Use of a topical haemoglobin spray for oxygenating pressure ulcers: healing outcomes

Abstract

A published evaluation (Tickle, 2015) of the use of a topical haemoglobin spray plus standard care in 18 patients with pressure ulcers showed that, following 4 weeks of treatment, the wound size reduced in 17 wounds and there was a progression toward healing in all 18. All but one of the wounds were over 2 months in duration at baseline. This article reports the results of the healing rates at 3 months of the 11 patients who continued to be treated with the haemoglobin spray. Nine of the 11 wounds healed, and 2 reduced in size by week 12 (i.e. 1 wound reduced from 30 cm^2 at baseline to 7 cm^2, while the other reduced from 6 cm^2 to 4 cm^2). Of the 10 patients who were experiencing wound pain at baseline, 9 were pain free by week 8. Rapid elimination of slough was observed in all patients. The 82% healing rate achieved at 3 months and the fact that most patients continued to receive the same standard care as they had in the 4 weeks before recruitment into the evaluation increases the likelihood that the clinical outcomes observed here can be attributed to the haemoglobin spray. Topical haemoglobin shows promise in terms of its ability to accelerate healing in chronic pressure ulcers.

■ pressure ulcers ■ wound healing ■ pilot study ■ chronic wounds ■ haemoglobin

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Most chronic wounds are linked to poor blood circulation and thus an inadequate oxygen supply, resulting in hypoxia, with tissue necrosis as a potential final outcome. In the absence of oxygen, several crucial processes involved in wound healing stop working (Schreml et al, 2010). As oxygen plays an important role in wound healing, supplying additional oxygen to the chronic wound may help promote healing (Tickle et al, 2015), particularly as wounded tissue requires considerably more oxygen than intact skin. In short, the combination of poor oxygenation and a hard-to-heal chronic wound could benefit from treatments that improve oxygen supply.

Topical oxygen therapy

The mechanism through which oxygen therapy is delivered to the wound to promote the oxygen-dependent process of wound healing is key to achieving a positive outcome (Gordillo and Sen, 2009; Dissemond et al, 2015). Unlike systemic oxygen therapy, topical oxygen does not rely on an (impaired) vascular system to deliver the oxygen to the wound site. Topical oxygen therapy is also considered to have fewer risks than hyperbaric oxygen therapy (Schreml et al, 2010). There are multiple methods of topical oxygen delivery (Dissemond et al, 2015):

- Topical pressurised oxygen therapy
- Topical continuous oxygen therapy
- Wound dressings that release oxygen
- Use of an oxygen diffusion enhancer.

Oxygen diffusion enhancer

This technology is based on the principle that haemoglobin, an oxygen transporter, can be applied to the wound bed as an aqueous solution to facilitate the diffusion of oxygen. Haemoglobin is a suitable transporter and, being soluble, can also transport oxygen molecules when not bound to an erythrocyte (Page et al, 1998). In an environment with a limited supply of oxygen, such as a hypoxic wound bed,

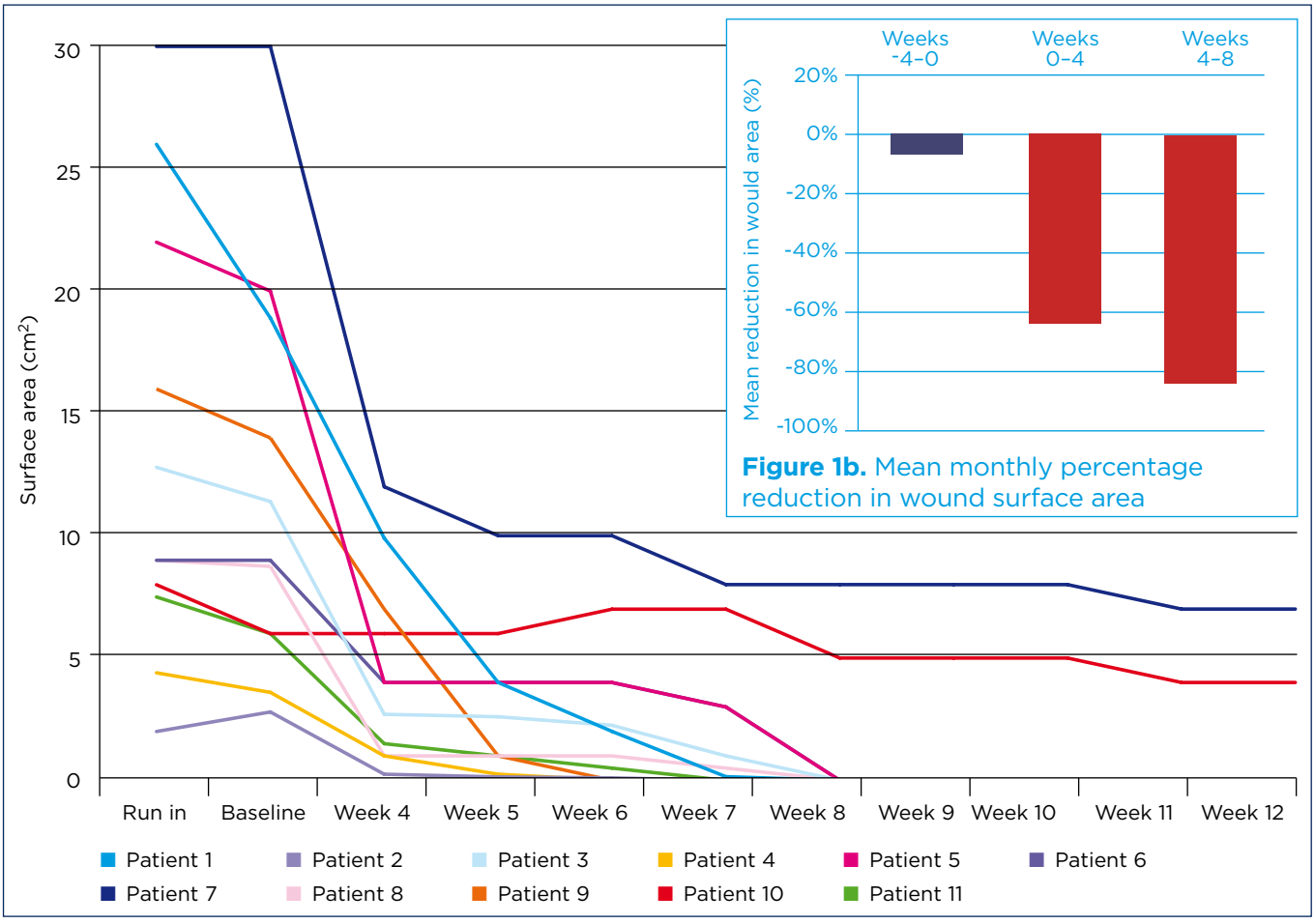

Figure 1b. Mean monthly percentage reduction in wound surface area

Figure 1a. Healing times for the 11 pressure ulcers treated with the haemoglobin spray after the end of the 4-week evaluation

oxygen diffusion from air increases by more than 800% when haemoglobin is added to water *in vitro* (Scholander, 1960).

Granulox is a haemoglobin spray. It comprises an aqueous solution containing haemoglobin extracted from porcine erythrocytes. The spray is indicated for the treatment of chronic wounds such as pressure ulcers, venous leg ulcers, arterial leg ulcers, mixed aetiology leg ulcers, diabetic foot ulcers, and surgical wounds healing by secondary intention.

Evidence base

There have been several evaluations, some comparative, on the efficacy of haemoglobin spray. In 2011, in Mexico, a randomised trial on chronic wounds in the lower limb found that, following 6 months, 13 out of 14 wounds treated with the haemoglobin spray healed compared with only 1 out of 14 in the control group (Arenberger et al, 2011). A Czech randomised trial published 2 years later, and involving 72 patients with chronic venous leg ulcers, found that, after 13 weeks, use of the haemoglobin spray was associated with a mean wound size reduction of 53% compared with a 21% mean increase for the control group, who received the same care with the exception of a sham spray (i.e. the same spray without the haemoglobin) (Arenbergerova et al, 2013). It should be noted that, although they have different lead authors, these two studies were written by the same team.

In a UK non-comparative evaluation, all 14 non-healing venous leg ulcers treated with the haemoglobin spray reduced in size during the 4-week treatment period (median reduction: 68% or 7.21 cm^2, with the mean baseline surface area reducing from 52.5 cm^2 to 45.29 cm^2) (Norris, 2014). All wounds showed a concomitant reduction in slough and an increase in granulation and epithelial tissue. The study design included a 4-week run-in period, with the only change to the treatment protocol during the subsequent 4-week treatment period being the introduction of the haemoglobin spray.

Bateman (2015a) undertook a similar evaluation on patients with chronic diabetic foot ulcers (DFUs). In this evaluation, 20 patients with DFUs of over 12 weeks' duration and a SINBAD score of ≤2 (indicative of sufficient vascular supply to promote healing) were treated with the haemoglobin spray for 4 weeks. Of these, 5 wounds healed, and the remainder reduced in wound size (mean and median reductions: 62% and 56%, respectively). In addition, the wounds, which were all sloughy at baseline, were slough-free by week 4. Later, Bateman (2015b) explored the reduction of slough in another evaluation, where

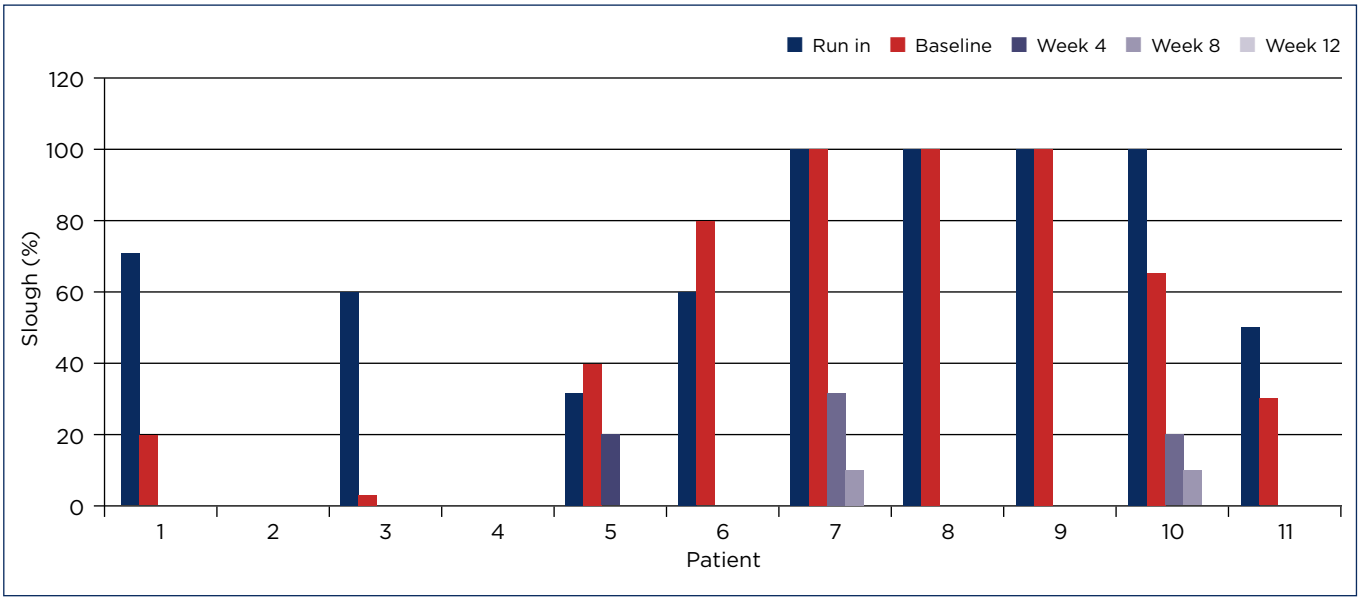

Figure 2. Percentage reduction in slough

Table 1. Wound location and healing times (n = 11)

Pt. no.	Age (years)	Wound duration*	Ulcer location	Wound surface area (cm^2)										
				Week										
				-4**	0***	4	5	6	7	8	9	10	11	12
1	46	5 weeks	Heel	26	18.9	9.9	4.0	2.0	0.2	0				
2	68	18 months	Heel	2.0	2.8	0.3	0.1	0.1	0					
3	44	3 weeks	Heel	12.8	11.4	2.7	2.6	2.3	1.0	0				
4	56	3 months	Heel	4.4	3.6	1.0	0.3	0						
5	44	12 months	Sacrum	22.0	20.0	4.0	4.0	4.0	3.0	0				
6	58	6 months	Sacrum	9.0	9.0	4.0	4.0	4.0	3.0	0				
7	66	2 months	Heel	30.0	30.0	12.0	10.0	10.0	8.0	8.0	8.0	8.0	7.0	7.0
8	81	3 months	Heel	9.0	8.8	1.0	1.0	1.0	0.5	0				
9	55	2 months	Heel	16.0	14.0	7.0	1.0	0						
10	87	3 months	Sacrum	8.0	6.0	6.0	6.0	7.0	7.0	5.0	5.0	5.0	4.0	4.0
11	81	3 months	Sacrum	7.5	6.0	1.5	1.0	0.5	0					
			Mean	13.3	11.9	4.5	3.1	2.8	2.5	1.2	1.2	1.2	1.0	1.0

* Pre-evaluation
** Run-in: 4 weeks before treatment with the haemoglobin spray started
*** Baseline

all 25 sloughy wounds (of varying aetiologies) were slough-free by 4 weeks; in all, 19 healed within this timeframe.

Case study evidence on the effect of the topical spray on DFUs is provided by Chadwick (2014), as well as by a number of congress presentations. In Chadwick's (2014) paper, 2 DFUs with durations of 12 and 9 months healed within 10 and 12 weeks, respectively, following application of the haemoglobin spray. One 12-month-old DFU (Texas score: A3) achieved a 20% reduction in 2 weeks, and the final patient, who also had a Texas A3 12-month-old wound, improved within 12 weeks.

A non-comparative evaluation exploring the efficacy of the haemoglobin spray on pressure ulcers was undertaken by Tickle (2015). The primary outcome measure was the percentage reduction in wound size after 4 weeks, and the secondary outcome measures were the occurrence of pain and any adverse events. After 4 weeks of treatment, 17 out of 18 wounds reduced in size. Although the evaluation design had a 4-week follow-up period, the patients were subsequently informally followed up for 3 months in order to identify how many wounds healed. This article describes these clinical findings.

Original evaluation: summary of design and results

Patients from four separate sites were recruited into the evaluation between November 2014 and January 2015. Inclusion criteria were patients aged ≥18 years with European Pressure Ulcer Advisory Panel (EPUAP) category 2–4 pressure ulcers. Exclusion criteria comprised category 1 pressure ulcers, clinical signs of infection, women who were pregnant or lactating, and an inability to tolerate or receive application of wound dressings. The treatment protocol stipulated that patients should continue to receive the same standard care (pressure relief plus wound dressings, including foams, alginates, Hydrofibers, and hydrogels) as they had before entry, but that after entry, the treatment would include the haemoglobin spray applied at every dressing change.

Data were collected on wound size (including depth), wound-bed characteristics, exudate levels, pain at dressing change, ongoing pain, and the occurrence of any adverse events. A standardised form was used across all four centres to generate consistent data. Ethics committee approval was not required as this was a non-comparative evaluation with a CE-marked product. All patients gave their written informed consent to participate.

The sample comprised 7 males and 11 females with a mean age of 65 years (range: 34–91 years). Nine patients had a sacral pressure ulcer, seven had a heel pressure ulcer, one had an elbow pressure ulcer, and one had a pressure ulcer on the hip. The average wound duration was 11 weeks (range 1 week to ≥52 weeks).

Reduction in wound size

At the end of the 4-week evaluation period, 17 of the 18 wounds had reduced in size. The mean endpoint wound size was 3.39 cm^2 (range: 0.15 cm^2–12 cm^2) compared with a baseline mean of 11.23 cm^2 (range: 0.25 cm^2–52 cm^2). The mean depth decreased from 0.97 cm to 0.37 cm.

Wound-bed characteristics

Slough and granulation tissue were measured as the percentage of tissue present on the wound bed. Exudate levels were assessed as none, mild, moderate, or severe. The mean percentage of slough on the wound bed reduced from 56% to 11% over 4 weeks, while the amount of granulation tissue present increased from a mean of 46% to 66%. There was a concomitant reduction in exudate levels, with 12 wounds (67%) having moderate to heavy exudate levels at baseline, compared with no heavily and 5 moderately (28%) exuding wounds at week 4.

Pain scores

There was also a reduction in pain scores, which were measured on a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (maximum pain). By the end of the evaluation, the mean VAS score for pain at dressing change reduced from 6.2 to 2.5 and that for ongoing pain decreased from 3.7 to 0.9.

Adverse events

No adverse events were recorded in the evaluation.

Three-month follow-up

As stated above, the formal evaluation ended at 4 weeks. However, it was possible to follow up 11 of the patients who continued to receive the haemoglobin spray after the initial 4-week period ended. Of the remainder, four patients were lost to follow up because they were discharged into the community and no longer under the care of the recruiting nurse, one patient died for non-wound-related reasons, and two stopped using the haemoglobin spray because they did not perceive that it was promoting healing. It was thought that there is a clinical value in presenting the healing outcomes of the 11 patients who continued to receive treatment with the haemoglobin spray after the evaluation ended.

The 11 patients were observed for a further 2 months. Of these, 9 of the 11 pressure ulcers healed within 8 weeks (82%), and the remaining two reduced in size—from 30 cm^2 to 7 cm^2 (-77%) and from 6 cm^2 to 4 cm^2 (-33%), respectively. The healing rates for all 11 patients are given in *Table 1* and *Figures 1a* and *1b*. Standard care provided before (i.e. the 4-week run-in period) and during treatment with the haemoglobin spray are summarised in *Table 2*.

Reduction in slough

At baseline, 9 of the 11 wounds were covered in slough, with a mean of 47% coverage (range: 5–100%). The amount of slough present in these wounds reduced markedly by week 4 (mean 14% wound bed covered with slough; range: 20–80%), as previously reported (Tickle, 2015), and only two wounds were still affected by week 8. In 2 wounds, the amount of slough present reduced from 100% to 30% and from 100% to 0% within 4 weeks. The results are illustrated in *Figure 2*.

Exudate

There was also a reduction in the amount of exudate present. The majority of the wounds were producing high levels of exudate at baseline, whereas by week 8, only 2 were exuding, with moderate levels in just 1 patient (*Table 3*).

Adverse events

No adverse events were reported during the 3-month follow-up period.

Pain scores

There was a marked reduction in ongoing pain and pain at dressing change by week 4 (note: 1 patient was paraplegic), as shown below.

Pain at dressing change:

At baseline, 10 of the 11 patients experienced pain at dressing change, with a mean VAS score of 7 (range: 6–10). At week 4, this had reduced to 4 patients, with a mean VAS score of 1.9. In 7 patients, the VAS score fell by ≥6 points between baseline

Table 2. Pressure redistribution and wound dressings used before and during treatment with the haemoglobin spray

Pt. no.	Type of pressure relief used	Wound dressings used		
		Run-in	Weeks 0–4	Weeks 5+
1	Dynamic mattress	Absorbent foam with soft silicone contact layer	Same as run in	Same as run in
2	None	Absorbent foam with soft silicone contact layer	Same as run in	Same as run in
3	None	Absorbent foam with soft silicone contact layer	Same as run in	Same as run in
4	None	Absorbent foam with soft silicone contact layer	Same as run in	Same as run in
5	Dynamic mattress and seat cushion	Calcium alginate and absorbent foam with soft silicone contact layer (week -4); Hydrofiber foam dressing (weeks -3 to 0)	Hydrofiber foam	Hydrofiber foam
6	Dynamic mattress and static heel protectors	Hydrofiber and polyurethane foam (weeks -4 to -2); alginate gel and polyurethane foam (weeks -2 to 0)	Alginate gel and polyurethane foam	Alginate gel and polyurethane foam
7	Dynamic mattress and static heel protectors	Hydrofiber and foam dressing with soft silicone contact layer (weeks -4 to -2); hydrocolloid and foam with soft silicone contact layer (weeks -2 to 0)	Hydrocolloid and foam with soft silicone contact layer	Hydrocolloid and foam with soft silicone contact layer
8	Dynamic mattress and static heel protectors	Polyurethane foam; alginate gel (used with the foam on weeks -2 to 0)	Polyurethane foam and alginate gel	Polyurethane foam and alginate gel
9	Dynamic mattress and static heel protectors	Hydrofiber foam dressing (weeks -4 to -2); absorbent foam with soft silicone contact layer (week -1)	Hydrofiber foam (weeks 0–3); absorbent foam with soft silicone layer (week 4)	Absorbent foam with soft silicone layer
10	Dynamic mattress and seat cushion	Silver-impregnated Hydrofiber (rope) and Hydrofiber foam	Silver-impregnated Hydrofiber (rope) and Hydrofiber foam	Silver-impregnated Hydrofiber (rope) and Hydrofiber foam
11	Dynamic mattress and seat cushion	Absorbent foam with soft silicone contact layer (weeks -4 to -2); Hydrofiber foam (weeks -2 to 0)	Hydrofiber foam	Hydrofiber foam

and week 4. Only 1 patient (no. 7) was still experiencing pain at weeks 8 and 12 (VAS score: 7).

Ongoing pain

At baseline, 10 of the 11 patients were experiencing ongoing wound pain, with a mean VAS score of 5 (range: 2–10). This reduced to 4 patients at week 4 (mean VAS score: 1). In 4 patients, the VAS score fell by ≥6 points during this period. Only one patient (no. 7) was still experiencing pain at weeks 8 and 12 (VAS score: 4).

Discussion

This article describes the healing outcomes achieved in the 11 patients, from Tickle's (2015) evaluation, who continued to be treated with the haemoglobin spray after the original 4-week follow-up period ended. Nine of the 11 wounds healed within 8 weeks and, while the remaining 2 had not healed at 12 weeks, they had decreased markedly in size. The large majority of these wounds were long-standing, with all

Table 3. Exudate levels: baseline versus weeks 4–12

Exudate level	Baseline	Week 4	Week 8	Week 12
None	0	6 (55%)	9 (82%)	9 (82%)
Mild	2 (18%)	4 (36%)	1 (9%)	2 (18%)
Moderate	7 (64%)	1 (9%)	1 (9%)	0
Severe	2 (18%)	0	0	0

but 2 having a baseline duration of 3 months or more. The standard care received by these patients in the 4 weeks before and during treatment with the haemoglobin spray was broadly similar, indicating that the outcomes are attributable to this novel treatment.

The findings also support Bateman's (2015b) observation that use of the haemoglobin spray is associated with a rapid reduction in slough, as only 2 wounds were still sloughy at week 8. In addition, there were no reports of adverse events in the 12 weeks covered here. The clinicians commented that they perceived the key benefits of the spray to be its ability to promote healing and reduce slough, as well as its pain-free application. Some patients also offered feedback, commenting on how happy they were that their ulcer had healed.

It should be noted that this was not a formal evaluation. Nevertheless, taken together, the reduction in wound size, slough, and pain all highlight the possibility of substantially improved healing when using the haemoglobin spray.

Two case studies have been presented to further illustrate clinical experience with the product. Case study 1 concerns one of the 11 patients followed up in this article, and case study 2 was chosen because it highlights the potential role that the spray can play in clinical practice.

Case study 1

This 52-year-old woman is obese and has a history of reduced mobility owing to her size and osteoarthritis in her hips and knees. She has type 2 diabetes that is controlled by metformin The patient informed her community nurse that she had a 'sore spot' on her bottom for approximately 3 months, but was too embarrassed to mention it before. This was the first sign of skin damage to this area, which was caused by repeated episodes of increased pressure and periods of reduced mobility and position change.

The tissue viability specialist assessed and examined the patient, and identified a deep pressure ulcer on the coccyx measuring 3.2 cm × 10.7 cm. The wound bed comprised approximately 70% overgranulated tissue, 10% granulation tissue, and 20% slough. There were moderate-to-high levels of highly viscous, thick exudate, and the peri-wound skin was showing evidence of maceration (*Figure 3*). The wound was extremely painful.

A high-specification pressure-relieving mattress, seat cushion, and repositioning regimen were used to provide pressure relief and assist with wound healing. The community nurses cleansed the wound daily with normal saline, packed it with a Hydrofiber dressing, and then covered it with a foam dressing. Despite this, the pressure ulcer did not reduce in size. It was agreed that the dressing regimen was appropriate for the wound size, tissue type, and exudate volume and type.

At the next assessment, the wound did not appear to be healing. Apart from the high exudate level, there were no obvious signs of infection. The tissue viability specialist decided to use the haemoglobin spray to help promote healing. It was applied at each dressing change after cleansing the wound and before packing it with the Hydrofiber.

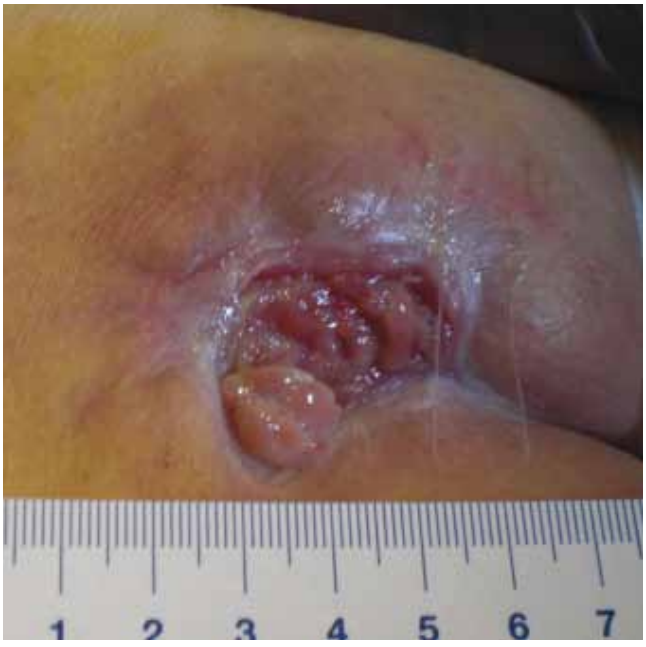

Figure 3. Case study 1: wound before treatment with the haemoglobin spray

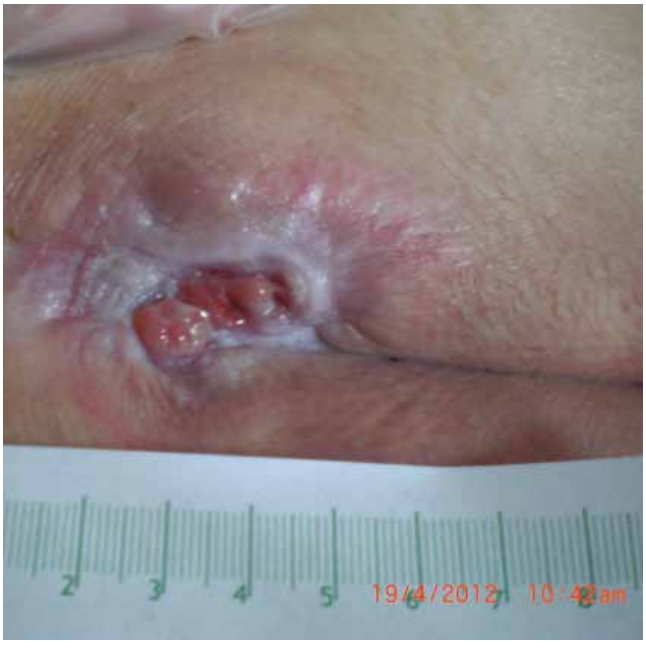

Figure 4. Case study 1: the wound after 4 weeks of treatment with the haemoglobin spray

During the next 4 weeks, the wound size decreased to 1.6 cm in length and 2.0 cm in width (-91%). The tissue type changed to approximately 60% granulation tissue and 40% overgranulation tissue (*Figure 4*). The exudate volume decreased, and its consistency changed to serous low viscosity. The patient also reported a decrease in her pain levels before and after dressing change. The multidisciplinary team concluded that, as the only change to the patient's treatment regimen was use of the haemoglobin spray, this must have influenced its progression toward healing.

Table 4. Case study 2: healing outcomes

	Day 0	Day 7	Day 14	Day 21	Day 28
Malodour	Yes	No	No	No	No
Biofilm/infection	Yes	No	No	No	No
Pain score: VAS 0–10	9	2	0	0	0
Exudate level	Moderate	Low	Low	None	None
Maceration	Yes	No	No	No	No
Slough (%)	10%	None	None	None	None
Erythema (cm^2)	$4cm^2$	None	None	None	None

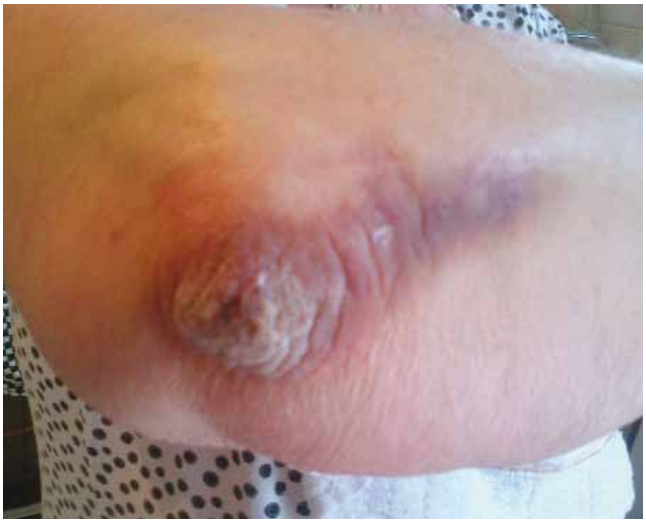

Figure 5. Case study 2: healing wound on day 21

Case study 2

A 68-year-old woman presented to an acute lead nurse in wound care with an 8-month-old, category 3 pressure wound on her left elbow. The patient had a 10-year history of deteriorating chronic obstructive airways disease (COAD) and spent many hours bent forward on her elbows resting on tabletops to aid her respiration ability. Before her acute admission, this wound had been managed by a district nurse. The patient had hypertension and COAD on maximum therapy, was obese, had poor mobility and continued to smoke.

On day 0, slough lined the wound bed, which was mildly malodorous. There was minor maceration on the peri-wound skin, and the wound was extremely painful (VAS score: 9). The haemoglobin spray was applied twice a week to the wound, and an absorbent foam with a soft silicone border was used as primary dressing. *Table 4* demonstrates the progression toward healing. The wound size reduced from day 0 (2.0 × 4.2 × 0.4 cm) to day 21 (0.2 × 0.2 × 0.0 cm) (*Figure 5*).

Conclusion

This article summarises the results of a published evaluation (Tickle, 2015) that measured the reduction in surface area of pressure ulcers achieved following 4 weeks of treatment with Granulox. As the majority of the patients continued using the product after the original evaluation ended, it was considered useful to publish an account of the final healing outcomes. Nine of the 11 wounds healed, and the remaining 2 reduced in size, highlighting the likely substantial healing benefits associated with the use of the haemoglobin spray compared with standard care alone. The next step would be to further substantiate these findings in a comparative clinical trial and quantify the healing outcomes achieved over standard care alone in patients with pressure ulcers. CWC

Declaration of interest: This evaluation was sponsored by Infirst, who provided the product for the study. Infirst did not have any control over the data collection or analysis.

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