the use of a haemoglobin spray over a 4-week period for participants who had non-healing wounds as determined by a run-in period where there was less than 20% reduction in wound area. The mean percentage reduction in 14 of the wounds was 53.8%, which is comparable to the wound reduction seen by Bateman (2015) where 20 participants had a mean reduction of 62.3%. Bateman (2015) only included participants with a SINBAD score of 2 or below. Seven of the 16 participants (44%) had a SINBAD score of 3 or above. SINBAD scores of 3 and above are predominantly associated with a significant increase in the length of healing time because of the presence of lower limb ischaemia and/or neuropathy with ulcer sizes of at least 1cm² and/or a depth reaching muscle, tendon or deeper (Ince et al, 2008). In this evaluation, wounds with a score of 3 or above did show reduction in wound surface: mean 43.9% (range 11.9–99.1%) (Figure 4). This provides preliminary evidence that topical haemoglobin may benefit this patient group. These data were collected from participants with an acknowledged widely varied age, comorbidities and common sites for DFU.

There were two comments that due to the porcine-source of the haemoglobin it would not be suitable for patients who avoid animal products. Vegans (but not all vegetarians) not only abstain from any food from animal origins, they will...
also avoid the use of all personal and household products from an animal origin, and avoid purchasing and using all animal-derived non-food products. This aversion to using products with an animal origin (particularly porcine in origin) could also be relevant for patients of certain religious persuasions, for example, practising Muslims or Jews; similar to the situation when animal-derived insulin (from cows and pigs) was the first type of insulin to be administered to humans to control diabetes.

Finally, seven patients did not have offloading. This was because they were prescribed offloading, but declined to use it.

Limitations

This evaluation has several limitations, mostly related to its multi-centred, non-blinded and non-comparative design. Haemoglobin spray was used as an adjunct to the standard care provided in the six participating centres, and it is possible that local guidelines on standard care varied between them. The participating clinicians included both nurses and podiatrists, which again may have introduced variations in practice. However, the evaluation design stipulated that the same standard care should be provided in both the run-in period and the subsequent 4-week evaluation, so while there may have been differences in the care offered between the different centres, it is unlikely that the results can be attributed to the introduction of a different standard of care once use of haemoglobin spray was initiated. While it would have been ideal to conduct the evaluation in a single centre, for practical and logistical reasons this was not possible. It should also be noted that this is not a controlled trial, but instead reflects real-life clinical practice, with participants having an acknowledged widely varied age, comorbidities and common sites for DFU.

It could be argued that the percentage reduction in slough recorded can be attributed to the use of sharp debridement; however, this does not take into account that these ulcers were also sharp debrided during the run-in period. These limitations should be borne in mind when interpreting the results.

Another limitation is the rudimentary measurement to calculate wound surface area (cm²) using the length and width measurements (Flanagan, 2003); this method is subjective and can result in over-estimation of wound area (Majeske, 1992; Goldman and Salcido, 2002). Again, due to resource and time issues, it was not possible to use planimetry or tracing.

Nevertheless, it is the view of these authors that this is a controlled trial, but instead reflects real-life clinical practice, with participants having an acknowledged widely varied age, comorbidities and common sites for DFU.

Conclusion

The principles of DFU treatment are to ensure adequate offloading, restoration of blood flow, treatment of infection, local wound care and a full holistic assessment (Bus et al, 2016; NICE, 2015). Even when gold standard interventions are in place DFUs can remain in a non-healing state. It is widely accepted that wound healing is a complex process of several phases: haemostasis, inflammation, proliferation and remodelling (Kane, 2001; Doughty and Sparks-DeFriese, 2012). One essential component is an adequate oxygen supply during all the phases (Schreml et al, 2010); if oxygen can be introduced to the hypoxic wound then this will remove persistent neutrophils, improve macrophage activity and help mediate cellular repair (Chadwick et al, 2015). This small evaluation of a topical oxygenation therapy on non-healing DFUs saw an encouraging reduction in wound surface area and progression to healing. The product was also found to be acceptable and very easy to use by both participants and clinicians. While the evidence for use of topical oxygenation in the management of hard-to-heal wounds is increasing, further research is required to look at optimal frequency of application, optimal treatment periods and the possible influence of secondary dressing choice. BJN

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Acknowledgements: Figure 2, and Table 1 are reproduced with permission from Wounds UK.
There was an overall positive reduction in wound size in 14 of the wounds
at the end of the 4-week evaluation period
and 13 of the 16 participants (81%) found the product ‘extremely easy to use’

The follow clinicians took part in this evaluation:
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Sharon Hunt, Nurse Practitioner Specialist in Tissue Viability,
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Joy Tickle, Tissue Viability Specialist, Shropshire Community NHS Trust

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KEY POINTS
■ The majority of diabetes-related amputations are preceded by chronic
non-healing ulceration
■ Peripheral arterial disease or local tissue hypoxia dramatically affects
patient outcomes, and there is an increasing body of evidence to support
the use of topical oxygenation therapy in non-healing wounds
■ This clinical evaluation explored the use of a topical haemoglobin spray in
17 patients with non-healing diabetic foot ulcers
■ There was an overall positive reduction in wound size in 14 of the wounds
at the end of the 4-week evaluation period
■ All clinicians involved were satisfied with the ease of use of the product
and 13 of the 16 participants (81%) found the product ‘extremely easy to use’