Evaluating the effect of a haemoglobin spray on size reduction in chronic DFUs: clinical outcomes at 12 weeks

ABSTRACT

A recent multi-centre observational evaluation investigated the effect of a topical haemoglobin spray (Granulox, Infirst), used as an adjunct to standard care, on wound size reduction in 17 patients (4 females/13 males) with 20 chronic diabetic foot ulcers (DFUs) over a 4-week period. In 14 of the 18 wounds that completed the evaluation (one patient dropped out due to an infection) there was a mean reduction of 53.8% (range: 11.9–100%). The product was acceptable to both patients and clinicians, who all found it easy to use. This article describes the outcomes for the remaining 13 patients (with 15 wounds) who continued using the spray after the 4-week evaluation ended. (Data are not available for two patients and the one patient who healed during the 4-week evaluation.) By 12 weeks, three wounds (20%) had healed, eight (53%) were progressing towards healing, three (20%) increased in size and one (7%) was slow healing.

Key words: Diabetic foot ulcer ■ Topical haemoglobin therapy ■ Wound healing ■ Slough reduction ■ Patient and clinician satisfaction

Diabetic foot ulceration is a common phenomenon, occurring in all specialties, that poses physical, psychological and financial burden to both patients and healthcare providers. Many patients with diabetic foot ulcers (DFUs) experience infection, tissue damage and deterioration, which can be followed by amputation and disability (Edmonds, 2007). Accordingly, healing times are often slow. Patients with SINBAD scores of ≥3 are at most risk of delayed healing (Ince et al, 2008). Clinicians, healthcare stakeholders and industry are constantly seeking to prevent, manage and improve outcomes in these patients through the development of innovative treatments and approaches to care. An example of a new treatment is the use of a topical haemoglobin spray (Granulox, Infirst) as an adjunct to standard care. This has been found to aid healing in venous leg ulcers (VLUs), (Arenbergerova et al, 2013; Norris, 2014), pressure ulcers (PUs) and DFUs (Tickle, 2015; Bateman, 2015a ; Haycocks et al, 2016). This article concerns the multi-centre evaluation published by Haycocks et al (2016), which investigated percentage reduction in DFUs following 4 weeks of treatment with the haemoglobin spray. While the formal evaluation ended at 4 weeks, most of the patients continued using the spray after this. Here, the authors describe the outcomes achieved in these patients after 12 weeks of treatment with the haemoglobin spray.

Topical haemoglobin therapy

As the human body is unable to store and retain oxygen, it requires the constant delivery of this molecule to all cells, along with glucose, collagen, proteins and metabolites, to ensure tissue function (Hauser, 1987; Timmons 2006; Chadwick et al 2015). When tissue cells become 'starved' of oxygen due to disease, injury or infection, they can become dysfunctional, which often results in wounds becoming static and the subsequent formation of necrotic tissue and slough (Flanagan 2000; Dow, 2001). Damaged or diseased tissue therefore requires a constant oxygen supply to maintain the healing process (Sen, 2009). DFUs are associated with impaired microvasculature function, which can result in hypoxia and thus non-healing. More information on the effects of hypoxia in DFUs is provided by Haycocks et al (2016). It is proposed that oxygen therapy can help address this.

Oxygen therapy can be delivered either topically (low-pressure delivery of pure oxygen to the wound surface) or systemically in the form of hyperbaric oxygen therapy (HBOT), where the patient inhales 100% oxygen under increased atmospheric pressure. However, given the poor availability of HBOT in the UK and lack of supporting evidence, the National Institute for Health and Care Excellence (NICE, 2015) states that it should not be used in the treatment of DFUs except as part of a clinical trial.

One form of topical oxygen therapy (Granulox, Infirst) uses haemoglobin as the carrier. Haemoglobin binds to oxygen, transporting it from the lungs to the tissues. Accordingly, topical haemoglobin therapy conveys oxygen from the atmosphere to the hypoxic wound in a process known as 'facilitated diffusion', with haemoglobin as the transporter. It is proposed that this increases uptake of oxygen in the wound. This is supported by Petri et al (2016) who found that the average oxygen saturation increased from 56.4% to 78.8% after 5 minutes of topical haemoglobin therapy. It is suggested that this increases uptake of oxygen in the wound bed, thereby providing an improved environment for wound healing (Arenbergerova et al, 2013; Babadagi-Hardt et al, 2014).

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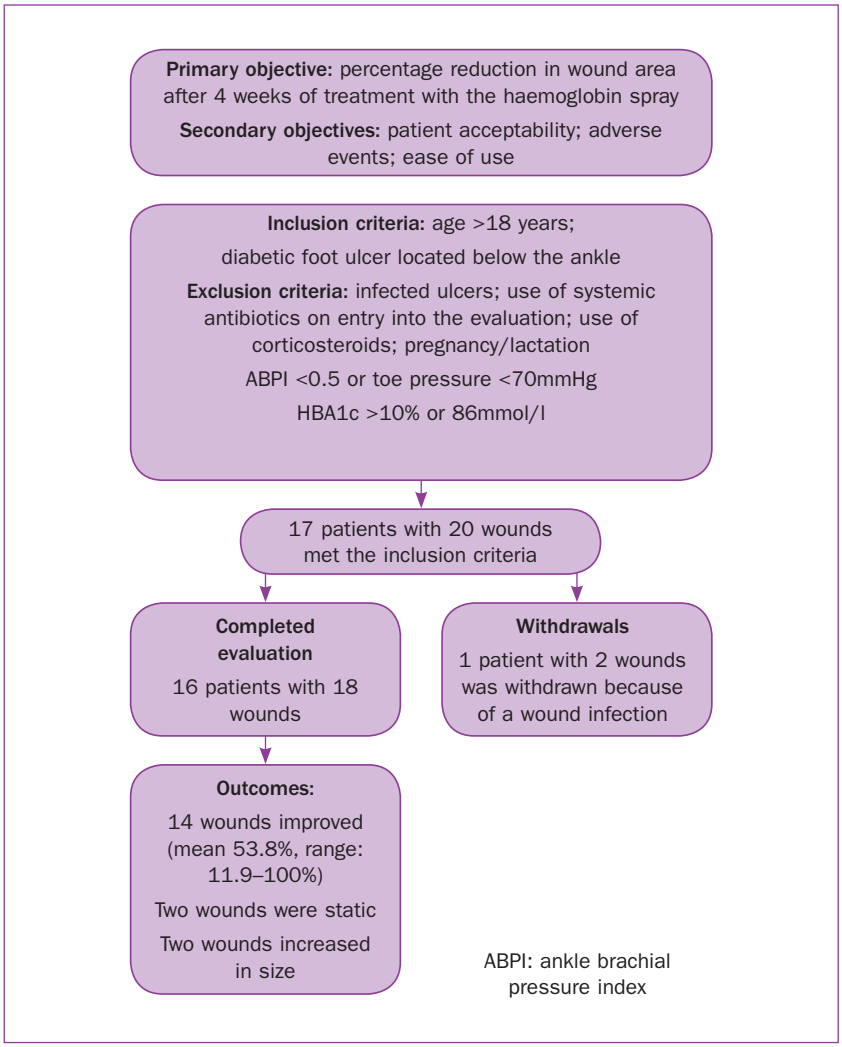


Figure 1. Results of the 4-week evaluation by Haycocks et al, 2016

Granulox

Granulox is a sterile topical haemoglobin spray containing a oxygen-haemoglobin solution derived from pig erythrocytes. It is indicated for slow healing or non-healing wounds, although it has also been used successfully on acute and sloughy wounds (Bateman, 2015a; 2015b; Hunt, 2015). The haemoglobin spray is simple to use, requiring little training. It can therefore be used by both specialists and generalist nurses, as well as by patients and their carers, promoting self-care (Hunt, 2015). To date, there have been no reported adverse effects. The distributors recommend that the spray be applied at least once every 72 hours, although an expert wound-care working group has acknowledged that there is insufficient evidence to determine optimum application rates. The working group also acknowledged that there is limited evidence on the long-term benefits of the spray, and emphasised that it is an adjunctive treatment and so should not replace standard care or be used as an interim treatment prior to referral to tissue viability or podiatry, or for revascularisation, diabetes management and/or plastic or general surgery (Chadwick et al, 2015).

Evidence overview

There is a steady growth of positive information and data on the benefits of using the haemoglobin spray on a variety of acute and chronic wounds. These are summarised below.

In a controlled clinical trial involving 36 patients with VLUs, Arenbergerova et al (2013) found that the haemoglobin spray was associated with a mean 53% reduction at 13 weeks versus no improvement in a control group.

Building on the positive results of randomised trials (Arenberger et al, 2011; Arenbergerova et al, 2013), several observational evaluations have been conducted in the UK. These found that, after 4 weeks of treatment, the spray was associated with a reduction in size in chronic VLUs (Norris, 2014), PUs (Tickle, 2015) and chronic DFUs (Bateman, 2015a; Wakenshaw and Ropper, 2015; Haycocks et al, 2016).

One of these investigators subsequently undertook 12-week follow-up of her original patients (Tickle and Bateman, 2015). Eleven of the 18 patients with PUs recruited into the Tickle's 4-week evaluation continued using the haemoglobin spray after the investigation ended; of these, 9 wounds had healed at week 12 and two had reduced in size (baseline vs endpoint: 30cm^2 vs 7cm^2 and 6cm^2 vs 4cm^2 for the two wounds respectively).

The haemoglobin spray has also been shown to eliminate slough in a variety of wound types by 4 weeks (Bateman, 2015b; Hunt, 2015) and to reduce pain within 2 weeks (Arenbergerova et al, 2013; Norris, 2014; Tickle, 2015; Tickle and Bateman, 2015b).

In all of these evaluations, patients and/or carers self-administered the haemoglobin spray when required, thereby demonstrating that it helps facilitate self-care.

Evidence on DFUs

Three papers have focused solely on DFUs. Chadwick (2014) published a pilot study concerning four chronic DFU: two of these ulcers healed within 12 weeks; one ulcer reduced by 20% within 2 weeks; and one ulcer improved only to develop a wound infection at 12 weeks.

A year later, Bateman (2015a) undertook a 4-week evaluation involving 20 patients with chronic DFUs and a SINBAD (Ince et al, 2008) score of ≤2. At baseline, the mean wound duration was 10 months (range: 3-18 months) and just over half (n=11; 55%) of the patients used off-loading equipment. After 4 weeks of treatment, five wounds (25%) healed and the rest all reduced in wound size (mean and median reductions: 62.3% and 53%, range: 18-94%) respectively. (All of the five patients who healed had a shorter baseline wound duration and were free of neuropathy and vascular deficiency; four were aged ≤28 years). All wounds were sloughy at the start of the evaluation, whereas all were deemed slough-free at week 4. The only method of debridement used was cleansing with saline. Finally, there was a marked decrease in exudate levels, with 65% of the patients having moderate or severe exudate at baseline, compared with 5% at week 4.

In 2016, Haycocks et al undertook another 4-week evaluation involving patients with DFUs, with a view to determining whether the results of Bateman (2015a) are reproducible. The Haycocks evaluation had a similar design to the one by Bateman (2015a), varying from it only in that it did not exclude patients with a SINBAD score of ≥3 and had a run-in period. This took place before the evaluation started and comprised 4 weeks for new referrals and 2 weeks

Table 1. Patient outcomes during the 12 weeks of treatment with the haemoglobin spray

Participant no. (ulcer)*	SINBAD score	Wound duration	Off-loading used	Wound surface area (cm^2)			% change: weeks 1 vs 12
				Week 1	Week 8	Week 12	
1	2	5 months	Yes	7.84	3	1.4	-82.1
2	3	6 months	No	12.16	6.6	5	-58.8
3	1	4 months	No	2.70	0.09	0	-100.0
4	4	8 weeks	Yes	8.96	0.08	0	-100.0
5	3	3 months	No	8.40	2.7	0.32	-96.19
6 (right)	2	24 months	Yes	2.25	3.3	4.6	104.4
6 (left)				3.30	2.72	7.4	124.24
7	2	12 months	Yes	0.55	0.5	0.18	-67.27
8	3	24 months	Yes	2.00	2.4	Discontinued	20
9	3	8 months	No	70.00	11.88	7.56	-89.2
10	2	3 months	Yes	57.00	15.08	11.98	-78.98
11 (1)	3	12 months	No	6.60	0.02	0	-100
11 (2)				10.88	3.63	2.16	-80.15
12	3	5 months	No	13.11	10.6	Discontinued	–24.64
14	3	9 weeks	Yes**	4.83	4.4	4.32	-10.56
							Mean: -39.3%

* Patient numbers are taken from the original evaluation by Haycocks et al (2016) ** During the weeks 1–4 only
Patients 8 and 12 stopped receiving the haemoglobin spray on weeks 9 and 11 respectively

for existing patients, during which patients received standard care only (defined as local best practice). Only patients meeting the inclusion criteria whose wound(s) decreased by ≤20% during the run-in period (and so were deemed chronic, despite provision of standard care) were included in the subsequent 4-week evaluation. The primary outcome measure was the percentage reduction after 4 weeks of treatment with the haemoglobin spray; secondary outcomes were patient acceptability, adverse events and ease of use. The design and results of the evaluation are summarised in *Figure 1*.

Seventeen patients (4 females and 13 males) with a total of 20 DFUs were recruited into the evaluation. Full details about their baseline demographic data and wound characteristics are given by Haycocks et al (2016). The average wound duration was 10.6 months (SD: 12.15; range 2–48 months).

One patient (no. 15), who had two wounds, was withdrawn from the evaluation at week 3 after developing a soft-tissue infection. Results therefore relate to 16 patients with 18 wounds. After 4 weeks of treatment with the haemoglobin spray, 14 of the wounds reduced in size, with a mean reduction of 53.8% (SD: 26.6%; range: 11.9–100%), two wounds remained static and two wounds increased in size. In one of the patients with static wounds (no. 14), the haemoglobin spray was only applied once weekly. In another patient (no. 7) the wound reduced in size by 27.3% during the first 2 weeks (from 0.55cm^2 to 0.4cm^2), only to increase by 363.6%, most likely due to a broken removable cast.

Although this was not an outcome measure, the investigators noted that use of the haemoglobin spray was associated with a reduction in slough, supporting the findings of previous audits (Bateman 2015a, 2015b; Hunt 2015). At the start of the evaluation, slough was present in 11 out of the 16 wounds, whereas at week 4 eight of these wounds were slough free and the remaining 3 had ≤50% slough. The spray performed well in terms of ease of use, with 14 of the 16 clinicians (81%) rating this with the highest score.

Wound progression at 12 weeks

After the formal 4-week evaluation by Haycocks et al (2016) ended, the investigators continued using the haemoglobin spray on the remaining patients. All of these patients received the same standard care as they had in the 4-week evaluation.

The rest of this article summarises the outcomes reported for 13 patients (with 15 wounds) who received up to 12 weeks of treatment with the haemoglobin spray. (This excludes the patient who healed at week 3 (patient no. 13), the patient who was withdrawn at week 3 because of an infection (patient no. 15) and two patients for whom further data were not available (patients nos 16 and 17)). To date, patient 13 has not experienced a recurrence of his DFU.

By week 12, three wounds had healed, eight wounds had improved, one wound was slow healing (defined as ≤20% reduction in size) and three wounds had deteriorated. More detailed results are given in *Table 1*.

Of the three wounds that healed, two had closed at week 9 and one at week 11. Of the eight wounds that were improving, five had decreased by over 75% by week 12. In one of these wounds (patient 12), the treating clinician felt that use of the

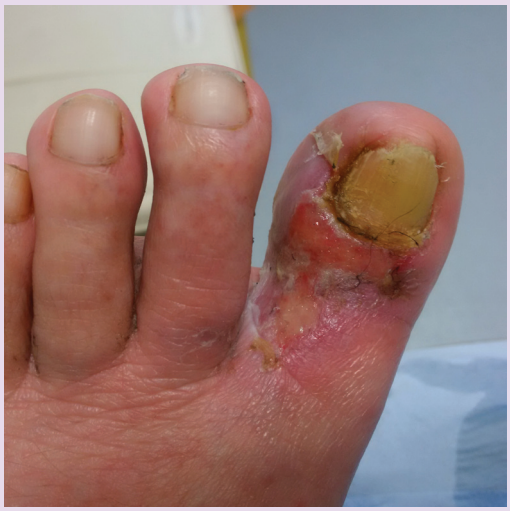
Box 1. Patient 3's story

My name is Beverley and I am a 47-year-old mother of two young children. I work part time in a large computer-based office and this is my story.

I have diabetes type 2 which is generally well controlled. I eat well, exercise three times a week and check my feet most days. My only vice is smoking. I have tried to stop but find it very difficult due to the anxiety and stress of being a single mother.

Four months ago, I noticed a small sore at the bottom of my big toe during one of my checks. I was not worried about it at first as it was tiny, and applied a basic plaster and kept it clean and dry. After a couple of days it began to hurt and leak fluid, so I made an appointment with my GP, who asked the practice nurse to look at it. I was told it was a diabetic wound and needed specialist care including cleansing and dressings. I was asked if I wanted to be referred to the diabetes specialist at the big hospital, but I didn't want to waste their time if my wound could heal quickly. I've always been worried about wounds to my skin as I know it's hard for us patients to heal as quickly as patients with no diabetic problems. I had to take some time off work as I couldn't drive with the wound, which was frustrating. I also found it hard to chase around after my children, who are at that active age.

After a couple of months of my wound being very slow to get better, I was referred to the wound specialist nurse who looked at my foot, took some blood and did some sensation tests. After the results came back, which were all normal, she asked if I wanted to try a new spray on my wound. I was happy to try it and liked the idea that I could do my own dressings at home. The nurse told me all about the red spray and gave me a little information card about it that I could take home. It seemed easy enough and I thought doing my own dressings at home would save me lots of time. I still went to see the nurse to get my wound checked regularly but I did the dressings myself, even at the general practice.



Wound on the dorsum of the hallux with slough and exudate plus mild malodour, The wound, which was of 4 months' duration, is seen here on day 1 of evaluation before the haemoglobin spray was first used

It took just over 8 weeks for my skin to get completely better and I was very impressed with the spray. I had a little pain at first but the wound was very comfortable after the first week or so, and the yellow liquid very soon stopped leaking. If I have any other wounds, which I hope I won't, I will ask for this spray from the start and would tell others to try it too.

Don't know why I was never asked to do my own dressings before: if patients can do it and want to do it, they should be given the choice. It saves our time and lets the doctors and nurses get on with those that can't help themselves.

Full patient consent was given to use the photograph of the wound and to include her evaluation data.

haemoglobin spray has kick started healing in a previously recalcitrant wound as the wound was 'visibly shallower' after the 10 weeks of treatment. However, the patient developed cellulitis in his left ankle at week 10, resulting in hospital admission, with the haemoglobin spray not being used for the next 38 days. (The infection was not considered to be related to the spray.) Treatment with the haemoglobin spray was resumed after the patient's discharge, as the patient reported that he was 'grateful for the treatment, as all the other dressings used previously had failed'. The wound is now continuing to decrease in size.

One wound (in patient 14) remained slow to heal. However, there was a reduction in slough and increase in the percentage of granulation tissue by week 12, although the exudate level remained moderate throughout. This patient had only received the haemoglobin spray once weekly in weeks 1–7, with application increasing to twice weekly (as recommended by the distributor) in weeks 8–12, but this had no affect on wound size. The patient developed an infection at week 13, when use of the spray was discontinued.

Three wounds in two patients increased in size. One patient (no. 6) had two wounds, with both increasing in size. The haemoglobin spray was applied every day throughout the treatment period, but there was no improvement in any of the parameters assessed. In the other patient (no 8), the treating clinician stopped using the haemoglobin spray at week 9, continuing with just standard care; this patient was referred for further pressure relief assessment and multidisciplinary foot team opinion. All three wounds were over 24 months' duration at baseline, and so were likely to be clinically challenging.

Figure 2 illustrates the progression towards healing in the 15 wounds from the run-in period to week 12.

No adverse events occurred during the 12 weeks that were considered to be related to the haemoglobin spray. As in the 4-week evaluation, the participating clinicians all regarded the spray as very easy to use. Of note is that slough was eliminated in all of the wounds of these 13 patients (100%) at week 12. This supports the findings of Bateman (2015a, 2015b) and Hunt (2015), who found in three samples totalling 150 patients that use of haemoglobin spray reduces or eliminates slough in acute, static and slow-to-heal wounds including DFUs, pressure ulcers, postoperative wounds, venous and arterial leg ulcers, skin tears, and wounds in intravenous drug users.

With regards to exudate levels, at 12 weeks there were no surprises. Patients whose wounds continued to progress towards healing had low levels of exudate and those wounds that had become static or were deteriorating had moderate levels, as would be expected at these stages.

Discussion

Hypoxia is common in the peripheral extremities of the diabetic population (Sen, 2009). In the event of injury, the hypoxia will impair tissue repair, often resulting in a deterioration in the condition of the wound and increasing the risk of amputation (O'Loughlin et al, 2010). This article describes the clinical outcomes of 13 patients with 15 wounds who continued using the haemoglobin spray after a 4-week evaluation in which they had participated had ended (Haycocks et al, 2016). The majority of the wounds in these patients had either healed or were progressing toward healing after a total of 12 weeks of treatment with the spray plus

standard care. Furthermore, all wounds were free of slough at this time point, while the patient whose wound had healed during the 4-week evaluation did not experience a recurrence.

Although these outcomes cannot be considered to be part of a formal evaluation, the results are consistent with and replicate those published by other clinicians on the efficacy of the haemoglobin spray when used as an adjunct to standard care of DFUs (Chadwick, 2014; Bateman, 2015a; Haycocks et al, 2016). When considering the outcomes presented here, the small sample size and variations in the standard care offered in the different centres must be borne in mind. As the evaluation was not controlled, it is not possible to determine the comparative efficacy of the haemoglobin spray against another product.

Future evaluations, therefore, should be conducted in single sites with larger cohorts and a longer follow-up period, with either a designated retrospective control or the design of a randomised controlled trial. It would also be useful to include acute as well as chronic wounds. Such steps forward are required to build a solid evidence base for this product and to augment patient and clinician confidence in it.

Box 1 outlines a patient's experience of using the haemoglobin spray (patient 3 in the evaluation).

Conclusion

The majority of the patients who continued using the haemoglobin spray either healed or improved, while all of the patients experienced a complete elimination of slough. It is recommended that further, more rigorous studies be undertaken with larger cohorts of patients to corroborate these findings.

In accordance with O'Loughlin et al (2010) it is vital that the management and prevention of DFU adopts a holistic approach due to the negative impact this disease process has on quality of life, mobility, mental health and social interactions. It is our clinical duty to explore and promote new ways of improving patient care and outcomes. **BJN**

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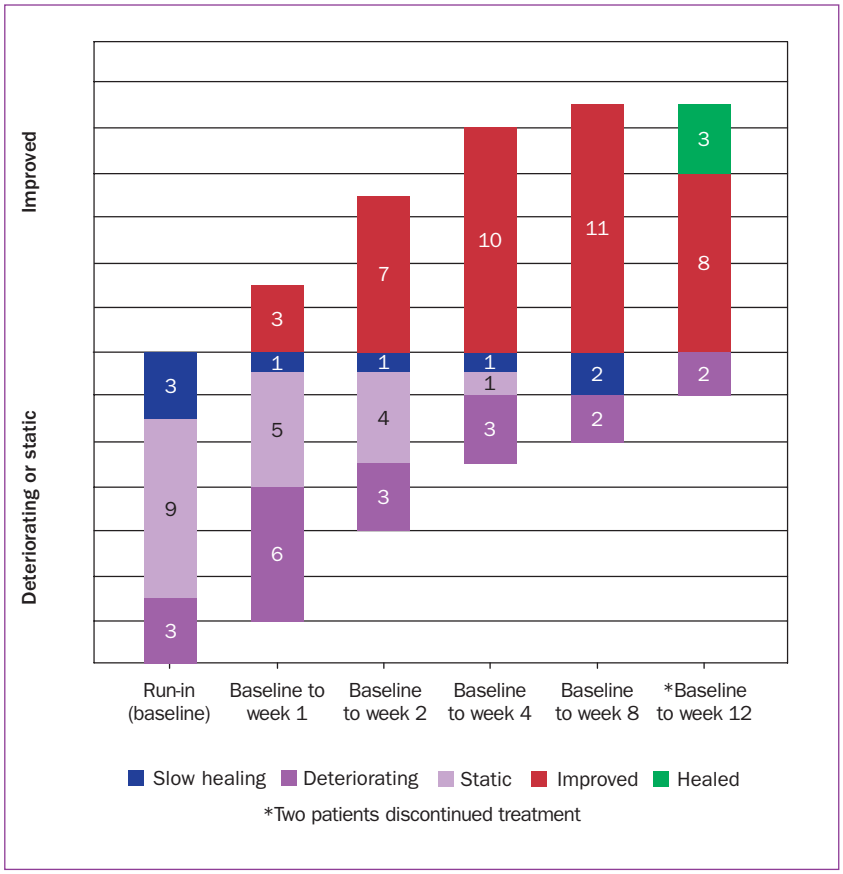

Figure 2. Progression towards healing in the 15 wounds treated with the haemoglobin spray plus standard care for up to 12 weeks. All healing outcomes are compared with baseline (run-in). Positive healing outcomes are above the central line; negative healing outcomes are below the line. Slow healing refers to wounds that decreased in size by ≤20%

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KEY POINTS

- An increased uptake of oxygen in the wound bed provides an optimum environment for wound healing
- It is vital that the management and prevention of diabetic foot ulcers (DFUs) adopts a holistic approach due to the negative impact this disease process has on quality of life, mental health and social interactions
- This clinical evaluation explored the use of a topical haemoglobin spray plus standard care in 13 patients with 15 non-healing DFUs for up to 12 weeks
- By week 12, three wounds (20%) had healed, eight (53%) had improved, three (20%) had healed, three (20%) had increased in size and one (7%) was slow healing

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