Expected outcomes from topical haemoglobin spray in non-healing and worsening venous leg ulcers

• **Objective:** To evaluate the effect of topical haemoglobin spray on treatment response and wound-closure rates in patients with chronic venous leg ulcers.

• **Method:** A linear regression model was used to forecast healing outcomes over a 12-month period. Simulated data were taken from normal distributions based on post-hoc analysis of a 72-patient study in non-healing and worsening wounds (36 patients receiving standard care and 36 receiving standard care plus topical haemoglobin spray). Using a simulated 25,000 'patients' from each group, the proportion of wound closure over time was projected.

• **Results:** Simulation results predicted a 55% wound closure rate at six months in the haemoglobin group, compared with 4% in the standard care group. Over a 12-month simulation period, a 43% overall reduction in wound burden was predicted. With the haemoglobin spray, 85% of wounds were expected to heal in 12 months, compared with 13% in the standard care group.

• **Conclusion:** Topical haemoglobin spray promises a more effective treatment for chronic venous leg ulcers than standard care alone in wounds that are non-healing or worsening. Further research is required to validate these predictions and to identify achievable outcomes in other chronic wound types.

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venous leg ulcer; topical haemoglobin; Granulox; wound healing

Chronic wounds are defined as those that have failed to 'proceed through an orderly and timely repair process to produce anatomic and functional integrity'.[1] Using a temporal perspective, some regard a chronic wound as one where healing time is longer than three weeks.[2] Guidelines suggest that patients with a wound size reduction of less than 40% within four weeks despite standard care should be re-evaluated and other treatments considered.[3]

A large proportion of venous leg ulcers (VLUs) remain unhealed for more than six months, with studies suggesting 20–50% persist for more than six months even when receiving standard compression treatment.[4] VLUs are the consequence of chronic venous insufficiency, where venous stasis and associated oedema lead to reduced blood flow. The resulting elevation in venous pressure leads to reduced capillary density[5] and the associated oedema impedes the diffusion of oxygen from the remaining capillaries to the tissue cells, both contributing to local tissue hypoxia.[6] Tissue hypoxia is a common cause of pathological processes in wound healing such as peripheral arterial occlusive disease, chronic venous insufficiency and diabetes mellitus.[7]

Oxygen demand by tissues increases during all phases of wound healing (inflammation, granulation, angiogenesis, re-epithelialisation and tissue reorganisation).[7] Improving the blood and oxygen supply to chronic hypoxic wounds has been shown to achieve positive outcomes via re–vascularisation surgery in peripheral arterial disease,[8] hyperbaric oxygen therapy[9] and, most recently, topical application of haemoglobin.[10]

Haemoglobin has the unique characteristics of absorbing oxygen in an oxygen-rich environment and releasing oxygen in an oxygen-poor environment. Haemoglobin, when added to a water solution *in vitro*, has been shown to improve oxygen transport by more than eight times in an oxygen-poor environment relative to no haemoglobin.[11]

In a chronic VLU study,[10] wounds that had previously failed to improve despite standard care and hospitalisation were treated for 13 weeks with a topical haemoglobin spray, Granulox, which contains 10% carbonylated haemoglobin, 0.9% NaCl, 0.7% phenoxyethanol, 0.05% N-acetylcysteine in aqueous solution.

In this prospective, rater-blinded, randomised controlled trial, all wounds received standard care of short stretch graduated external compression bandaging (Idealbinde, Hartmann, Heidenheim, Germany) and a non-medicated nanofibre dressing (Nanotextile, Elmarco, Liberec, Czech Republic) with gauze

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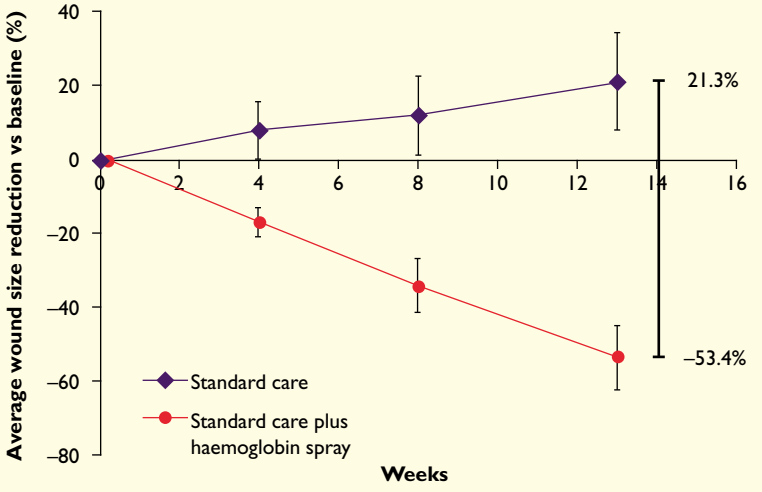
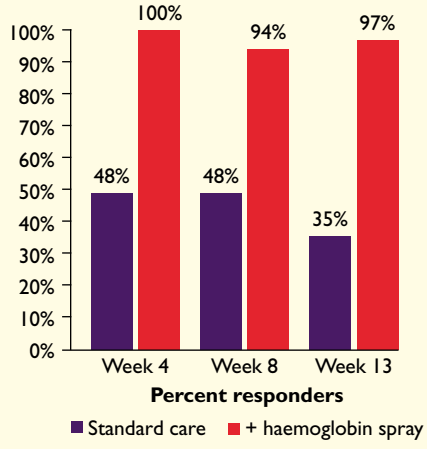
Fig 1. Average wound size change by week vs baseline in previously non-healing wounds; error bars represent 95% confidence interval



fixation. The control group (n=36) received standard care plus sham treatment with normal saline (0.9%) spray and the experimental group (n=36) received standard care plus the haemoglobin spray. Patients were recruited over a four-month period and those who had shown no improvement in wound size in the two-week run-in period while receiving standard care in a specialist wound care unit were included in the study. Patients who had vasculitis or non-vascular leg ulceration, who were receiving systemic antibiotics, corticoid steroids or oral immunosuppressants, were pregnant, had infected wounds or an ankle–brachial pressure index <0.8 were excluded from the study. Compression therapy was started two weeks before study inclusion, if not alread. Each subject received daily dressing changes and reapplication of bandages. The mean duration of ulcers before treatment was two years, with a range of three months to six years.

Fig 2. Treatment response, any wound size reduction, in previously non-healing wounds at weeks 4, 8, 13



Changes to the wound surface area were recorded over 13 weeks in both groups. Wound margins were traced onto a triple-layer film and electronically scanned, and the wound surface area was measured using computer-aided analysis. The mean reduction in the experimental group (haemoglobin spray group) showed a 53% (week 0 = 18.6cm^2, week 13 = 10.2cm^2) wound size reduction ($p<0.0001$) compared with an enlargement of 21.3% (week 0 = 17.5 cm^2, week 13 = 20.2 cm^2) in the standard care group over the same period (Fig 1). Overall, there was a 75% difference in average wound size reduction between the two groups.

Objective

Using the data acquired, we wanted to evaluate the effect of topical haemoglobin spray on the observed treatment outcomes in a large patient population with chronic VLUs.

Method

Post-hoc analysis of data

Three key clinical questions were formulated:

- What treatment response rates can be expected?
- What healing outcomes can be expected beyond the initial trial period of 13 weeks?
- What are the implications for wound care?

Based on a post-hoc analysis of the 72-patient study,[10] a linear regression model was used to forecast healing outcomes over a projected 12-month period. Simulated data were taken from normal distributions based on data from the 31 patients who completed the study in the standard care group plus sham spray (standard care group) and the 34 patients who completed the standard care plus topical haemoglobin spray study group (haemoglobin spray group). The simulation was based on 25,000 'patients' from each group and the proportion of wound closures over time was projected.

Treatment response data used for stimulation

In the original study[10] a treatment response rate of 100% at four weeks was found in the haemoglobin spray treated group compared to 48% in the standard care group. At weeks 8 and 13 the results (Fig 2), show a sustained difference in response rate of 46% and 62%, respectively.

Of 34 patients in the haemoglobin spray group, 33 showed a reduction in wound size by week 13 (97%), while in the standard care group, a reduction in wound size was seen in 11 of 31 patients (35%) who completed the trial at week 13. At 13 weeks, one patient (3%) in the haemoglobin spray group had an enlarged wound while 20 of the 31 patients (65%) in the standard care group had an enlarged wound.

Post-hoc responder analysis

Responder analysis was conducted by counting the number of patients who achieved any reduction in wound size versus the baseline at week 4, relative to all patients who completed the study for each treatment group. The analysis was repeated for weeks 8 and 13.

No response data were received for the two patients who had dropped out of the study in the haemoglobin spray group or the five patients who had dropped out of the standard care group.

Wound healing trajectory simulation

The simulation approach used a three–step process with: (S1) tests for normality of healing outcomes achieved at 13 weeks for each of the two study groups as a basis for selecting an appropriate healing distribution (Shapiro-Wilk test); (S2) model selection based on regression of the observed average wound size reductions; and (S3) sampling of wound healing trajectories from the expected distributions at week 13 and projecting trajectories to wound closure using the healing trajectory method selected.

Wound care burden simulation

Using the simulation model developed, the total number of 'open wound weeks' for each treatment group was evaluated for the full range of the confidence interval of outcomes observed in the post-hoc analysis. The resulting difference in overall open wound weeks provides an indication of expected implications for overall clinical caseload.

Results

S1: selecting a method to predict time to wound closure

The literature suggests that healing rates at four weeks are reliable predictors of positive healing outcomes[12] and that a simple metric of percent wound-size reduction is nearly as accurate as more complex logarithmic ratios.[13]

Relative to linear wound size reductions expressed as a percentage reduction compared with baseline, wound healing tends to slow down just before wound closure and it is this behaviour that logarithmic functions can capture. A logarithmic function is a form of exponential decay that gradually slows to reflect a decrease in the rate of healing. Donohue and Falanga[14] showed that there was little practical difference in outcome prediction accuracy between logarithmic models of epithelial migration and a linear model in a study across more than 25,000 patients. Analysis of the data in the Arenbergerova et al. study[10] shows that the average healing rate observed at week 4 is a reliable predictor of the average healing at weeks 8 and 13. This is demonstrated by the high correlation coefficient achieved from a linear regression of the average healing rates achieved at weeks 4, 8 and 13 at R^2=0.999 for the haemoglobin spray group and R^2=0.985 for the standard care alone group. These results suggest that using a simple linear model can be justified.

A linear model would be more conservative in quantifying a difference between the two groups. In practice, the linear model underestimates time to healing in both groups, with the underestimation in the standard care group greater than in the haemoglobin spray group. This is due to the non-linear relationship between the change in rate of healing and time to wound closure. The linear projection approach chosen will therefore underestimate the difference between expected healing times for the haemoglobin group and the standard care group.

For the purpose of this exercise, a linear projection methodology was adopted, as it would not falsely overstate the benefits achievable through haemoglobin treatment.

S2: recognising the non-linear influence of variations in healing speed

As the wound healing rate slows, the time to wound closure will get disproportionately longer. As such, it is important to know not only the average wound healing rates achieved but also the variation in wound healing rates. A wider variation in the distribution of wound healing rates will create a disproportionately longer 'fat tail'. As Fig 3 shows, a 25% slower wound healing rate will increase the time to healing by much more than 25%. Similarly, a 25% increase in healing rate in a slower healing wound will have a much bigger impact than the same 25% increase would have for a faster-healing wound.

To reflect the expected time to healing accurately, it is not possible to simply take the average or median healing rate. The analysis of an expected healing

Fig 3. Healing time difference from same increase/decrease in healing speed

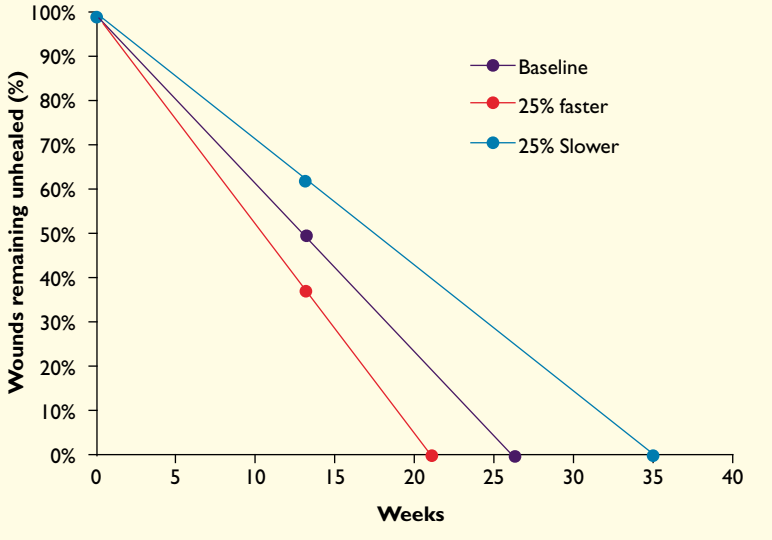
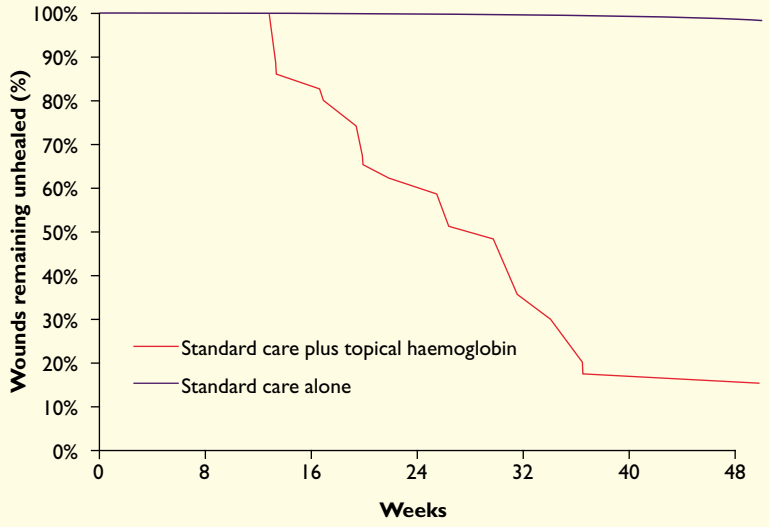


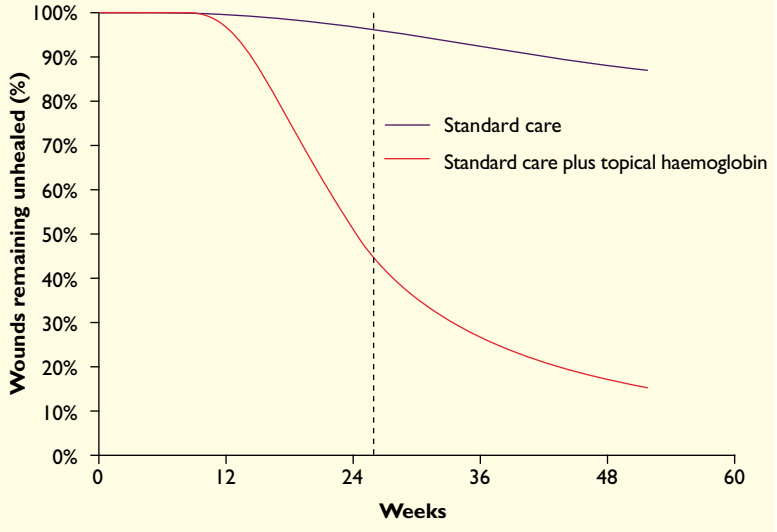
Fig 4. Linearly projected wound persistency by treatment group in previously non-healing wounds



trajectory must consider the variation in healing speeds achieved within each group.

If a linear healing trajectory is applied to each patient in each group, the expected time to wound closure may be plotted for each group. It is important to remember that the wound healing rate often slows down just before wound closure and that final wound closure is likely to occur slightly later than the linearly predicted closure time.[15] The proportion of wounds healed at six months can be estimated at 47.1% (n=16/34) in the haemoglobin spray group and at 0.0% in the standard care group. At 12 months, this increases to 85.3% in the haemoglobin spray group (n=29/34), and 3.2% in the standard care group (n=1/31). Fig 4 shows the projected wound persistency for each group. While these results are clearly statistically significant, the question of reliability persists.

Fig 5. Wound persistency from simulated populations of 25,000 patients for each treatment group in previously non-healing wounds



S3: Simulating healing outcomes for a larger patient population

To simulate the full range of outcomes and time to wound closure for each treatment group, it is necessary to sample 'new' patients from a distribution that is in line with the observed and expected variance in healing rates. To further test the sensitivity of the results, it is also necessary to consider the confidence intervals for the observed means in each treatment group. Finally, a statistical distribution model that can be used to sample simulated 'patients', in accordance with predictions made from the observed results, needs to be selected.

To select a statistical distribution model, the healing outcomes for the two groups were analysed for significant difference from a normal distribution at 13 weeks using Shapiro-Wilk test ($p<0.05$) and Q–Q plots to identify outliers. The Shapiro-Wilk showed that the test for normality could not be rejected for the haemoglobin spray group ($p<0.17$), so a normal distribution can be reliably used to sample patients. However, the standard care group does not pass the test for normality, with more patients showing substantial worsening than the normal distribution would predict and one outlier showing substantial improvement. This drives up the standard deviation, so the observed healing rate distribution in the standard care group fails tests for normality ($p<0.01$), as shown in Table 1.

Justification for use of the normal distribution to sample patients in the simulated trial

Although the data from the standard care group fails the test for normality, a normal distribution was used to sample patients in both groups. This was considered suitable because a normal distribution model for the standard care group predicts a healing rate of 12.4% at 12 months, which is higher than the 3.2% observed in the standard care alone group (i.e. the trajectories for each of the actual 31 patients in the study). Normal distribution should

Table 1. Shapiro-Wilks test for normality at 13 weeks

	Standard care plus topical haemoglobin	Standard care
W	0.96	0.90
p–value	0.17	0.01
α	0.05	0.05
Normal	Yes	No

therefore be considered as a conservative model, reducing the difference, in terms of estimating the possible difference in healing outcomes between the haemoglobin spray and the standard care group.

Using the observed normal distributions in outcomes from the trial, a large number of wound healing trajectories, 25,000, were simulated using the mean healing rate at 13 weeks for each group and projected through to the expected time of wound closure. The results show a median time to healing of 24 weeks for the haemoglobin spray group of just under six months. It was not possible to estimate a median healing time for the standard care group as fewer than half of the patients were predicted to go on to complete healing.

Of the simulated wounds in the standard care group that were predicted to heal within the first 12 months, the median healing time was 32 weeks, but only 12% were healed, compared with 85% in the haemoglobin spray group. The simulation further suggests that 55% of patients in the haemoglobin spray group will achieve wound closure by 26 weeks. This compares with 4% in the standard care group. At 12 months, 85% of the wounds in the haemoglobin spray group were closed, versus 12% on standard care group (Fig 5).

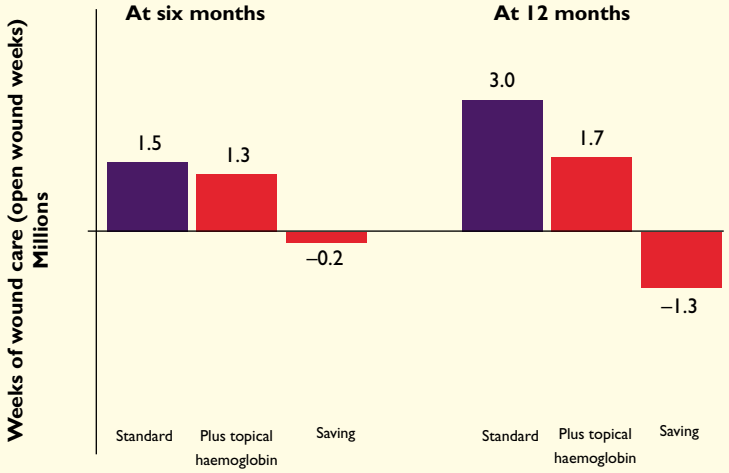
These results will vary slightly, depending on the samples drawn but multiple runs of the same large number of simulations reveal very small variations due to the large number of patients simulated.

Wound burden: best and worst case scenarios

With an increased rate of healing and reduced variability in healing outcomes, a faster time to wound closure should translate into an overall reduction in the wound care burden. Indeed, the average number of wound care weeks that are needed over a six and 12 month-period show a rapid decrease when haemoglobin spray treatment is introduced. An average of 22 open-wound weeks are observed in the haemoglobin spray group compared to an average of 26 weeks in the standard care group over the first six months, a 15% reduction. Over a 12-month period, a 43% reduction in the overall number of open–wound weeks in the haemoglobin spray group compared with the standard care treatment group is found. At 12 months, assuming effective recurrence prevention, only 15% of patients remain unhealed in the haemoglobin spray group compared with 88% of patients remaining unhealed in the standard care alone group.

The prevalence of chronic VLUs in the UK is estimated to be 0.1–0.3%.[15] Applying the lower end of this estimate (0.1%) to the UK population of 60 million would suggest a reduction of 0.2 million wound–care weeks within six months and 1.3 million care weeks within 12 months (Fig 6). These projections have not been adjusted to account for: the expected slowing of wound healing before wound closure; the possible need to treat patients for other reasons; or the systematic underestimate in the difference between the groups as discussed above. The real-life difference in such a large population may be greater or smaller.

Fig 6. Wound persistency from simulated populations of 25,000 patients for each treatment group in previously non-healing wounds



To test these predictions of potential savings for reliability, the analysis was repeated across the minimum and the maximum points in the 95% confidence interval of the observed healing rate outcomes at 13 weeks for both groups. That is, the analysis was repeated using the 'best' value within the 95% confidence interval for the standard care group and compared with the expected 'worst' value for the standard care plus haemoglobin spray group. This is therefore a 'worst case' scenario; put simply, there is a 99.75% probability that the results attained would be better than this level. The results, shown in the 0.25% column in Table 2, suggest that, even in this case, there is a 3.2 times higher risk of a wound remaining unhealed under standard care versus standard care plus topical haemoglobin spray..

Discussion

Post-hoc analysis of results in the manner used in this study is driven by assumptions. Although linear models have been found to predict healing outcomes reliably in more than 70% of cases after four weeks,[17] the simulation approach in this paper does not fully consider the expected slowing of wound healing in the weeks before wound closure and therefore underestimates the time to full epithelialisation by several weeks. However, this slowing of healing would not be expected to occur over a shorter time in the standard care group and, as such, would suggest even larger benefits could be achieved with haemoglobin spray treatment compared with standard care alone.

Table 2. Simulated healing outcomes at 6 and 12 months for best estimate, and 5% worst outcome for topical haemoglobin group, 5% best for standard care alone are and 0.25% worst likely combined outcome for topical haemoglobin.

Outcome	Six months				12 months			
	Best estimate	Topical haemoglobin worst 5%	Standard care best 5%	0.25% (5% and 5%)	Best estimate	Topical haemoglobin worst 5%	Standard care best 5%	0.25% (5% and 5%)
Standard care alone								
Healed (%)	3.7%	-	7.7%	7.9%	12.7%	-	20.8%	21.1%
Mean open wound weeks	25.8	-	25.55	25.5	49.5	-	47.6	47.6
Standard care plus topical haemoglobin								
Healed (%)	55.1%	40.7%	-	40.6%	85.1%	75.0%	-	75.1%
Mean open wound weeks	21.9	23.3	-	23.4	28.4	33.11	-	33.1
Difference								
Increase in proportion of patients healed (%)	51.4%	37.0%	47.4%	32.7%	72.4%	62.3%	64.3%	54.1%
Relative risk (RR) of remaining unhealed without topical haemoglobin	2.1	1.6	2.1	1.6	5.9	3.5	5.3	3.2
Reduction in mean open wound weeks (average)	–3.8	–2.5	–3.6	–2.2	–21.1	–16.3	–19.3	–14.4

From the analysis presented, the benefits are apparent from haemoglobin spray treatment with resource utilisation benefits expected within six months in terms of average open-wound weeks per patient per wound treatment episode. This is supported by a six-month study[18] that showed 93% of wounds closed with haemoglobin spray treatment at six months compared with 7% of wounds closed at six months under standard care. It is recognised that standard care will vary between different care systems.

Study limitations and directions for future research and analysis

The results in the trial reported by Arenbergerova et al.[10] were captured in a clinical trial setting with only chronic venous leg ulcers and did not follow patients through to complete wound closure. It would therefore be desirable to capture data relative to standard care in other chronic wound populations and to follow patients for a longer time period to enable a better estimate for healing rates and time to wound closure for patients treated with haemoglobin spray.

The 'recruitment' of 'patients' through data simulation as opposed to controlled prospective enrolment is a clear limitation to the interpretation of the study findings. While every effort has been made to ameliorate these limitations and to ensure that the methods used do not overestimate possible benefits, the simulations are based on the relatively small samples from the original study. However, the improvements predicted by this study are so marked that, at the very least, they provide strong support for the undertaking of further clinical trials.

Further research should also evaluate the total cost of resources for standard care and a care regimen with the haemoglobin spray so that the value of reduced frequencies of hospitalisation, reduced incidence of infection and other potential direct and indirect cost and clinical outcome benefits can be estimated in normal care populations.

Finally, prospective and retrospective case-control and case-series studies from real-life care settings should be conducted as a basis for quantifying any impact on the viability of the closed wounds and wound recurrence rates. In the meantime, for chronic VLUs, it is clear that wound care weeks are likely to be substantially reduced with haemoglobin spray as add-on therapy to standard care.

Conclusions

When used in conjunction with standard care in VLU patients who have failed to improve under

standard care alone, topical haemoglobin spray achieves a reliable and positive wound healing response within four weeks.

More than half of patients treated with haemoglobin spray as adjunct therapy would be expected to achieve wound closure within six months, versus fewer than one in 20 patients on standard care alone; this represents a risk ratio for remaining unhealed of 2:1 at six months for patients remaining on standard care alone. At 12 months, there is up to a 5.9 times higher risk of remaining unhealed for standard care alone.

It therefore appears reasonable that wound care providers consider including haemoglobin spray in the treatment pathway for wounds that fail to improve under standard care alone. ■

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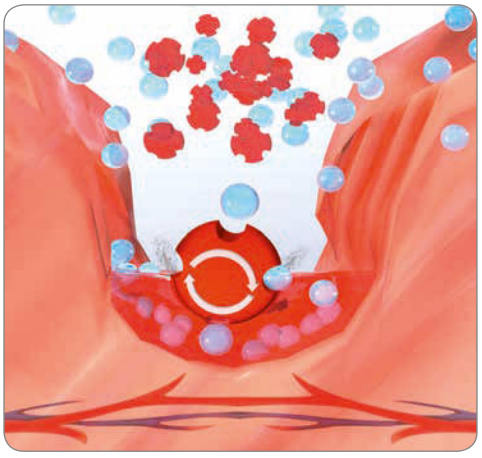
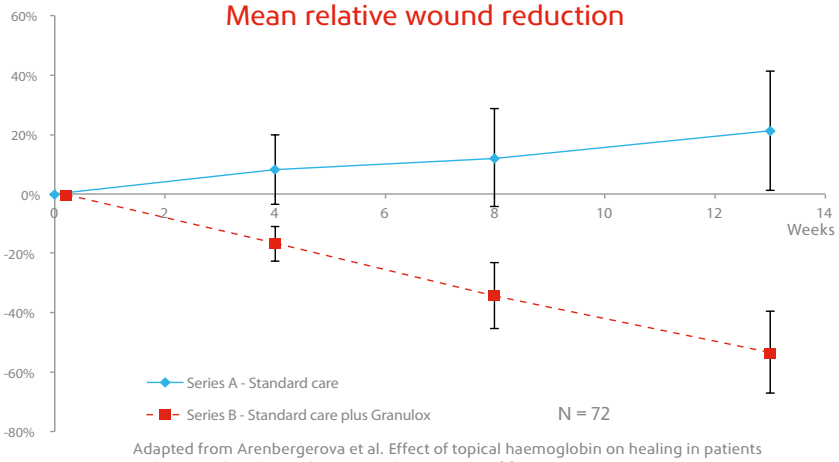
Accelerate wound healing with Granulox



Granulox is a haemoglobin spray which acts to increase oxygen supply to chronic wounds to aid healing.

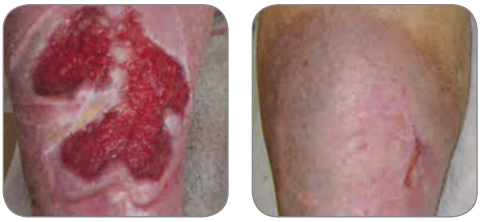


Adapted from Arenbergerova et al. Effect of topical haemoglobin on healing in patients with venous leg ulcers. The Dermatologist 2013; 64 (3): 180-186.

Adding Granulox to standard care for venous leg ulcers delivered an average 53% reduction in wound size after 13 weeks

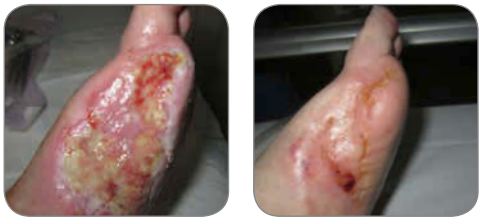
Case Studies

Start of treatment | After 15 weeks



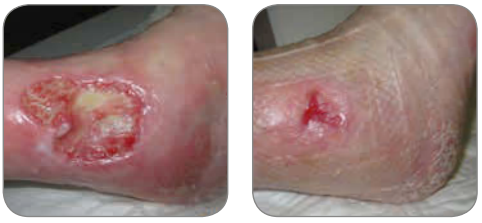
Patient:
43 years, male, venous crural ulcer
Existing for 8 years before Granulox

Start of treatment | After 8 weeks



Patient:
65 years, female, amputation wound
Existing for 8 weeks before Granulox

Start of treatment | After 22 weeks



Patient:
85 years, female, arterial crural ulcer
Existing for 7 years before Granulox

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Harnessing the healing powers of oxygen

If you would like to find out more, get in touch with **Fredrik Elg, Granulox Product Director UK**, to arrange for an evaluation of Granulox as a first step towards formulary inclusion at your Trust or CCG.
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