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 One participant, with two ulcers, had to be withdrawn due to infection.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

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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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).

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 (PO_2=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 during pregnancy, owing to the lack of sufficient data in these treatment areas or patient groups.

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

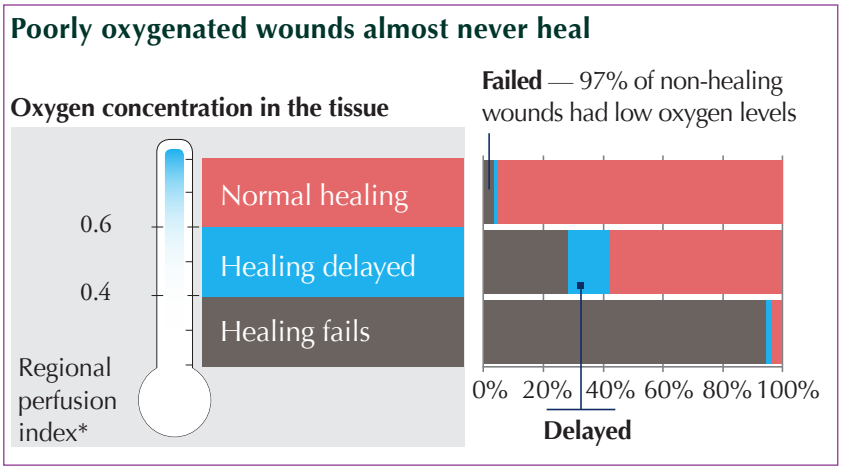


Figure 1. Reduced oxygen levels lead to delayed or failed healing and poorly oxygenated wounds almost never heal (Hauser, 1987)

*** Regional perfusion index: oxygen levels in wound versus oxygen levels in upper-body skin.**

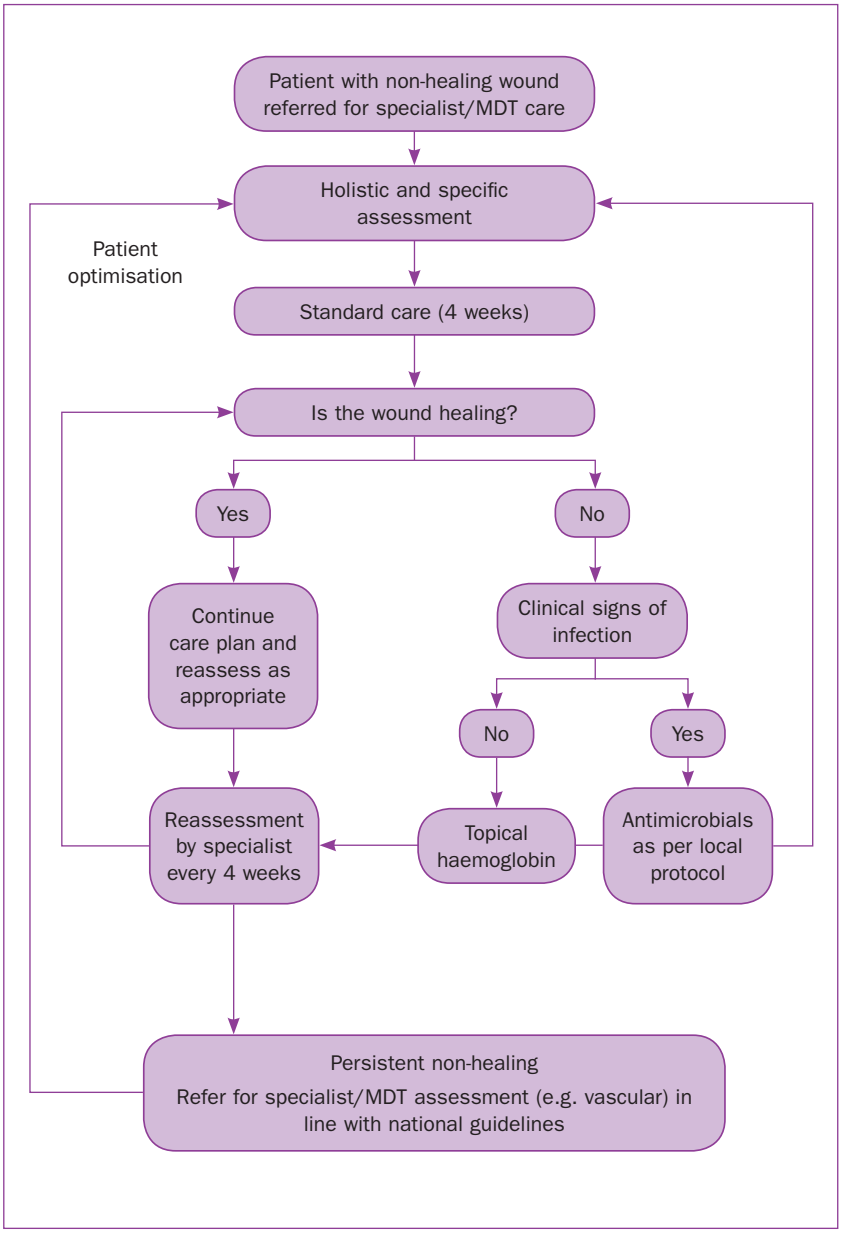


Figure 2. Practical advice (in clinical practice) for the use of Granulox topical oxygenation therapy (Chadwick et al, 2015)

Table 1. Summary of previously published evidence on the use of Granulox in wound healing

Reference	Article type	Key points
Arenberger et al, 2011	Overview of results from a clinical trial, therapy observations and single-patient uses of haemoglobin spray	■ 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
Barnikol and Pötzschke, 2011	Case study of oxygen optimisation, including daily application of haemoglobin spray	■ 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
Arenbergerova et al, 2013	Haemoglobin spray 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 treatment group was 53.4%, statistically significantly more than in the control group ■ Mean values of absolute reduction for the treatment 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) ■ Treatment group had 48% reduction in necrotic tissue (17% in control) and 42% reduction in fibrin tissue (vs 12%) ■ Treatment group had 75% increase in granulation (18% in control) and 78% increase in epithelialisation (vs 7%)
Babadagi-Hardt et al, 2014	Case study of leg ulcer treatment with compression therapy and haemoglobin spray 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
Chadwick, 2014	Observational pilot study of 4 patients with non-healing DFUs	■ 20% wound reduction in a recalcitrant non-healing ulcer of >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
Norris, 2014	A multi-centre observational pilot study in non-healing venous leg ulcers; 17 patients recruited and a 4-week endpoint	■ 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 cm^2 to 45 cm^2 and all the wounds of the remaining 14 patients improved
Bateman, 2015	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	■ 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
Hunt, 2015	Evaluated the effectiveness of haemoglobin spray in 100 patients who presented with sloughy wounds	■ 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
Tickle, 2015	A multi-centre observational evaluation of 19 patients with pressure ulcers, with a 4-week endpoint	■ 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
Wakenshaw and Roper, 2015	10 wounds with different aetiologies treated with haemoglobin spray for 8–10 weeks	■ 75% of patients progressed towards healing ■ 2 patients were excluded due to non-compliance and 2 due to infection

Source: Adapted from Chadwick, 2014

Table 2. Inclusion and exclusion criteria

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

haemoglobin spray from the company representatives, although its application is simple and straightforward.

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 <70mmHg 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

Table 3. Patient demographics

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

* SINBAD score: Ince et al (2008)

† 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

	Area (cm^2)			Slough (%)		Granulation tissue (%)		Epithelial tissue (%)		Exudate level		Primary dressing used	Total no. of primary dressing changes
Participant no. (ulcer)	W1	W4	% change	W1	W4	W1	W4	W1	W4	W1	W4		
1	7.84	4.40	-43.9	40	0	0	30	50	70	Moderate	None	Mepilex Border, changed every 72 hours	8
2	12.16	7.50	-38.3	60	0	40	60	10	40	Severe	None	Aquacel non-adherent foam and crepe bandage; K-Soft. Changed every 72 hours	8
3	2.70	1.00	-63.0	40	0	10	20	50	80	Moderate	None	Aquacel Foam Adhesive, changed every 72 hours	8
4	8.96	5.75	-35.8	50	0	50	60	0	40	Severe	None	Mepilex Border, twice weekly	8
5	8.40	4.00	-52.4	60	0	30	40	10	60	Severe	Mild	Mepilex Border Adhesive, changed every 72 hours	8
6 (right)	2.25	2.25	0.0	0	0	100	100	0	0	Moderate	Moderate	Melolin	28
6 (left)	3.30	1.96	-40.6	0	0	100	100	0	0	Moderate	Moderate	Melolin	
7	0.55	2.55	363.6	0	0	100	100	0	0	Mild	Mild	Allevyn Adhesive	16
8	2.00	1.62	-19.0	0	0	100	100	0	0	Severe	Moderate	Durafiber; KerraMax Care	28
9	70.00	12.00	-82.9	100	0	0	70	0	30	Severe	Moderate	Aquacel Ag; Mepilex Heel	12
10	57.00	18.60	-67.4	65	0	35	100	0	0	Moderate	Mild	Granugel and Aquacel Foam (W1–W2); Aquacel Foam (W3–W4)	10
11 (1)	6.60	0.06	-99.1	65	0	35	10	0	90	Mild	Mild	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	10
11 (2)	10.88	4.75	-56.3	80	15	20	85	0	0	Mild	Mild		
12	13.11	11.55	-11.9	100	50	0	50	0	0	Severe	Severe	ActivHeal Foam	8
13	0.12	0.00	-100.0	0		100		0		Mild	None	Allevyn Adhesive	5
14	4.83	4.83	0.0	60	<10	40	≥90	0		Moderate	Moderate	Zetuvit and Aquacel for W1–W2; Aquacel and sterile gauze for W3; Aquacel and Biatain for W4	4
15 (lower)	1.53	0.40*	-73.9	20		80		0		Moderate		Biatain and Zetuvit, W1–W3	3
15 (upper)	0.30	1.20*											
16	0.21	0.12	-42.9	0	0	100	100	0	0	Moderate	Mild	Mepilex	12
17	0.18	0.28	55.6	0	0	100	100	0	0	Mild	Mild	Mepilex	12

*Stopped trial at week 3 due to wound becoming infected

Table 5. Results: patient and clinician experience

Participant no.	Adverse events?	Did participant or nurse stop using Granulox?	Give comments on ease of use of Granulox and its acceptability to participants
1	None	No	Participant happy to use independently under supervision. No issues expressed
2	None	No	Participant happy to use independently
3	None	No	Participant said 'it dried my wound up'. 'Comfortable and no pain'
4	None	No	Participant found it easy to use once foot positioned
5	None	No	Participant found it easy to use independently. 'Less wet exudate. And reduced dressing changes'
6	None	No	Extremely easy to use. No adverse reactions
7	None	No	Some issues with the nozzle blocking up but otherwise easy to apply. Participant continued until June 15, wound healed 19/8/15
8	None	No	Easy to apply. No adverse events
9	None	No	Excellent ease of use. Participant extremely pleased with ulcer progress during this period
10	None	No	Wound progression good. Extremely simple to understand and use
11	None	No	So simple to use
12	None	No	(Blank)
13	None	No	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
14	None	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	Participant happy as long as you warn them it's very red and resembles blood. Problem with vegetarian participants due to animal product
15	Yes	Stopped trial at week 3 due to (upper) wound becoming infected	Difficult if participant has an issue with porcine ingredient
16	None	No	Easy to use. Participant dresses wound themselves
17	None	Participant forgot to use Granulox but was advised to apply it when they went back home	Participant reported clogging and difficulty spraying Granulox, despite changing the nozzle

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 cm^2) and week 2 (0.4 cm^2), a reduction of

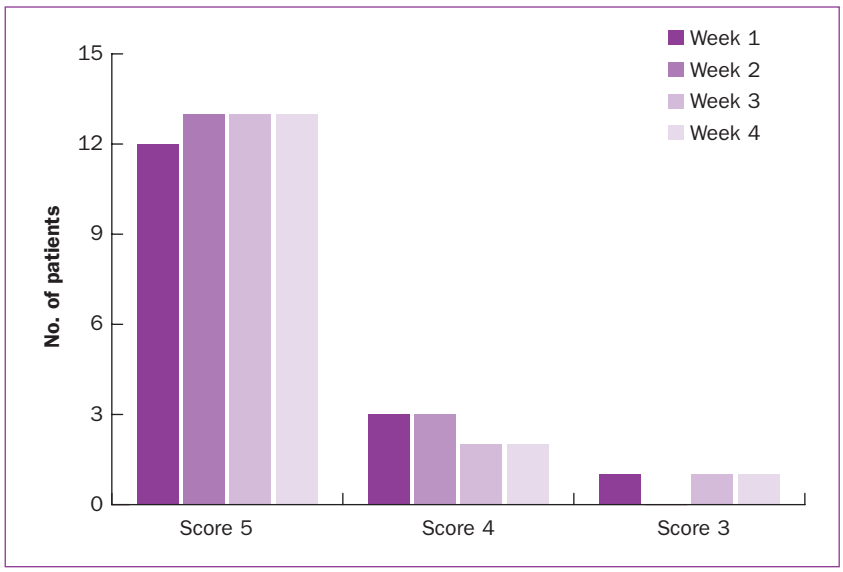


Figure 3. Frequency of responses regarding ease of use by participants (score of 5 being most positive, 1 least positive)

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.

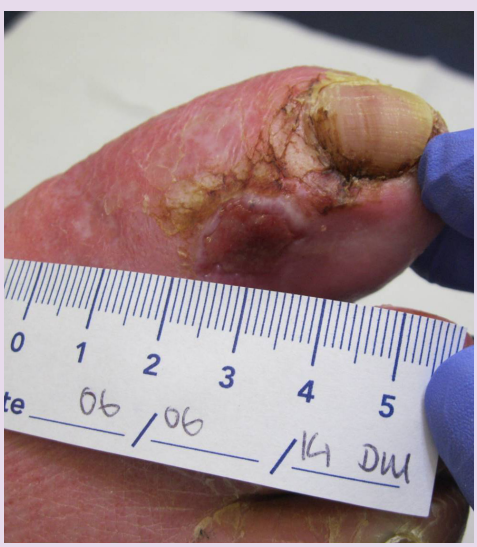
Although not one of the pre-set objectives, it was interesting to note that the 11 wounds that had slough present at the start of the trial showed at least a 50% reduction (or a complete resolution) of slough at week 4, and exudate levels also improved in the majority of cases (*Table 4* and *Figure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

Discussion

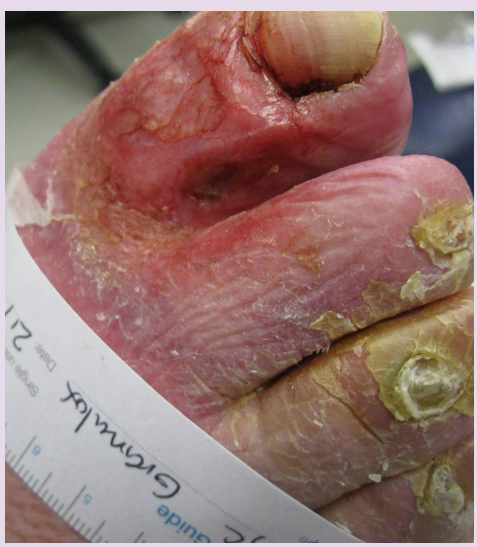
Peripheral arterial disease or local tissue hypoxia dramatically affects participant outcomes and a tissue oxygen concentration below 40% is said to drastically reduce healing rates (Hauser et al, 1987). This small multi-centre observational evaluation explored the use of a haemoglobin spray over a 4-week 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 1cm^2 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

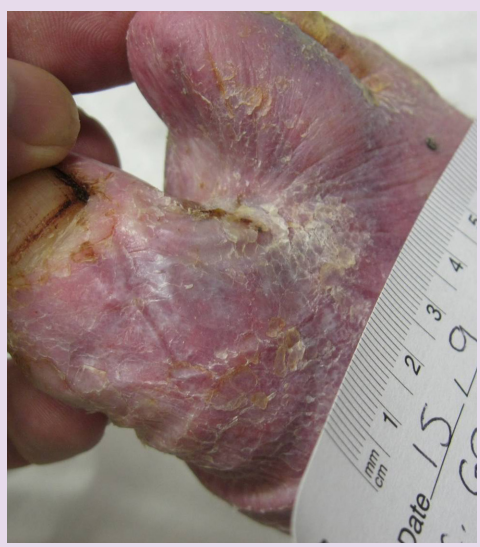
Clinical example



Chronic neuropathic DFU with a duration of over 2 years



Same wound after 4 weeks treatment with the topical haemoglobin spray



After 12 weeks of treatment, the wound has healed

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 trail, 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 (cm^2) 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 a more accurate, precise and validated method of wound measurement is needed (to also include wound volume). These systems also offer an opportunity to reduce intra-observer bias, as a single clinical expert can perform the markup on data collected by potentially many different clinicians at the point of care. This would be of benefit and should be incorporated into future wound assessment studies of this nature (Bowling et al, 2013).

Future work would benefit from the inclusion of a randomised control arm of 'standard of care' only, which should be compared with that of 'standard of care with intervention'. This would allow a more robust comparison of wounds treated with topical oxygenation therapy.

Figure 4. Frequency of SINBAD scores and mean percentage reduction. Note this excludes patients who did not use Granulox at every dressing change: patient 7 who experienced some difficulties with the nozzle; patient 14 who was given Granulox only once a week; patient 15 (withdrawn); patient 17, who did not use Granulox between dressing changes on one occasion

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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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'

The follow clinicians took part in this evaluation:
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