The clinical effectiveness of haemoglobin spray as adjunctive therapy in the treatment of chronic wounds

Objective: To investigate wound healing after application of adjunctive topical haemoglobin spray in patients with chronic wounds.
Method: Consecutive patients with a diversity of chronic wounds (defined as <40% reduction in wound size within 4 weeks) were treated with standard wound care plus haemoglobin spray and evaluated over a 26-week period. Results were compared with a retrospective cohort of 50 consecutive patients treated with standard wound care alone.
Results: We evaluated 50 patients for a 26-week evaluation period, during which 45/50 patients (90%) treated with haemoglobin spray were completely healed compared with 19/50 retrospective control patients (38%) (p<0.001). Mean time to complete wound healing was 6.6 weeks (range: 3–22) in the haemoglobin spray group compared with 11.4 weeks (range: 3–25) in the control group (p=0.01). Cox proportional hazards analysis model adjusting for baseline wound size and months wound present also yielded significant treatment effects. Exudate, slough and pain levels were all reduced to a greater extent versus control group.
Conclusion: Haemoglobin spray resulted in a higher number of healed wounds and a faster rate of healing, as well as a positive impact on other wound parameters. These results are in accordance with other published data and supports the adjunctive use of haemoglobin spray in patients with a wide variety of chronic wounds of all sizes and origins.
Declaration of interest: Sharon Hunt and Fredrik Elg provide advisory services to pharmaceutical and other healthcare organisations, including but not limited to, infirst Healthcare Ltd. Infirst Healthcare provided the haemoglobin spray free of charge to the study centre but did not have any influence on the design of the evaluation or the collection of the data. Infirst Healthcare also provided independent support for data management, statistical analysis and medical writing to help the authors publish the results of this evaluation.

chronic wounds • haemoglobin • topical oxygen therapy • wound healing

Wound healing, as a normal biological process in the human body, is achieved through four precisely and highly programmed phases: haemostasis, inflammation, proliferation, and remodelling.[1] Chronic wounds are those that have not proceeded through this wound healing process and have failed to heal following 2–4 weeks of standard care and require further intervention.[2] Chronic wounds have diverse aetiologies but the most common generally tend to fall into four categories: venous leg ulcers (VLUs), pressure ulcers (PUs), diabetic foot ulcers (DFUs) and leg ulcers associated with arterial insufficiency.[3] Chronic wounds can also result from trauma, surgery or burns.

Oxygen and adequate blood supply have long been recognised as being critical for effective wound healing.[4] Restoration of the macro- and micro-circulation is essential for the oxygen delivery needed for the reconstruction of new vessels and connective tissue.[5] Vascular insufficiency and oedema associated with venous stasis causes a reduction in oxygen delivery, and since wound healing processes rely on oxygen, the sustained lack of oxygen in the tissue causes crucial healing processes to stop and antimicrobial resistance to diminish, thereby increasing the risk of uncontrollable infections with the associated risks of amputations and death.[4,5] Few technologies have been found to be effective at delivering improved oxygenation, however, a recently approved technology for use in chronic wounds, topical haemoglobin spray (Granulox, infirst Healthcare Ltd, London, UK) aims to address this challenge by facilitating diffusion of oxygen into the wound bed.[6–9] The mechanism of action of haemoglobin spray, which comprises purified haemoglobin, is based on the use of haemoglobin as an oxygen carrier. It improves the availability of oxygen in the wound by binding atmospheric oxygen and transporting it to the wound bed, aiding diffusion.

Consensus recommendations have been developed to determine where such a topical haemoglobin spray fits into the treatment paradigm[2] and this evaluation was conducted according to these guidelines to determine their use in clinical practice. The results were compared with a retrospective cohort using the same inclusion and exclusion criteria, treated the previous year with standard wound care alone, i.e. before the introduction of haemoglobin spray into the clinic.

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Aim

The primary objective of this real-life evaluation was to investigate wound healing after application of adjunctive topical haemoglobin spray in patients with chronic wounds compared with a retrospective cohort who received standard wound care alone. Other wound healing attributes, including mean percentage wound size reduction compared with baseline, exudate levels, percentage of slough, and pain levels, were also assessed.

Methods

This evaluation was conducted in a single primary care clinic in a large UK general hospital in patients with a variety of chronic wounds. Patients were recruited consecutively in January 2015 and haemoglobin spray was applied twice a week until the wound was healed. The control patients were identified retrospectively in consecutive order from patient notes from the same clinic during the same period the previous year, January 2014. The control patients had to meet the same inclusion/exclusion criteria as the haemoglobin spray patients. All patients were followed for a period of 26 weeks so that the time to healing and any subsequent recurrence (if applicable) could be monitored.

This evaluation was not conducted as a formal clinical study, but rather a 'real-life' assessment of the use of haemoglobin spray in a wound care clinic. Patients were selected for treatment in line with the consensus recommendations developed by Chadwick et al.,[2] which recommend haemoglobin spray treatment if patients have failed to respond after 2–4 weeks of standard care. The same inclusion and exclusion criteria were applied to both patient cohorts. Inclusion criteria comprised of patients with a wound that had failed to heal substantially, defined as <40% reduction in surface area (as measured using a sterile paper ruler) during the last 4 weeks despite standard care, as delivered within the UK NHS Trust. Patients were excluded in line with the product labelling, if they had acute limb ischaemia, infected wounds at baseline, or were pregnant or actively lactating.

Ethics Committee approval was not required at the time the evaluation was conducted, in line with the NHS policy on clinical evaluations of CE-marked products used within their licensed indications without randomisation. Patients were required to give verbal consent following an explanation and review of the product and information leaflet before receiving the haemoglobin spray in line with the Declaration of Helsinki. This procedure was documented by the clinician in the patient notes. For the patients who were under 18 years of age, consent from the parent or guardian was also obtained.

Patients in the treatment group were given standard wound care plus haemoglobin spray, the control group included retrospective chronic wound patients who were selected consecutively during the same period the previous year. Both groups were cared for in the same clinical setting by the same clinical team. Patients in both groups were maintained on the same dressing type they were using before the evaluation i.e. no change in the treatment apart from the addition of the haemoglobin spray in the haemoglobin spray group. Dressings in both groups were generally changed twice per week, with additional dressing changes made in between if needed. In the haemoglobin spray group, the spray was applied by the patient at each dressing change until wound closure. All the haemoglobin spray applications and dressing changes were carried out by the patient or their carer. Dressing changes in the control group were carried out by district nurses, community health-care assistants or tissue viability nurses since this was the standard practice at the time. Debridement in both groups was carried out as needed, based on the opinion of the surgeon or the wound care nurse, with the need for surgical (sharp) debridement being classed as an adverse event.

Data on wound size and wound healing attributes, including exudate levels, percentage of slough, and pain levels, were collected for both groups using a standard data-collection sheet based on the Applied Wound Management Assessment documentation, which is the standard wound care documentation used in the NHS Trust. Wound size was measured using a sterile paper ruler, while exudate levels and percentage of slough were measured evaluated using the Wound Healing and Wound Exudate Continuum.[10] Pain levels in both groups were evaluated using the McGill Pain Index, with the pain levels at the time of the assessment scored on a 10cm visual analogue scale (VAS) from 0—no pain to 10—worse pain possible. All pain assessments were

Table 1. Baseline characteristics

	Haemoglobin spray group (n=50)	Control group (n=50)
Mean age (range), years	51.9 (9–90)	49.7 (8–92)
Gender (male/female), n	22/28	23/27
Mean duration of wound at week 0 (range), months	2.3 (1–8)	3.2 (1–10)
Mean wound size at week 0 (range), cm^2	31.6 (0.2–311)	98.4 (0.6–1492)
Mean pain score	4.6	3.2
Cause of wound (n):		
Trauma	22	19
Active leg ulcers related to chronic venous insufficiency	12	9
Diabetic foot ulcers	3	8
Burns	5	6
Post-surgical wounds	5	5
Pressure ulcers	2	2
Moisture wounds	1	0
Post-infection wounds	0	1

conducted before the dressing change for consistency. The data-collection sheets were completed for each patient whenever they attended the wound care clinic, usually on a weekly basis while the wound was still present. Once the wound had healed the patients were seen on a regular basis by the nursing team as needed (such as for monitoring of underlying conditions).

Statistical analysis

Statistics are reported using a chi-squared test for group level (nominal) data and an unpaired two-tailed t-test for numeric (parametric) values, except where data was clearly not normally distributed, where Mann-Whitney U-tests were computed. Proportions were evaluated using chi-squared tests. Statistical significance was defined as $p<0.05$. Sensitivity analyses to account for possible baseline differences, included a Cox proportional hazard regression model for time to wound healing adjusting for baseline wound size and months wound present, and analysis of covariance (ANCOVA) for wound size reduction, including baseline wound size and months wound present. No adjustments for multiple statistical analysis were made.

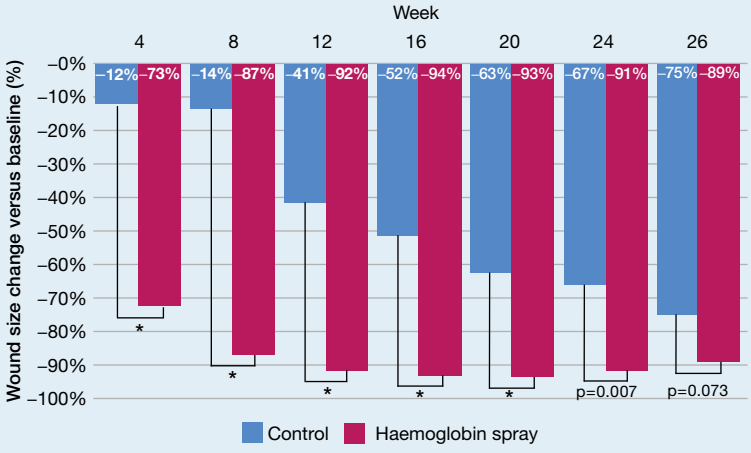
Results

Patient disposition

A total of 100 patients were included in this evaluation: 50 in the haemoglobin spray group, and 50 in the retrospective control group. The demographic details of the patients are shown in Table 1. All patients were followed for 26 weeks, however, four patients were lost to follow-up (all in the control group) and seven patients died (one in the haemoglobin spray group and six in the control group). None of the deaths were related to the wounds or to the treatment the patients received. There were an additional four patients lost to follow-up after eight weeks in the control group, with patients moving and records no longer being available. Apart from the one death, there were no patients lost to follow-up in the haemoglobin spray group.

The most common chronic wounds were due to trauma, including self-harm wounds and ulcers related to chronic venous insufficiency, DFUs and PUs (Table 1). The length of time that the wound had been present before the evaluation varied between the two groups. Wounds had been present for an average of 2.3 months (range 1–8 months) in the haemoglobin spray group compared with 3.2 months (range: 1–10 months) in the control group (difference: 0.9 months, t test p=0.02). The average baseline wound size was also larger in the control group 98.4 cm^2 (range: 0.6–1492 cm^2) compared with haemoglobin spray 31.6 cm^2 (range: 0.2–311 cm^2) (difference: 66.8 cm^2, t-test p=0.09), which was due to two patients in the control group who had very large wounds of >1000 cm^2 at baseline. The median wound size was similar in the two groups, at 9.4 cm^2 in the control group and 7.9 cm^2 in the haemoglobin spray group. If the two patients with the large wounds were excluded from the analysis, then the revised mean size in the control group was 47.8 cm^2, with the difference between the two groups no longer being statistically significant (p=0.42). A non-parametric Mann Whitney U-test, as suggested by the big difference between the means and the medians, indicated there was no significant difference in wound size distribution (Mann-Whitney U-test, p=0.87). Mean pain scores were also different between the two groups at baseline, but in this case the haemoglobin spray group had a higher pain score (mean score: 4.6) compared with the control group (mean score: 3.2) (difference: 1.4, t-test p=0.04).

Fig 1. Mean wound size change versus baseline by week (*p≤0.001)



Wound healing

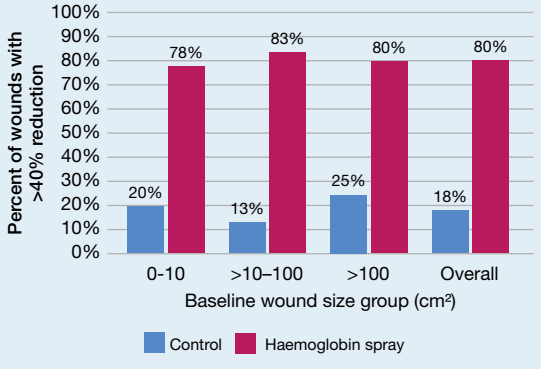
At week 12, 40 out of 50 patients (80%) were fully healed in the haemoglobin group and 11 out of 50 patients (22%) were fully healed in the control group. At the end of the 26-week evaluation period, 45 out of 50 patients (90%) treated with the haemoglobin spray were completely healed compared with 19 out of 50 patients (38%) in the control group (difference: 52%, z-test $p<0.001$). When excluding patients who did not complete the follow-up period due to death or patients moving, the difference was 44% (z-test, $p<0.001$). In the haemoglobin group, the mean time to complete wound healing was significantly faster at 6.6 weeks (range: 3– 22 weeks) compared with 11.4 weeks in the control group (range: 3–25 weeks) (difference: 4.8, t-test p=0.01). These findings of greater and faster wound healing were confirmed in a Kaplan-Meier survival analysis and a Cox proportional hazards analysis model controlling for baseline wound size and months wound present (to take into account differences at baseline), with these results also showing significant treatment effects in favour of the haemoglobin spray group ($p<0.001$).

Differences between the treatment groups were detected by week 1, with a statistical significant difference in terms of mean percentage wound size reduction compared with baseline, mean of 31% reduction in wound size in the haemoglobin spray group versus 5% reduction in the control group

Fig 2. Wound size change versus baseline wound size (cm^2) (weeks 1 to 26)

Sample size at baseline: 0–10 cm^2 n=27 (haemoglobin spray) n=26 (control), >10–100 cm^2 n=18 (haemoglobin spray) n=16 (control), >100 cm^2 n=5 (haemoglobin spray) n=8 (control).
Patients who died or were lost to follow-up are excluded

Fig 3. Wounds achieving >40% reduction in 4 weeks, by baseline wound size



Sample size at baseline: 0–10 cm^2 n=27 (haemoglobin spray) n=26 (control), >10–100 cm^2 n=18 (haemoglobin spray) n=16 (control), >100 cm^2 n=5 (haemoglobin spray) n=8 (control).
Patients grouped by wound size. Analysis excluded 1 patient in the control group who died in week 2

(difference: 26%, t-test p<0.001) and by week 4, the reduction in wound size was 73% for patients in the haemoglobin spray group versus 12% in the control group (difference: 61%, t test p<0.001) (Fig 1). By week 8, this difference had increased to a difference of 87% versus 14% (difference: 73%, t-test p<0.001) and at week 12 it was 92% versus 41% (difference: 51%, t-test p<0.001) in favour of the haemoglobin spray. If the two patients in the control group with very large wounds were excluded from the analysis, results were unaffected, with mean reductions of 14% in the control group and 87% in the haemoglobin group (p<0.001).

A slight increase in mean wound size was seen in the haemoglobin spray group from week 20 to week 26 in 3 patients who stopped haemoglobin spray treatment early before the wound was fully closed and subsequently deteriorated and whose notes recorded an increase in wound size. An additional two patients stopped haemoglobin spray treatment just before achieving wound closure but these patients did not relapse within the evaluation period. By completion of the evaluation at 26 weeks, patients in the haemoglobin spray group had a mean wound size reduction of 89% compared with 75% in the control group (not significant) (Fig 1). To analyse whether the baseline differences in wound size and duration of wound influenced the percentage wound size reduction results, an ANCOVA regression model was fitted with baseline wound size and months wound present as covariates. The treatment effect was still highly significant after adjustment for these baseline factors (p<0.05 at each measured time-point up to week 24).

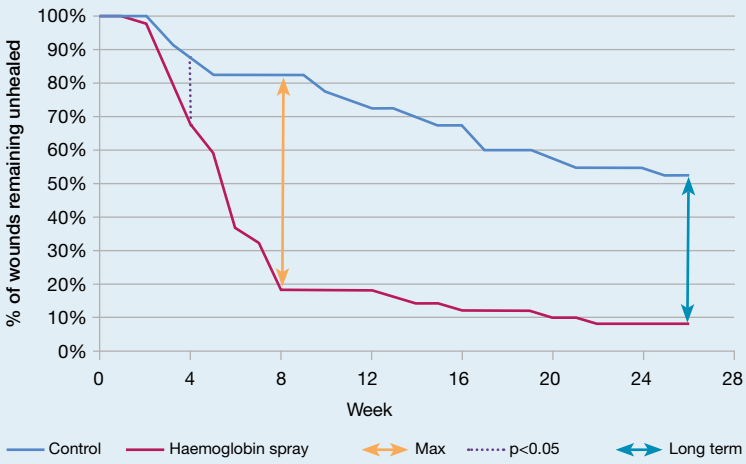
In an analysis of the rate of wound size change by baseline wound size, a wound size reduction of 32% was seen in the haemoglobin group versus 4% in the control group at week 1 for the smallest wound sizes (0–10 cm^2), a wound size reduction of 34% in the haemoglobin group versus 9% in the control group at week 1 for the larger wounds (10–100 cm^2), and for very large wounds (>100 cm^2) a wound size reduction of 16% was seen in the haemoglobin group versus 1% in the control group at week 1 (although it should be noted that the number of patients in some of the groups was small). This pattern of superior wound size reduction in favour of haemoglobin spray could also be seen at all subsequent weeks up to week 26 (Fig 2). It is also of note that approximately 80% of wounds had been reduced by >40% within 4 weeks in the haemoglobin group for all wound size categories, compared with only 13% to 25% in the control group segments (Fig 3).

In terms of the number of wounds that had not healed by completion of the evaluation, i.e. had not achieved full epithelialisation by week 26, there was a significant difference in favour of haemoglobin spray already after 4 weeks (difference: 21%, t-test p=0.03), with the maximum difference of 64% being seen between the groups at week 8 (18% of haemoglobin spray-treated patients had non-healed wounds compared with 82% of control patients). By completion of the evaluation at week 26, there was 44% difference between the two groups, with 8% of haemoglobin spray-treated patients still having wounds that had not healed completely compared with 52% of control patients (Fig 4).

Pain assessment

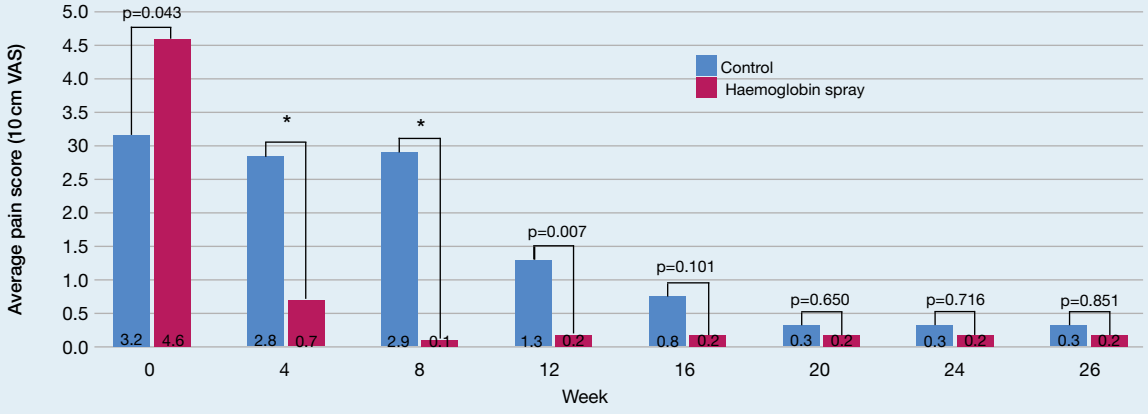
Pain levels were evaluated for all patients who reported pain at baseline (38 patients in the haemoglobin spray group and 32 patients in the control group). Significant benefits were apparent as early as week 1 for haemoglobin spray-treated patients, with a 40% mean reduction in pain scores in the haemoglobin group compared with a 13% in the control group. This difference increased by week 4, where there was an 86% mean reduction in pain scores in the haemoglobin group compared with a 16% reduction in the control group. Average pain scores for each group reflected this trend (Fig 5), with average pain scores of 0.7 and 2.8 for haemoglobin spray versus control patients at week 4 (difference: 2.1, t-test $p<0.05$), which then increased slightly to 2.9 for control patients compared with 0.1 for haemoglobin spray patients at week 8 (difference: 2.8, t-test $p<0.05$). This greater improvement in pain scores in the haemoglobin group was seen despite the average baseline scores being higher for haemoglobin spray patients (4.6) compared with controls (3.2). At the end of the evaluation period, the mean pain scores in the two groups were similar, being

Fig 4. Wounds remaining unhealed (baseline to week 26)



Excluded 5 patients who died in the control group, 5 that were lost to follow-up and 1 patient who died in the haemoglobin spray group (control n=40, haemoglobin spray n=49)

Fig 5. Average reported pain score (baseline to week 26) *p<0.001



Healed wounds were considered pain-free unless reported as painful following healing during follow-up (none were reported). All wounds included up to week of death or loss of follow-up

Fig 6. Mean wound slough coverage (baseline to week 26). Healed wounds were considered as slough-free.*p≤0.001

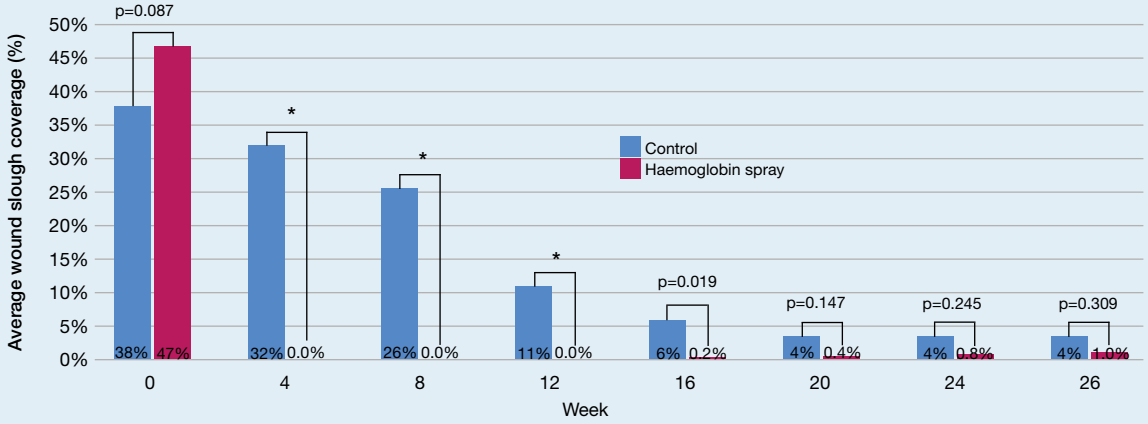
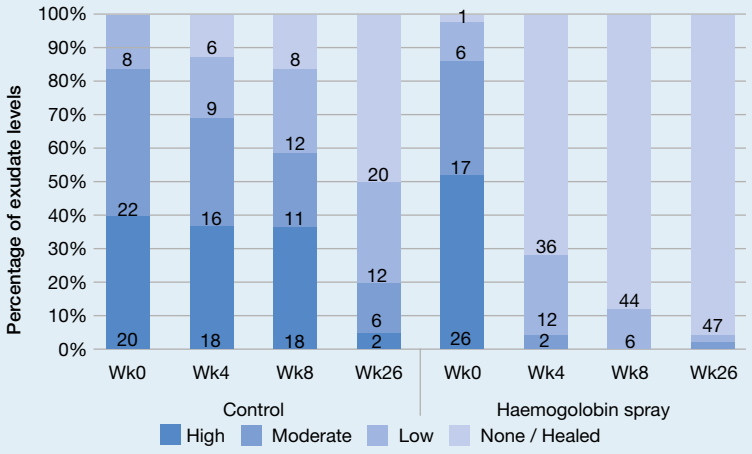


Fig 7. Distribution of exudate levels by week (baseline to week 26)



Including all wounds up to date of death or loss of follow-up

0.2 and 0.3 for haemoglobin spray versus control (not significant), with only one patient still having pain in the haemoglobin group (pain score: 10). This patient stopped using haemoglobin spray in week 16 when the patient's first can of haemoglobin spray ran out. In the control group, four patients had remaining pain at week 26.

Slough levels

As an indicator of wound healing quality, coverage of fibrinous tissue (slough) was assessed using the Wound Healing Continuum.[10] At baseline, mean slough coverage was slightly higher at 47% in the haemoglobin spray group compared with 38% in the control group (difference: 9%, t test p=0.09). By week 4, slough was completely eliminated in the haemoglobin spray group, while in the control group 39 wounds (80%) remained sloughy and with a 32% mean slough coverage. This difference between the groups persisted in favour of the haemoglobin spray group at all timepoints up to week 16 (t-test, p<0.05) (Fig 6). There was a slight re emergence in slough levels between week 16 and week 26 in the haemoglobin spray group, which appeared in the 3 patients who stopped using haemoglobin spray early before their wounds were fully healed and who subsequently suffered wound deterioration and associated slough re-emergence. There was no slough recurrence in any of the wounds that continued treatment with the haemoglobin spray, with all haemoglobin treated wounds being slough free from week 4 onwards.

Exudate levels

To provide an indication of wound management complexity, persistency of wound exudate levels was evaluated using the Wound Exudate Continuum.[10] In the haemoglobin spray group, patients with high or moderately high levels of exudate at baseline experienced a rapid reduction following haemoglobin spray treatment. At baseline, 43 patients (86%) in the haemoglobin group had high or moderately high levels of exudate compared with 42 patients (84%) in the control group, but by week 4, only 2 patients (4%) in the haemoglobin group had high or moderately high levels of exudate compared with 34 patients (68%) in the control group (p<0.001) (Fig 7).

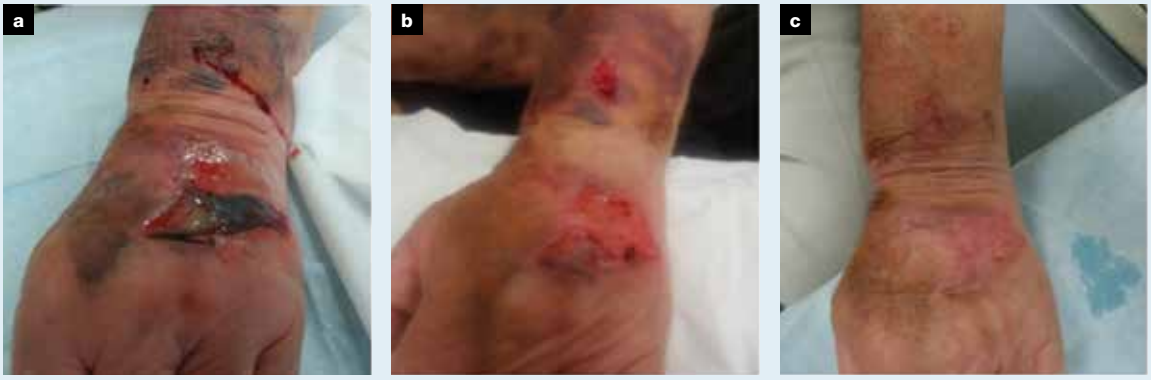
Adverse events

There was a total of 16 wound-related events in the control group, but no events in the haemoglobin spray group. The events in the control group comprised eight unplanned surgeries for wound debridement, and eight wound infections that required antibiotic treatment.

Discussion

Chronic wounds can have a significant negative impact on patients' quality of life and wellbeing, both physically and psychologically. Patients with chronic wounds may experience pain, exudate and odour, often resulting in poor sleep, loss of mobility and social isolation, as well as negative emotions such as stress, concern about physical symptoms, lack of self-worth and despair.[11–13] These factors can have life-changing consequences, with patients giving up hobbies, having

Fig 8. Photographs from patient with chronic wound treated with haemoglobin spray. Patient with chronic wound (due to trauma) at day 0 (**a**). Week 2 following haemoglobin spray treatment (**b**). Week 4 following haemoglobin spray treatment (**c**)



reduced contact with family and friends and, for some, loss of income.[12,13]

It has long been recognised that local oxygen delivery is crucial to successful wound healing since wound tissue requires a constant supply of oxygen to meet the increased metabolic demands of the healing process,[5] but the body has no capacity for oxygen storage.[14–16] Without oxygen, developing tissue cells can become inert and dysfunctional, resulting in wounds becoming static, necrotic and sloughy.[17] Enhanced blood flow through revascularisation, angioplasty or bypass grafts are broadly recognised as effective but not all patients are suitable for treatment. This is particularly relevant for elderly patients, who are more prone to chronic non-healing wounds, and for whom there are substantial risks associated with performing surgical procedures since increasing age has been found to be an important risk factor for post-operative morbidity and mortality.[18]

Non-interventional oxygen therapies, such as topical or hyperbaric oxygen therapies, have only had modest results, possibly due to the challenges in achieving diffusion of oxygen into the wound bed[19] and, in the case of hyperbaric oxygen therapy, are also associated with significant risks.[20] However, emerging technologies present novel approaches to future wound care.

A novel approach to wound care is an adjunctive topical haemoglobin wound spray (Granulox) that aids wound healing by acting as an oxygen transporter, facilitating diffusion from the surrounding air and improving oxygen availability in the wound bed.[7–9] Studies to date suggest that haemoglobin spray can achieve substantially increased oxygen levels in tissue in as little as 20 minutes.[21] Furthermore, improved healing associated with topical haemoglobin has been shown in controlled studies on lower limb wounds,[6,8] and a number of recent UK case series evaluations investigating chronic ulcers have also shown effectiveness of haemoglobin spray in promoting healing.[17,21–24]

Here, patients included in the evaluation presented with wounds resulting from trauma (including self-harm wounds), a variety of ulcer types, burns, and postsurgical wounds. A retrospective control group from the same clinical setting over the same period in the previous year was used for comparison. The only known difference in care between the groups was that for the control group the dressing changes were typically done by a district nurse, community health-care assistant or tissue viability nurse, whereas the dressing changes in the haemoglobin spray group were conducted by the patient or their regular carer. This difference is not thought to have favoured the haemoglobin spray group although high levels of patient satisfaction in terms of ease of use and overall experience associated with self-care use of haemoglobin spray have been previously reported.[17]

Results from this evaluation showed improvement in wound healing over the entire 26-week follow-up period when haemoglobin spray was added to the standard wound care regimen. Mean time to complete wound healing was also significantly shorter in the haemoglobin group (6.6 weeks) compared with the control group (11.4 weeks). Most patients treated with standard wound care alone did experience wound healing over the course of the evaluation. However, the accelerated healing in the haemoglobin spray group resulted in substantial benefits both for patients, in terms of pain reduction and exudate levels, and for care providers in terms of reduced resource needs. Fig 8 shows the improvement in a patient treated with haemoglobin spray.

Rapid wound healing (mean time to complete wound healing of 6.6 weeks in the haemoglobin group compared with 11.4 weeks in the control group) also resulted in associated improvements in indicators of wound healing quality and complexity such as slough and exudate levels, as well as on pain levels. These effects, particularly on slough levels, suggest that the additional oxygen may facilitate the natural inflammatory response to infection and accelerate the wound-healing process.

However, it is important to note that increased demands for oxygen will be seen throughout the wound healing process[25] and haemoglobin spray treatment must continue until full wound closure is achieved, as premature discontinuation can result in a wound returning to a state of hypoxia and wound healing stopping or worsening. This may have been the case in those patients in this evaluation who stopped treatment with haemoglobin spray prematurely before complete wound healing, however, this would need to be investigated more fully to determine if there were any other underlying factors present that may have been a barrier to effective wound healing. Of the five patients who stopped haemoglobin spray early, one patient stopped in the week just before wound closure was observed at week 16. Of the remaining four patients, three worsened and for the last remaining patient healing slowed substantially, taking another four weeks to completely heal, despite having achieved 97% wound size reduction in the preceding 16 weeks using the haemoglobin spray. However, there were no wound recurrences recorded during the follow-up period.

Fewer wound infections and surgical interventions were seen throughout the study in the haemoglobin spray group compared with the control group, suggesting that accelerated healing through increased oxygen diffusion may reduce infection levels and have a positive impact on the frequency of surgical debridement. This is an interesting finding that needs to be verified in further studies.

Limitations of the evaluation

This evaluation uses a prospective evaluation group and a retrospective control group as comparison. It must therefore be acknowledged that some of the results obtained may not be as robust as they could be in a formal randomised, fully blinded clinical study.

There was a difference between the groups in terms of wound management, since dressing changes in the

control group were conducted by a health-care professional, while haemoglobin spray patients generally self-treated or were treated by their carer, which reflects a change in the departmental practices over time. As such, the authors acknowledge that future well-designed, prospective, randomised studies may reduce any potential bias changes in clinical practice between the two cohorts, no matter how small. Finally, in this evaluation, we used a disposable paper ruler to measure wounds as this is a simple and conventional method for quantifying wound size whereby the maximal length is multiplied by the maximal perpendicular width and $\pi/4$ to calculate area (in the shape of an oval). However, it must be acknowledged that this technique can prove inaccurate and does not fully account for changes in wound shape. The precision and reliability of digital planimetry over more conventional methods of ruler measurements and acetate tracings have been demonstrated and may be considered for future studies.[26]

Conclusion

The advantage of this real-life evaluation is that it gives a real insight into the potential benefits of adopting haemoglobin spray in routine clinical practice, however, no procedures were pre-specified or mandated and standard care management was based on individual patient need. Furthermore, exclusion criteria were minimal and, as such, patients were included with a wide variety of underlying conditions, including mental health issues in the patients with self-inflicted trauma wounds, thereby ensuring a wound population representative of the real-world caseload in a primary care setting. In conclusion, the results of this in patients with a diversity of persistent chronic wounds are positive and support the addition of haemoglobin spray to standard wound care regimens. It is of particular note that the haemoglobin spray was effective across a broad selection of chronic wounds, including trauma wounds, burns, and ulcers resulting from vascular insufficiency, as well as in a range of wound sizes from $<10\,cm^2$ to $>100\,cm^2$, highlighting the versatility of the treatment. The incorporation of haemoglobin spray technology into standard wound care regimens not only resulted in rapid wound healing, but was also associated with significant reductions in pain, exudate and slough levels, which are important factors for patients as well as the treating clinicians. However, further well-designed, controlled clinical studies are required to support these clinical findings and to further establish the mechanism by which improving oxygen levels using haemoglobin spray reduces pain, exudate and slough levels. **JWC**

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Reflective questions

- For what type of chronic wounds has adjunctive haemoglobin spray been shown to be effective?
- When does a wound become 'chronic' and warrant consideration of adjunctive therapies?
- How long do you need to maintain treatment to lead to full wound closure?

References

1 Guo S, DiPietro LA. Factors affecting wound healing. J Dent Res 2010; 89(3):219–229. https://doi.org/10.1177/0022034509359125
2 Chadwick P, McCardle J, Mohamud L et al. Appropriate use of topical haemoglobin in chronic wound management: consensus recommendations. Wounds UK/EMWA Special. 2015; 1-4
3 Markova A, Mostow EN. US skin disease assessment: ulcer and wound care. Dermatol Clin 2012; 30(1):107–111. https://doi.org/10.1016/j.det.2011.08.005
4 Whitney JD. The influence of tissue oxygen and perfusion on wound healing. AACN Adv Crit Care 1990; 1(3):578–584. https://doi.org/10.4037/15597768-1990-3013
5 Gottrup F, Dissemond J, Baines C. et al. Use of oxygen therapies in wound healing. J Wound Care 2017; 26(suppl 5): S1–S43. https://doi.org/10.12968/jowc.2017.26.Sup5.S1
6 Arenberger P, Engels P, Arenbergerova M et al. Clinical results of the application of a hemoglobin spray to promote healing of chronic wounds. GMS Krankenhaushyg Interdiszip 2011; 6(1): Doc05. https://doi.org/10.3205/dgkh000162
7 Dissemond J, Kröger K, Storck M, et al. Topical oxygen wound therapies for chronic wounds: a review. J Wound Care 2015; 24(2):53–63. https://doi.org/10.12968/jowc.2015.24.2.53
8 Arenbergerova M, Engels P, Gkalpakiotis S et al. Effect of topical haemoglobin on healing in patients with venous leg ulcers. EWMA Journal. 2013; 13(2):25–30.
9 Scholander PF. Oxygen transport through hemoglobin solutions. Science 1960; 131(3400):585–590. https://doi.org/10.1126/science.131.3400.585
10 Gray D, White R, Cooper P, Kingsley A. Applied wound management and using the wound healing continuum in practice. Wound Essentials 2010; 5:131–129. http://bit.ly/2usUKtt
11 Hamer C, Cullum NA, Roe BH. Patients perceptions of chronic leg ulcers. J Wound Care 1994; 3(2):99–101. https://doi.org/10.12968/jowc.1994.3.2.99
12 Bianchi J. Quality of life. In: The missing link: the key to improved wound assessment. An educational supplement in association with BJN. MA Healthcare Ltd, London, 2012; pp 10-11
13 Upton D, Hender C. The cost of mood disorders in patients with chronic wounds. Wounds UK 2012; 8(1):107–109.
14 Schreml S, Szeimies RM, Prantl L, et al. Oxygen in acute and chronic wound healing. Br J Dermatol 2010; 163(2):257–268. https://doi.org/10.1111/j.1365-2133.2010.09804.x
15 Rodriguez PG, Felix FN, Woodley DT, Shim EK. The role of oxygen in wound healing: a review of the literature. Dermatol Surg 2008; 34(9):1159–1169.
16 Sen CK. Wound healing essentials: Let there be oxygen. Wound Repair Regen 2009; 17(1):1–18. https://doi.org/10.1111/j.1524-475X.2008.00436.x
17 Hunt SD. Topical oxygen-haemoglobin use on sloughy wounds: positive patient outcomes and the promotion of self-care. Wounds UK. 2015; 11(4):90–94.
18 Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg 2006; 203(6):865–877. https://doi.org/10.1016/j.jamcollsurg.2006.08.026
19 Winfeld B. Topical oxygen and hyperbaric oxygen therapy use and healing rates in diabetic foot ulcers. Wounds 2014; 26(5):E39–E47. http://bit.ly/1VSqu0C
20 Plafki C, Peters P, Almeling M, et al. Complications and side effects of hyperbaric oxygen therapy. Aviat Space Environ Med 2000; 71(2):119–124.
21 Petri M, Stoffels I, Jose J, et al. Photoacoustic imaging of real-time oxygen changes in chronic leg ulcers after topical application of a haemoglobin spray: a pilot study. J Wound Care 2016; 25(2):87–91. https://doi.org/10.12968/jowc.2016.25.2.87
22 Tickle, J. A topical haemoglobin spray for oxygenating pressure ulcers: A pilot study. Br J Comm Nurs 2015; 20(Suppl Wound Care): S12-S18. https://doi.org/10.12968/bjcn.2015.20.Sup3.S12
23 Chadwick P. Pilot study: haemoglobin spray in the treatment of chronic diabetic foot ulcers. Wounds UK. 2014;10(4):76–80. http://bit.ly/1PVVcnW
24 Bateman SD. Topical haemoglobin spray for diabetic foot ulceration. Br J Nurs 2015; 24(Suppl 12):S24–S29. https://doi.org/10.12968/bjon.2015.24.Sup12.S24
25 Castilla DM, Liu Z-J, Velazquez OC. Oxygen: implications for wound healing. Adv Wound Care (New Rochelle) 2012; 1(6):225-230. doi:10.1089/wound.2011.0319
26 Khoo R, Jansen S. The evolving field of wound measurement techniques: A literature review. Wounds 2016; 28(6):175–181