Topical haemoglobin – High potential for improved outcomes in chronic venous leg ulcers, based on post hoc analysis and simulation of wound closure outcomes

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Abstract

Background: Topical haemoglobin promises a reliable treatment for chronic ulcers. Recent clinical research shows significant improvement in healing-rates with haemoglobin spray as add-on therapy to standard care but did not fully explore expected implications for care.

Method: Post-hoc analysis of data from the pivotal study and simulation to attempt to answer key questions on implications for care. Three questions are addressed:

1 What treatment response rates can be expected from haemoglobin spray?
2 What healing outcomes can be expected if projected forward?
3 What overall wound-burden implications can be expected for patients and carers?

Results: Post hoc analysis of the trial data showed a 100% treatment response rate in the haemoglobin arm at 4 weeks vs a 48% treatment response rate in the standard care alone arm at the same time. Simulation results using linear regression predicts a 55% wound closure rate at 6 months in the haemoglobin arm, vs 4% in the standard care alone arm, and over a 12 month simulation period predicts an overall reduction in wound burden by 43%, with 85% of wounds expected to have healed in the haemoglobin spray arm by 12 months and 13% in the standard care alone arm. Results were robust across the full range of the 95% confidence interval for healing-rate outcomes at 13 weeks.

Conclusion: Topical haemoglobin promises a significantly more reliable treatment for chronic venous leg ulcers than standard care alone and with substantial expected reductions in overall treatment period as shown in several case series elsewhere. Further research should attempt to estimate the impact achievable in other chronic wound types vs standard care alone for these wound types and to explore whether improved speed and quality of healing translates into reductions in wound recurrence rates.

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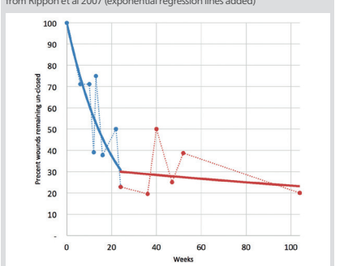
Introduction

Chronic wounds are wounds that do not heal within a reasonable amount of time, or which are predicted to be slow healing. Kantor and Margolis (2000) and Cardinal, Eisenbud, and Harding (2008) among others have showed that wound size reduction at 4 weeks is a good predictor of healing outcomes and guidelines suggest that patients with a wound-size reduction of less than 40% within 4 weeks despite standard care should be re-evaluated and other treatments considered (Steed et al 2006).

Venous leg ulcers is one of the most common types of chronic wounds, recently estimated in a point prevalence study to represent 20% of complex wounds, compared with 3% for arterial leg ulcers, and 7% for mixed arterial and venous leg ulcers, and 9% for diabetic foot ulcers (Hall 2014). A large proportion of venous leg ulcers remain unhealed for more than 6 months, with studies suggesting 20-50% persisting for more than six months even when receiving gold standard compression treatment (Rippon et al 2007).
As illustrated in **Figure 1,** it can also be noted that ulcers which have persisted for more than 6 months despite gold standard care, have low prospects of healing.

Figure 1. Average healing outcomes of 33 studies by week of study adapted from Rippon et al 2007 (exponential regression lines added)



Venous leg ulcers are the consequence of chronic venous insufficiency, where venous stasis and associated oedema leads to reduced blood flow and reduced levels of oxygen availability (Moysidis 2012). The venous stasis causes elevated pressure in the veins and leads to a reduced capillary density (Jünger, Hahn et al 1999, Jünger, Klyscz et al 1999) and the associated oedema results in slowing of the diffusion of oxygen from the remaining capillaries to the tissue cells (Jünger, Steins et al 2000). Tissue hypoxia is a common aetiology for pathological processes in wound healing such as peripheral arterial occlusive disease (pAOD), chronic venous insufficiency (CVI), and diabetes mellitus (Schreml 2010).

Summary of the design of the Arenbergerova et al 2013 study

Product: Granulox® haemoglobin spray (10% carbonylated haemoglobin, 0.9% NaCl, 0.7% phenoxyethanol, 0.05% N-acetylcysteine in aqueous solution). Non-haemoglobin arm received the same product but without haemoglobin.

Design: Prospective, randomised, single blind, monocentric study, N=72 (2x36) with haemoglobin spray or sham product added to standard care: Compression and non-medicated thin, air-permeable, nanofibre textile dressing. Wounds were treated daily.

Inclusions and exclusions: Patients >18 years of age with a venous leg ulcer min 1.6 cm wide and max 50 cm^2 persisting for >8 weeks. Ankle brachial index (ABI) of more than 0.8. Patients with vasculitis or were treated with antibiotics or immunosuppressive drugs such as corticosteroids, were pregnant, or which showed significant wound-size reduction during a one week warm-in period prior to randomization where excluded.

End-points: Percent wound-size reduction at 13 weeks, primary end-point. With secondary endpoints including average pain scores and interim measures over the study period. For more details see Arenbergerova et al 2013.

Oxygen demand is increased for all phases of wound healing inflammation, granulation, neoangiogenesis, re-epithelisation and tissue reorganisation (Schreml 2010). Improvement of blood and oxygen supply to chronic hypoxic wounds has been shown to achieve positive outcomes, i.e. via re-vascularisation surgery in peripheral arterial diseases (Nordgren, Hiatt, Dormandy 2007), hyperbaric oxygen therapy (Kranke, Bennett et al 2012), and recently via topical application of haemoglobin (Arenbergerova et al, 2013).

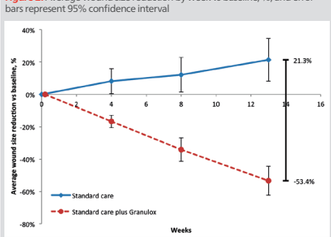
Haemoglobin is the oxygen transporting element in red blood cells and has the unique characteristic of absorbing oxygen in an oxygen-rich environment and releasing oxygen in an oxygen poor environment, and has been shown to improve oxygen transport by more than 8 times in an oxygen poor environment relative to no haemoglobin in vitro (Scholander 1960).

Dr Arenbergerova and her colleagues (2013) conducted a randomised control trial of standard care plus haemoglobin spray compared with standard care plus sham product (no haemoglobin) in 72 patients with chronic venous leg ulcers which had failed to improve despite standard care and hospitalisation. The product in this trial was Granulox® haemoglobin spray (10% carbonylated haemoglobin, 0.9% NaCl, 0.7% phenoxyethanol, 0.05% N-acetylcysteine in aqueous solution). The non-haemoglobin arm received the same treatment but the spray-product was without haemoglobin.

The design was a prospective, randomised, single-blind, monocentric study, N=72 (2x36) with haemoglobin spray or sham product added to standard care: Compression and non-medicated thin, air-permeable, nanofibre textile dressing. Wounds were treated daily. Inclusions and exclusions: Patients >18 years of age with a venous leg ulcer min 1.6 cm wide and max 50 cm^2 persisting for >8 weeks. Ankle brachial index (ABI) of more than 0.8. Patients with vasculitis or were treated with antibiotics or immunosuppressive drugs such as corticosteroids, were pregnant, or which showed significant wound-size reduction during a one week warm-in period prior to randomization where excluded. End-points: Percent wound-size reduction at 13 weeks was primary end-point. Secondary endpoints included average pain scores and interim measures over the study period. For more details see Arenbergerova et al 2013.

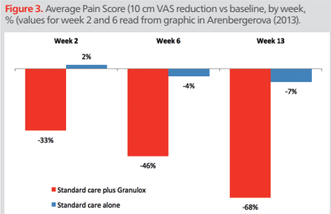
Patients were treated for 13 weeks and showed a statistically significant 53% average wound-size reduction in the haemoglobin arm vs no significant improvement in the non-haemoglobin arm over the same period, with a 74% difference in average wound size reduction between the two groups, more than three times the difference the study was designed to detect. See **Figure 2**.

Figure 2. Average wound size reduction by week vs baseline, %, and error bars represent 95% confidence interval



Although the study also assessed average pain scores using a VAS scale and showed a 60% lower average pain scores at 13 weeks vs standard care alone as a key quality of life metric (See **Figure 3**), the paper did not attempt to estimate the care implications from their findings.

Figure 3. Average Pain Score (10 cm VAS reduction vs baseline, by week, % (values for week 2 and 6 read from graphic in Arenbergerova (2013).



This paper therefore sets out to try to estimate what the potential implications are from these very promising results by raising 3 key clinical questions:

1 What treatment response rates can be expected from haemoglobin spray?
2 What healing outcomes can be expected if projected forward?
3 What overall wound-burden implications can be expected for patients and carers?

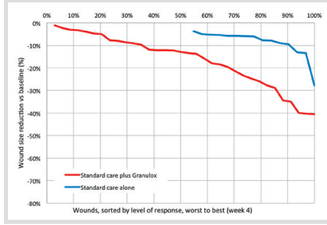
Results

1. What treatment response rates can be expected from haemoglobin spray?

When a new treatment is considered, it is not only important to know what the average benefit achievable is, it is also important to know in what proportion of patients a positive response to treatment can be expected and the relationship to standard care. To estimate the response rate of haemoglobin spray when added to standard care, the proportion of patients with any wound size reduction at 4 weeks for both treatment groups was recorded.

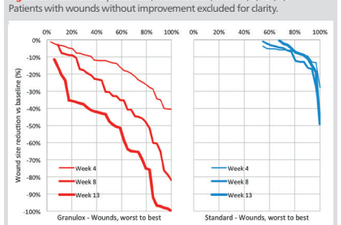
Results show a treatment response rates of 100% at 4 weeks for the haemoglobin spray treated arm vs 48% in the standard care alone treatment arm, a 52% difference and more than double the response rate vs standard care alone (Z-Score 4.82, p-value is 0.00003).

Figure 4. Treatment response rate, worst to best (%), at week 4. Patients with wounds worsening excluded for clarity.



A similar analysis was performed for the response rates at 8 weeks and 13 weeks to enable an evaluation whether the positive response rates were sustained. The results, as illustrated in **Figure 5**, show a difference in response rate of 46% at week 8 (Z-Score is 4.12. The p-value is 0.0002) and at 13 weeks, the difference was 62% (The Z-Score is 5.30. The p-value is 0.00001).

Figure 5. Treatment response rate, worst to best, Week 4, 8, 13 (%). Patients with wounds without improvement excluded for clarity.



All but one of the 34 patients completing the trial in the haemoglobin spray arm showed a wound size reduction by week 13 (97%). Two patients showed temporary worsening of their wounds by week 8. In comparison, the standard care group only saw a wound size reduction in 11 out of the 31 patients (35%) who completed the trial at week 13. Hence, more than twice as many patients experienced a wound size reduction in the haemoglobin spray treatment arm vs the standard care alone treatment arm. No patient in the haemoglobin spray arm, who completed the trial, had an enlarged wound, while 20 of the 31 patients in the standard care group who completed the trial had worsened (65%).

These results suggests haemoglobin spray provides a reliable adjunctive treatment in chronic venous leg ulcers, with positive results achieved within 4 weeks in a very high proportion of patients which have failed to achieve improvement under standard care.

2. What healing outcomes can be expected if projected forward?

How long to expect time to wound closure to take? Only one wound achieved complete wound closure over the 13 weeks of data available from Arenbergerova et al (2013), so average time to wound closure cannot be calculated. To estimate the expected impact on time to healing we adopted a three step approach;

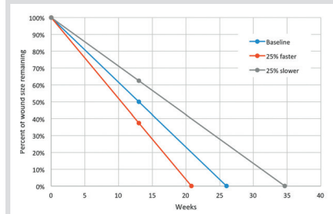
A. Select an appropriate method to predict time to wound closure,
B. Ensure recognition of the non-linear relationship between variations in healing speed and the time to wound healing, and
C. Project the healing outcomes – Simulating healing outcomes for a bigger sample

A. Select an appropriate method to predict time to wound closure
The literature suggests that initial healing-rates, even at just 4 weeks, are reliable predictors of positive healing outcomes – e.g. Cardinal, Eisenbud, and Harding (2008) and that a simple metric of percent wound-size reduction is nearly as good as more complex logarithmic ratios for predicting outcomes – e.g. Margolis et al (2003). Relative to linear wound size reductions, expressed as a percentage reduction vs baseline, wound healing tends to slow down just before wound closure and it is this behaviour which logarithmic functions can capture. Logarithmic functions is a form of exponential decay functions which gradually slows to reflect the slowing of healing rates. Donohue and Falanga (2003) 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 (2013) shows that the average healing-rate observed at week 4 is indeed a reliable predictor of the average healing at weeks 8 and 13, as demonstrated by a very 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 treatment group and R^2=0.985 for the standard care alone group.

These results suggests that a more simple linear model can be justified. Also, the use of a linear model will be more conservative in quantifying a difference between the two groups. Due to the non-linear relationship between change in healing speed and time to wound closure the chosen linear projection approach will under-estimate the expected time to complete wound closure particularly for the slower-healing standard care wounds. Therefore, for the purpose of this exercise, a linear projection methodology was adopted.

B. Ensure recognition of the non-linear relationship between variations in healing speed and the time to wound healing
As the wound healing rate slows, the time to wound closure will get disproportionately longer and as such it is important to not only know 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 illustrated in **Figure 6**, a 25% slower wound healing rate will create a much longer increase in time to healing than a 25% improvement. Similarly, a 25% increase in a slower healing wound will have a much bigger impact than the same 25% variation would have for a faster healing wound.

Figure 6. Healing time difference from same increase / decrease in healing speed (weeks).

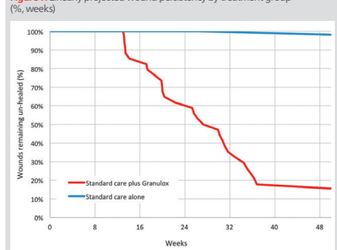


To accurately reflect the expected time to healing it is therefore not possible to simply take the average or the median healing rate. The analysis of expected healing trajectory must consider the variation in healing speeds achieved within each group.

If we apply a linear healing trajectory, to each of the patients in each group we can plot the expected time to wound closure for each group (while recognising that wound healing often slows down just before wound closure and that final wound closure is likely to occur slightly later than the linearly predicted time for closure, i.e. as indicated by Cardinal, Phillips, Eisenbud et al (2009), we can estimate the proportion of wounds healed. At 6 months the proportion of wounds healed can be estimated to 47.1% in the haemoglobin spray arm, and to 0.0% in the standard care arm. At 12 months to 85.3% in the haemoglobin spray arm (16 patients in the Standard care plus haemoglobin spray sample), and 3.2% in the Standard care group (one patient in the standard care alone study sample). **Figure 7** shows the projected wound persistency for each group.

The results from forecasting the healing trajectories suggests a very large difference in anticipated healing outcomes from the healing-rates achieved in the Arenbergerova et al (2013) study. While the results are clearly statistically significant, it still raises the question of reliability.

Figure 7. Linearly projected wound persistency by treatment group (%, weeks)



C. Project the healing outcomes – Simulating healing outcomes for a bigger sample
To simulate the full range of outcomes, time to wound closure, for each treatment group, it is necessary to sample 'new' patients from a distribution 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 to ensure that the analysis considers the possibility of a 'lucky sample'. Finally, an appropriate and conservative statistical distribution model 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. This test showed that the test for normality could not be rejected for the haemoglobin spray arm (p<0.13). With more patients than the normal distribution showing substantial worsening and one outlier showing substantial improvement, and driving up the standard distribution, the observed healing rate distribution in the standard care group failed test for normality (p<0.005), as shown in **Figure 8**.

Figure 8. Shapiro Wilks Test for Normality at 13 weeks

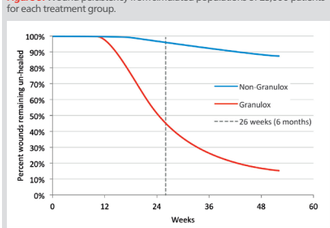
Shapiro Wilk Test		
	Standard care plus plus Granulox® arm	Standard care alone arm
W	0.95	0.89
p-value	0.11	0.01
alpha	0.05	0.05
normal	Yes	No

When using a standard distribution model for the standard care group, this model predicts a wound closure rate of 12.4% at 12 months, substantially higher than the 3.2% predicted from the actual observed in the standard care alone group (i.e. the trajectories for each of the actual 31 patients in the study, as shown in **Figure 7**). The standard distribution should therefore be considered as a conservative model (reducing the difference) in terms of estimating the possible difference in healing outcomes between standard care plus haemoglobin spray vs standard care alone.

Using the predicted normal outcome distribution, a large number of wound healing trajectories were sampled (25,000) 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 arm, just under six months. No median healing time was possible to estimate for the non-haemoglobin spray arm as less than half of the patients were predicted to go on to complete healing.

Of the simulated wounds in the non-haemoglobin spray treatment arm that were predicted to heal within the simulated first 12 months, the median healing time was 32 weeks (for those that healed), but only 12% were healed, vs 85% in the haemoglobin spray arm. The simulation further suggests 55% of patients to achieve wound closure at 6 months (26 weeks) in the haemoglobin spray arm (45% remaining un-closed) vs 4% in the standard care alone arm, 51% more in the haemoglobin spray arm, and 85% and 12% respectively for the two groups at 12 months, 73% more in the haemoglobin spray arm. See **Figure 9**. These results will vary slightly depending on the samples drawn but multiple runs of the same large number of simulations reveal very small variations.

Figure 9. Wound persistency from simulated populations of 25,000 patients for each treatment group.



3. What overall wound-burden implications can be expected for patients and carers?

With an increased rate of healing, and reduced variability in healing rate outcomes, a faster time to wound closure should translate into an overall reduction in wound care burden, i.e. the number of patients that needs to be cared for over time. Indeed, the total average number of wound care weeks that are needed over a 6 month period and a 12 month period show a rapid impact on overall wound burden. An average of 22 open wound weeks is observed in the haemoglobin spray arm vs an average of 26 weeks in the non-haemoglobin spray arm over the first 6 months, a 15% reduction. Over a 12 month period, a rapidly increasing impact is observed, with a 43% reduction in overall number of open wound weeks in the haemoglobin spray group vs the standard care alone treatment group. The difference will continue to increase, assuming similar recurrence rates, as at 12 months, only 15% of patients remain unhealed in the haemoglobin spray group, vs 88% of patients remaining unhealed in the standard care alone group.

With an estimated prevalence of 0.1-0.3% for chronic venous ulcers in the UK (SIGN) , applying the lower end of this prevalence estimate (0.1%) to the UK population (60 million) wound care reductions above suggest a possible reduction of the number of wound care weeks in the UK.

As illustrated in **Figure 10**, this reduction would correspond to 0.2 million care weeks within 6 months, and 1.3 million care weeks within 12 months (not adjusted for expected slowing of wound healing just before wound closure and the possible need to treat patients for other reasons).

These results for healing outcome benefits are robust across a large range of uncertainty. To test for reliability, the analysis was repeated across the min and the max points in the 95% confidence interval of observed healing rate outcomes at 13 weeks for both groups, i.e. repeated using the 'best' value within the 95% confidence interval for the standard care group and compared with the expected 'worst' value for the stand care plus haemoglobin spray group. The combined probability representing the 99.75% likelihood of a number larger than this difference between the groups at 6 and 12 months. The results, shown in the 0.25% column in **Figure 11**, suggests that even in the 0.25% probability case, there is a 3.2 times higher risk (RR) of a remaining unhealed wound under standard care alone.

Figure 10. Expected number of wound care weeks to 6 months, 12 months, by treatment regimen.

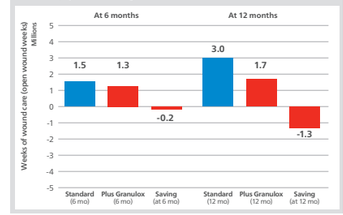


Figure 11. Simulated healing outcomes at 6 and 12 months for best estimate, and 5% worst outcome for haemoglobin spray arm, 5% best for standard care alone are and 0.25% worst likely combined outcome for haemoglobin spray.

	6 months				12 months			
Outcome	Best Estimate	Granulox Worst 5%	Standard care Best 5%	0.25% (5% and 5%)	Best Estimate	Granulox Worst 5%	Standard care Best 5%	0.25% (5% and 5%)
Standard care alone								
Healed (%)	3.7%	3.7%	7.74%	7.9%	12.73%	12.73%	20.84%	21.08%
Mean open wound weeks	25.8	25.8	25.55	25.5	49.46	49.46	47.65	47.56
Standard care plus Granulox								
Healed (%)	55.1%	40.7%	55.1%	40.6%	85.14%	75.04%	85.14%	75.14%
Mean open wound weeks	21.9	23.3	21.9	23.4	28.37	33.11	28.37	33.13
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 of remaining unhealed without Granulox	2.1	1.6	2.1	1.6	5.9	3.5	5.3	3.2
Reduction in Mean open wound weeks	– 3.8	– 2.5	– 3.6	– 2.2	– 21.1	– 16.3	– 19.3	– 14.4

Discussion

The results from this analysis shows that topical haemoglobin spray, when used as add-on to standard care in venous leg ulcer patients which have failed to improve under standard care alone, achieves a reliable and positive wound healing response within four weeks. Patients treated with haemoglobin spray as add-on therapy is expected to achieve wound closure in more than half of patients within 6 months, vs less than one in twenty patients on standard care alone, representing a risk-ratio for remaining unhealed of 2.1 at 6 months for patients remaining on standard care alone. At 12 months, there is a 5.9 times higher risk of remaining unhealed for standard care alone.

While this analysis is clearly robust in light of the possible range of healing outcomes at 13 weeks, the duration of the trial, the simulation of the healing trajectories for these patients going forward is driven by assumptions. Although analysis of wound size change vs baseline at just 4 weeks has been found to correctly and reliably predict healing outcomes in more than 70% of cases (e.g. Kantor and Margolis, 2000), the simulation approach in this paper does not fully consider the expected slowing of wound-healing in the weeks before wound closure and therefore under-estimates time to full epithelisation by on average several weeks. However, this slowing of healing would not be expected to be shorter in the standard care arm and as such would suggest even larger benefits with haemoglobin spray treatment achievable vs standard care alone.

From the analysis presented here, the benefits from haemoglobin spray treatment are apparent and robust, with resource utilisation benefits expected already within 6 months in terms of average wound-care weeks per patient per wound treatment episode. This is also supported by the earlier 6 month study in Mexico (Arenberger, Engels et al 2011), that showed 93% wound closure with haemoglobin spray treatment vs 7% wound closure at 6 month under standard care, while recognising that standard care in Mexico is different from standard care in Europe.

Directions for future research and analysis: The results in the trial reported by Arenbergerova et al (2013) were captured in a clinical trial setting with only chronic venous leg ulcers and did not follow patient through to complete wound closure. As such there is benefit from capturing similar data relative to standard care in other chronic wound populations as well as to follow patients for a longer time period to enable better estimates for healing rates and time to wound closure for patients treated with haemoglobin spray.

Further research should also evaluate total cost of resource utilisation for standard care and care-regimen with haemoglobin spray such that the value of reduced frequencies of hospitalisations, 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 case-case series from real-life care settings should be conducted as a basis for quantifying any impact on viability of the closed wounds and wound recurrence rates. In the mean-time, for chronic venous leg ulcers, it is clear that wound care weeks are likely to be substantially reduced with haemoglobin spray as add-on therapy to standard care.

Summary of the post hoc responder and simulation analysis approach

Post hoc responder analysis:
Responder analysis was conducted by counting the number of patients that achieved any wound-size reduction vs the baseline at week four in all patients who completed the study for each treatment group. The analysis was also repeated for weeks 8 and 13. No response data was available for the two patients which dropped out of the study in the haemoglobin spray arm, or the five patients which dropped out of the standard care alone arm.

Wound healing trajectory simulation:
The simulation approach used a three step process with **(1)** tests for normality of healing outcomes achieved at 13 weeks for each of the two study arms as a basis for selecting an appropriate healing distribution (Shapiro-Wilk Test), **(2)** model selection based on regression of the observed average wound size reductions, and **(3)** sampling of wound healing trajectories from the expected distributions at week 13 and projecting trajectories to wound closure using the healing trajectory method selected.

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The role of Granulox® in chronic wound healing Two case studies

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The role of Granulox® in chronic wound healing Two case studies

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10-12 November 2014 |

Abstract

Throughout the decades, the importance of oxygen in wound healing is well acknowledged and research continuing in this field highlights how hypoxia and absence of oxygen in a wound is closely associated with delayed healing. Although delayed wound healing has a great impact on patients quality of life, it also increases the burden of wound management which is a vast economic cost to the NHS. This poster presents two patients with chronic wounds.

Patient 1 has chronic venous insufficiency due to past history of DVT and IDVU. He has had chronic leg ulcers for more than four years. Although Doppler assessment with compression therapy has been used over the years, the ulcer has failed to heal even with different wound care approaches.

Patient 2 has a dehisced sternal wound of six years duration which due to recurrent infection has failed to heal. Despite having several evidence based wound care therapies, the sternal wound has still not healed and the patient's quality of life is disrupted.

Both wounds had a lack of oxygen supply which had resulted in neovascularisation hence the great impact on wound healing phases. Using topical haemoglobin to both wounds resulted in greater oxygen supply to the hypoxic wound bed which kick started the process of healing.

The leg ulcer of Patient 1 is completely healed and the sternal wound of Patient 2 has reduced considerably in size with the mid part showing epithelisation.

Key words:
Chronic wound, Oxygen, Haemoglobin, Wound healing

Introduction: The role of oxygen in wound healing

The importance of oxygen to the wound healing process has been well researched in recent years.

This research shows tissue perfusion and oxygenation are crucial factors to optimise wound healing (Chambers, Leaper 2011)[1]. Howard et al (2013)[2] also mentioned that oxygen demand increases during the process of tissue repair to meet complete wound healing.

However, Bishop (2008)[3] stated that since oxygen is not stored in the tissue, continuous oxygen supply to the wound is paramount for tissue repair to occur. Hence lack of oxygen in a wound as a result of disrupted circulation due to some physiological disorders leaves the injury site hypoxic which can lead to impaired healing (Sen 2009)[4].

This case report presents the successful management of chronic wounds from two different patients using an adjuvant oxygen therapy Granulox® (Fig 1).

Granulox® is not yet widely used in the UK but usage has been reported with good results internationally. [5,6,7,8].

Case report 1
Chronic venous insufficiency from DVT

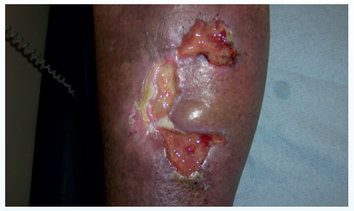


Fig 3A 23.02.2012

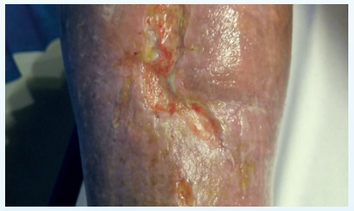


Fig 3B 09.07.2014

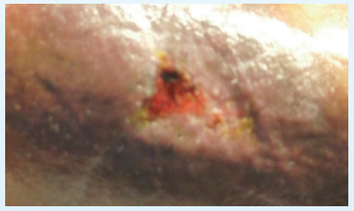
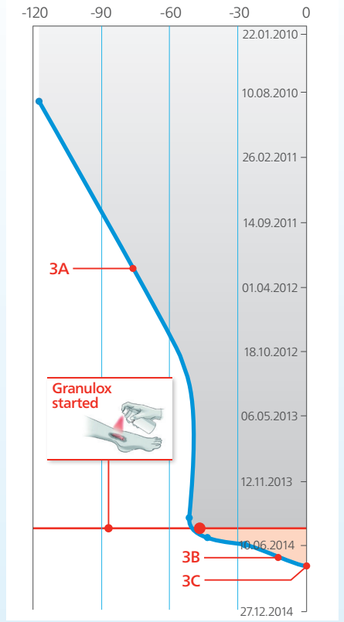


Fig 3C 06.08.2014

Fig 2
Wound size, cm^2



A 40 year old male patient was diagnosed with chronic venous insufficiency following recurrent episodes of DVT, a result of continuous IVDU. The patient developed oedema and venous leg ulcers. The ulcer started 5 years ago with several episodes of wound deterioration.

The patient has had a Doppler assessment to determine the ABPI prior to starting full two layer compression (k2 system®). During the past four years, the ulcer has gone through different phases of wound healing but never healed completely (Fig 2). Patient has now given up IDVU and taken a day job in a rehab unit. Having a painful leg constantly impacts on his day to day job.

Due to an increase in pain, odour and high exudate, the patient has developed non-compliance and is removing bandages after a few days hence he was referred to me for re-assessment and advice.

Having noted all the above, the main goal was to improve his quality of life by minimising the pain and healing the ulcer. Prior to re-assessment, the wound bed was being dressed once weekly by the Practice Nurse, the ulcer being cleansed using normal saline solution, antimicrobial impregnated tulle dressing applied to ulcer, protected with absorbent pad (high exudate) and k2 compression applied from toe to knee.

O/E: Wound bed measures 10 cm x 5 cm. Sloughy, greyish colour, malodour present and high exudate also noted. Edges were slightly red and macerated (Fig 3A).

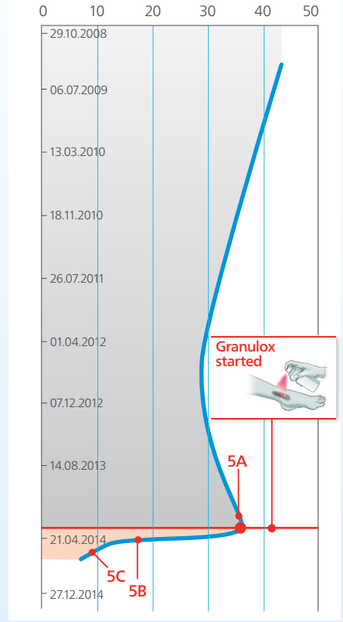
Due to the nature and appearance of the ulcer, the patient was started on a haemoglobin solution (Granulox®), sprayed 5-10 cm from above the ulcer directly in the wound bed. The wound was then covered with a highly absorbent pad (Keramax care®) due to high exudate and an activated charcoal dressing to reduce malodour. Surrounding skin was moisturised with an emollient followed by k2 compression bandaging from toe to knee. The plan indicated to continue weekly with the new regime. **Fig 3B shows the wound bed after 3 weeks of Granulox®.** Significant improvement has been noted and the charcoal dressing is no longer being used as the odour is considerably reduced.

Wound margins have reduced further on the 4th week, the patient reports taking less analgesia when at work and is able to keep compression on for the whole week as no leakage or pain was present.

On the 5th week, the edges of the wound bed were merging together and the wound bed appeared red and healing with the surrounding skin looking healthier. There was less exudate and Granulox® was continued until the final stage of healing and the patient is now in compression hosiery as both oedema and exudate are well controlled (Fig 3C).

Case report 2
Sternostomy secondary healing wound

Fig 4
Wound size, cm^2



A 57 year old lady had an emergency sternotomy 6 years ago. Due to her recurrent ill health, the wound has had several episodes of infection requiring IV ABX.

She had a dehisced sternal wound which had not responded to the any treatment so far in healing. As a consequence she was being seen by District Nurses on a daily basis.

However, the exudate was not contained appropriately and the tissue in the wound bed had a thick, dull colour yellow and was quite malodorous at a size of 9.5 cm x 4.5 cm (Fig 4). This patient was then referred to Tissue Viability and on initial examination it was noted that the wound bed was stagnant as described by both the patient and staff.

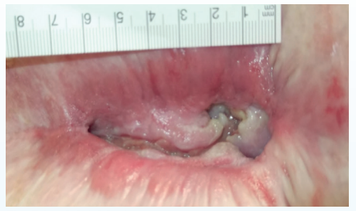


Fig 5A 16.04.2014

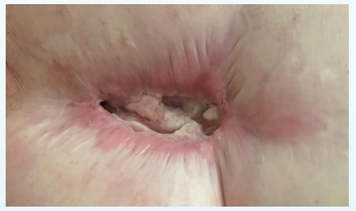


Fig 5B 12.08.2014

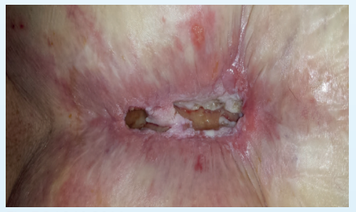


Fig 5C 16.10.2014

The patient was started on Granulox® on 22 April 2014, applied daily on in the wound bed after being soaked for 5 minutes in Prontosan® solution followed by the antimicrobial dressing previously used. Her secondary dressing was also re-assessed in order to contain the exudate more effectively.

2 weeks later, on review of the wound, there was no malodour and the patient reported the dressing staying drier for longer periods of time (Fig 5A). The wound bed had only 50% slough and 50% of the ulcer was red granulation.

The size was currently 9.0 cm x 3.5 cm and although there wasn't much improvement in size, the tissue type appeared healthier than when compared with 2/52 ago.

3 weeks later, the wound was re-assessed and, after 5 weeks of Granulox®, the wound was now 100% granulated and had the size 6.0 cm x 1.7 cm.

Although not completely healed, the patient's quality of life had vastly improved. She is now having dressing change 3 times weekly instead of daily and the exudate is not a problem for her anymore. She can now wear normal clothes after several years (Fig 5C).

Observations, conclusions & discussion

Oxygen plays a major role in wound healing (Sen 2009)[4]. Being in a hypoxic state due to poor vascular supply due to underlying health conditions, both wounds were left stagnant for years and despite a variety of products used, it was impossible to move the wound bed through the healing phase.

Failing to identify lack of oxygen in both wounds led to poor wound management and eventually impacting on the patients quality of life. After a thorough examination of the wound bed and constant treatment updates made on the evidence base of wound healing, a slight adjustment was made to their normal dressing regime.

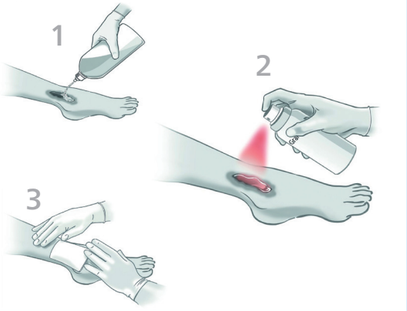
A topical oxygen adjuvant therapy was applied to the wound bed in the form of Granulox®. The Granulox®, sprayed from 5-10 cm above the wound bed, acted through the process of facilitated diffusion to improve the oxygen supply through the wound exudate.

This stimulated the healing process once again and corrected the hypoxic state to an oxygenated state. Granulox® has re-iterated the importance of oxygen supply in wound healing through a more cost effective and user friendly way.

Granulox® can be applied in any care setting and is easy to use, simply applied before any regular (air permeable dressing is used) (Fig 6).

Two case reports have been presented where topical haemoglobin solution has been used in chronic wounds to change the nature of the wound bed and lead towards healing. Both case reports greatly increased the patient's confidence and their quality of life has been enhanced.

Fig 6



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Granulox® in practice: 4 patient case studies

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Presented at Wounds UK Annual Conference
10-12 November 2014 |

Introduction

The risk of lower extremity amputation for people with diabetes is more than 20 times those without diabetes.

Amputations are associated with non-healing foot ulcers, many of which are hypoxic or ischemic due to vascular complications of their condition.

While re-vascularisation surgery has been proven successful for the treatment of patients with a clear arterial cause of the ischemia, this option is not available for many patients.

Research with Granulox® has shown that topical application of haemoglobin can facilitate oxygen diffusion and make oxygen from air available to the tissue in the wound base at a substantially higher rate than unaided diffusion.

Granulox® haemoglobin spray (Fig 1) was recently approved in the EU but is still to achieve tariff, formulary and guideline inclusions in the UK.

As a basis for evaluating Granulox® for formulary inclusion, Birmingham Community Healthcare NHS Trust decided to evaluate Granulox® for possible local formulary and guideline inclusion.

This paper presents the results from this product evaluation, conducted in four patients which have failed to respond to standard care.

The evaluation was set to evaluate the ability of Granulox® to achieve wound healing in non-healing foot ulcers.

Fig 1. Granulox® Haemoglobin Spray

Method

Over a six month period, March to July 2014, four patients which had failed standard treatment approaches were selected to receive Granulox® as an add-on treatment to their current care.

All patients were recruited following verbal product information provision and agreement to evaluate the product in line with the Birmingham Community Healthcare NHS Trust evaluation policy.

All wound care regimens, evaluations and outcomes were monitored using regular patient follow-up. Patients were provided with Granulox® as an add-on to standard care for a minimum period of 4 weeks and for as long as any benefit was observable, or until wound closure.

The four patient case profiles are detailed on this poster.

Case study 1
Ischemic wound to the apex of the second toe

85 year old Caribbean man with ischemic wound to the apex of the second toe on the right foot.

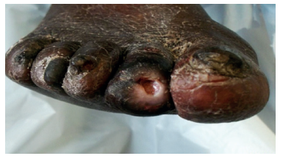
Duration of the wound was more than 12 months prior to Granulox® initiation. The patient was initiated 13.03.14, applied twice weekly. Type 2 diabetic for over 30 years, smokes 10-15 cigarettes per day and drinks whiskey every day.

Bone is exposed at the base of the wound and told there is no pulse below the knee but surgeons are unwilling to do a 3.5 hour bypass operation on it. He is reviewed twice weekly. Bone at base removed 27.07.2014.

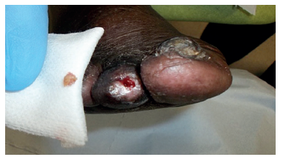
Treatment response

- The patient was initiated on Granulox® in March 2014, applied 2 times per week.
- Ulcer decreased in size from 4mm x 5mm to 2mm x 2mm (-80%).
- Pain level decreased from 7 > 4. Wound is still ongoing. He has currently up to 11.08.14 had 41 applications of Granulox®.
- Continuing with Granulox® as substantial improvement was noticed.

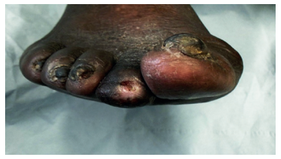
02.05.14



27.06.14



11.08.14



Case study 2
Ischemic foot ulcer, right side metatarsal phalangeal

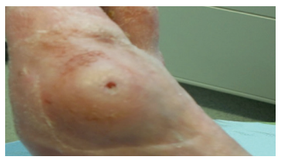
83 year old Caucasian man with ischemic foot ulcer to side of right metatarsal phalangeal joint. Seen by vascular surgeons who indicated that surgery is too risky.

Ulcer present since December 2013. Commenced on Granulox® 03.04.14. Wound 2mm by 2mm stagnant with no improvement since January 2014.

Treatment response

- The patient was initiated on Granulox® in April 2014.
- Achieved complete wound closure in 6 weeks.
- The wound was resolved 15.05.14, after 12 applications of Granulox®.

10.04.14



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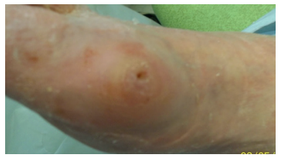
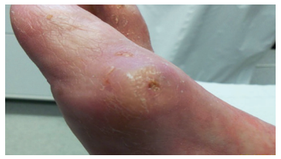


29.05.14



Case study 3
Rheumatoid arthritis deformities. Two large ulcers on apex and side of the right big toe

63 year old Caucasian male with severe rheumatoid arthritis deformities affecting both his hands and feet.

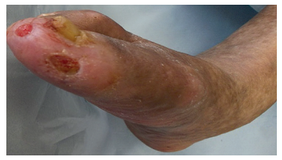
Seen by vascular consultant and diagnosed with narrowing of tibial artery below the knee. Two large ulcers on the apex and side of the right big toe (hallux).

Commenced Granulox® 24.03.14. Wound size of the wound on the medial side of hallux 14mm x 9mm and Ulcer apex of right hallux 6mm x 9mm.

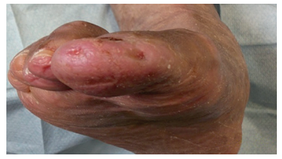
Treatment response

- Patient was initiated on Granulox® in April 2014.
- Achieved both wound closures within 12 weeks.
- Toe resolved 28.07.14 after a total of 34 applications of Granulox®.
- Ulcer apex of right hallux 6mm x 9mm wound resolved 27.06.14 after 27 applications of Granulox®.

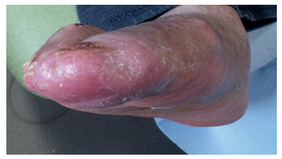
10.04.14



12.06.14



07.08.14



Case study 4
Right and left heel wound

Black British Caribbean lady 49 years old. Smokes roll-up cigarettes but general health is good.

Wound treatment started 16.05.2014. She received tramadol, paracetamol and ibuprofen (8 of each tablet per day every 4 hours, a large dose of pain killers).

When first seen, she used to set her alarm to wake herself up at night to ensure that she got pain medication every 4 hours. Even when cleansing the wounds with saline the patient was in a lot of pain. Pain score 11 out of 10. Reviewed twice weekly.

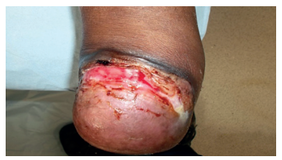
At start of Granulox® on 16.06.14, Right heel wound size 24mm length x 78 mm width, and Left heel wound 22mm length x 77 mm width.

Treatment response

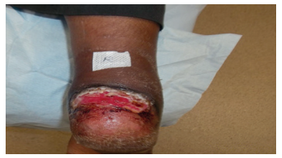
- The patient was initiated on Granulox® in June 2014.
- Achieved wound closure in 8 weeks of the right heel wound after a reduction from 24mm length x 78 mm width (16.06.14 to 11.08.14) and 16 applications of Granulox®.
- Pain level decreased from 11 to 4.

Right wound

19.06.14



03.07.14



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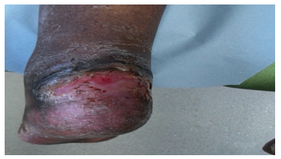
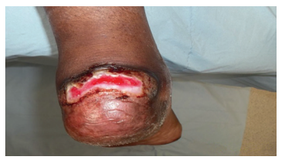


Left wound

19.06.14



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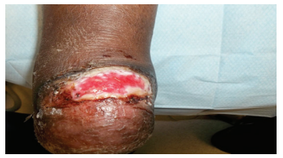
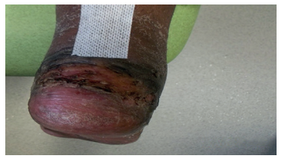


11.08.14



Results & conclusion

Results in the evaluation were extremely positive. The four patients had failed to achieve complete wound closure despite several adjustments to their care regimens prior to Granulox®, with:

- three of the four patients achieving complete wound closure;
- one showing significant improvement;
- and one patient remaining static.

This was based on a total of 5 wounds for the four patients.

When questioned all four patients were happy with the product and podiatrist team stated that the product was simple to use.

The results of this evaluation indicate that Granulox® provides a high treatment response rate even in patients who have failed standard care.

Birmingham Community Healthcare NHS
NHS Trust

Granulox® product evaluation in non-healing diabetic foot ulcers

Achieving healing in 2 out of 4 cases where standard care failed

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10-12 November 2014 |

Introduction

There is an expectation for 7,000 amputations in people with diabetes in England in 2014/15. Most of these amputations are associated with non-healing diabetic foot ulcers.

A common aetiology of many of these wounds is a hypoxic or ischemic status of the wound tissue. While re-vascularisation surgery has been proven successful for the treatment of patients with a clear arterial cause of the ischemia, this option is not available for many patients.

Research has shown that topical application of haemoglobin can facilitate oxygen diffusion and make oxygen from air available to the tissue in the wound base at a substantially higher rate than unaided diffusion.

Granulox® haemoglobin spray (Fig 1) was recently approved in the EU but is yet to achieve tariff, formulary and guideline inclusions in the UK. As a basis for formulary inclusion, the Salford Royal Hospital NHS Foundation Trust decided to evaluate Granulox®.

This paper presents the results from this product evaluation, conducted in three patients which have failed to respond to standard care. The evaluation was set to evaluate the ability of Granulox® to achieve wound healing in non-healing foot ulcers.

Figure 1
Granulox® can be applied in any care setting and is easy to use, simply apply before any regular (air permeable dressing is used)

Patient 1
Neuropathic diabetic foot ulcer after amputation

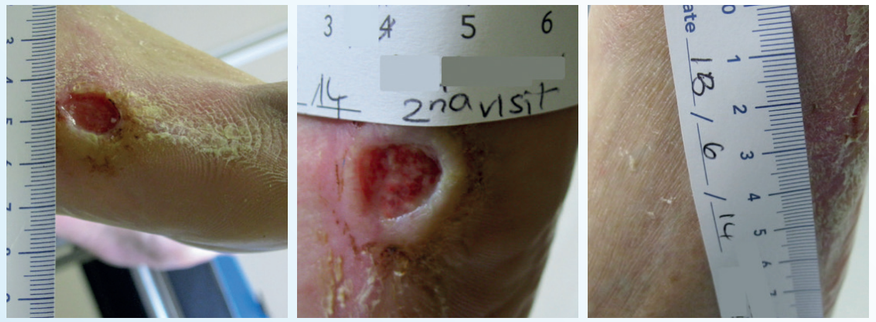
Male, 46 years old. Type 2 diabetes for 13 years.

Neuropathic feet, no clinically significant vascular disease. History of foot ulceration for 6 months with complications leading to amputation of 5th ray in May 2013.

The post-amputation wound failed to heal. Over a 9 month period. Various preparations, including foams and hydrogels were used without achieving wound closure. The patient was initiated on Granulox® in February 2014 and was applied 3 times per week. Wound size at Granulox® initiation at the end of February was 14 x 9 mm (Figure 2A).

Figure 2

(A) Baseline | (B) Week 2 | (C) After healing



Patient 2
Neuropathic diabetic foot ulcer

Male, 66 years old, Type 2 diabetes for 14 years.

History of foot ulceration for 8 years and had a previous forefoot amputation in 2008.

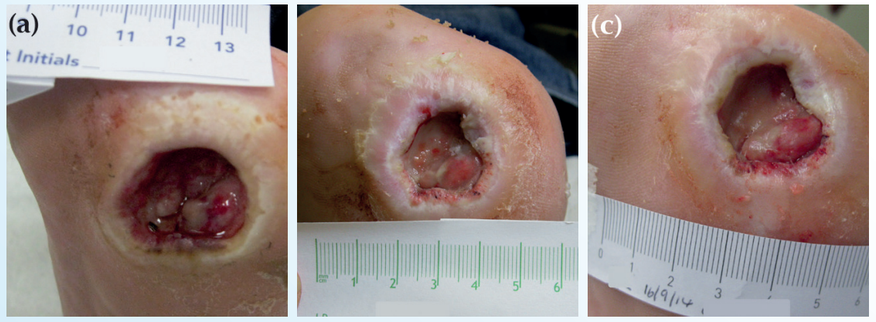
The current wound is a plantar, neuropathic, large wound which has persisted for more than 12 months.

Over the 12 months prior to Granulox® initiation, the wound was treated with superabsorbers and foams without any significant improvement. Granulox® was applied 7 times per week.

Wound size at Granulox® initiation at the end of July was 30 x 20 x 5mm (Figure 3A).

Figure 3

(A) Baseline | (B) Week 1 | (C) Week 2



Patient 3
Neuropathic foot ulcer

Male, 67 years old, Spina bifida with no notable co-morbidities or disease history.

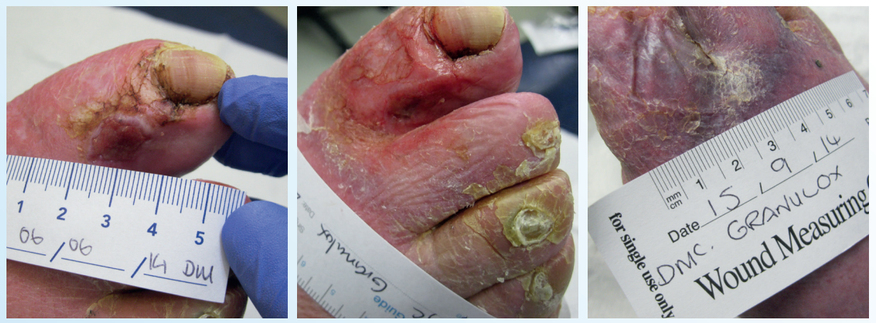
Non-healing digital superficial wound present for more than 12 months.

Prior to Granulox® initiation the wound was treated with protease modulating dressing and hydrofibrebut failed to achieve wound closure.

Granulox® was initiated in May 2014 and applied 3 times per week. Wound size at Granulox® initiation was 12 x 9 mm (Figure 4A).

Figure 4

(A) Baseline



Method

Over a seven month period, February through July 2014, three patients which had failed standard treatment approaches as per current Salford Hospital treatment guidelines were selected to receive Granulox® as an add-on treatment to their current care.

All patients were recruited following verbal product information and agreement to evaluate the product in line with the Salford Hospital evaluation policy. All wound regimens, evaluations and outcomes were monitored at regular patient follow-up.

Patients were to be provided with Granulox® for a minimum period of 4 weeks and for as long as any benefit was observable, or until wound closure.

Results

Results in the evaluation was highly positive. The four patients had failed to achieve complete wound closure despite several adjustments to their care regimens prior to Granulox®, with two of the four patients achieving complete wound closure, one showing significant improvement, and one patient remaining static.

Patient 1 – Healed
Achieved full wound closure in just over 3 months, after being persistent for 12 months and static for 2 months (Figure 2C).

Patient 2 – 20% reduction
After two weeks of treatment at press time, showing >20% wound size reduction in just two weeks (Figure 3C).

Patient 3 – Healed
Achieved complete wound closure within 10 weeks after being persistent for more than 12 months (Figure 4C).

Discussion/Conclusion

The results of this evaluation indicate that Granulox provides a high treatment response rate even in patients who has failed standard care.

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Two case studies of wound management with a topical haemoglobin solution (Granulox®)

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Introduction & Method

One common component of chronic foot ulcers of different aetiologies is ischaemia causing localised hypoxia in the wound bed. The poor perfusion may be due to macrovascular or microvascular disease.

The case studies presented here reflect both scenarios; one patient with diabetes and peripheral atrial disease and one with systemic sclerosis and Raynaud's disease. Various wound care treatments had previously been used without resolution of these chronic wounds. Use of topical haemoglobin solution (Granulox) led to reduced pain, improvement in the wounds and healing in one patient.

Foot wounds of over 4 weeks duration with no sign of progress were selected for treatment with Granulox.

Wounds were sharp debrided and Granulox topical haemoglobin solution applied with a non-adherent dressing and sterile gauze once a week for the period of 4 weeks (fig 1).

Patients were assessed for foot pain and wounds areas measured and photographed as per routine treatment.

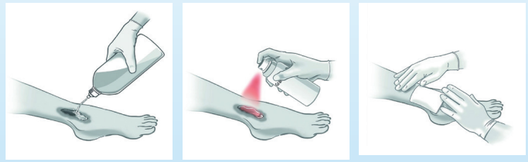
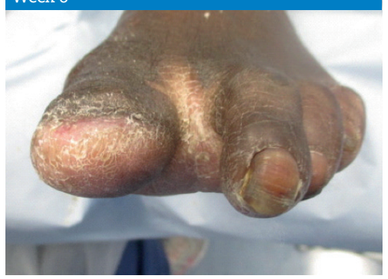


Fig 1.

Case Study One: Female, 51 years of age

Week 1

Week 6



Previous history: 1. Type 2 Diabetes Mellitus for over 20 years, Amputation of right 3rd toe, ESRF – On Dialysis, Hypertension, Previous C.Diff infection (still requiring isolation), Previous OGD – oesophagitis (2012), Bilateral cataract surgery, peripheral neuropathy.

Medication: Gliclazide, Aspirin, Folic Acid, Ketovite, Alfacalcidol, Cholecalciferol, Renvela Sachets, Aransep, Gabapentin, Ondansetron, Metoclopromide, Gabapentin, Levomepromazine, Movicol, Atorvastatin, Venofer.

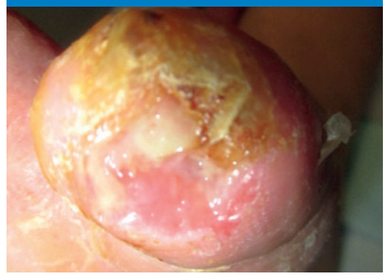
Background: The patient had an amputation of the left 2nd toe following dry gangrene secondary to microvascular disease – a recent arterial duplex reported calcification of the distal vessels but no evidence of haemodynamically significant stenosis.
The patient used a surgical shoe for mobilising.
Despite regular debridement and dressing with Advadraw, the amputation site remained static 4 weeks post amputation.

Method: Granulox was applied weekly, following sharp wound debridement, and dressed with NA Ultra and sterile gauze for a period of 4 weeks.

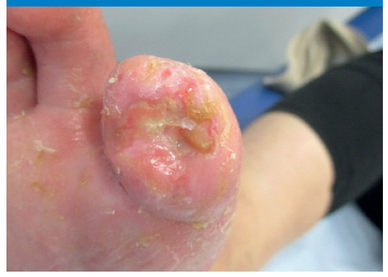
Outcome: The wound responded to treatment with complete healing at 6 weeks.

Case Study Two: Female, 61 years of age

VAS score: 75



VAS score: 40



Previous history: Limited cutaneous systemic sclerosis (LcSSc or CREST syndrome), ANA positive, anti-centromere antibody positive, cardiolipin IgM positive, Raynaud's phenomenon, Toe ulcer with autoamputation of distal right long toe, Seborrhoeic dermatitis Protein S deficiency.

Medication: Losartan, Omeprazole, Ferrous sulphate, Clopidogrel, Stemetil, Iloprost infusions.

Background: The patient had dry gangrene to the apex of the right 1st toe following an acute episode of Raynaud's disease. The apex of the toe auto-amputated leaving exposed bone. The patient used a Darco shoe with PPT insert for offloading. Despite regular debridement and dressing with by a range of dressing types (including Acticoat, Inadine, Aquacel), the amputation site remained static 12 months following auto-amputation.

Method: Granulox was applied weekly, following sharp wound debridement, and dressed with NA Ultra and sterile gauze for a period of 4 weeks.

Outcome: The wound remained static but the patient reported a decrease in pain which was noted on the VAS score from 75 to 40.

Discussion

Wound tissue oxygenation is essential for physiological healing as chronic hypoxia impairs all processes necessary for healing. Chronic hypoxia impairs neovascularization and decreases fibroblast proliferation, collagen synthesis and expression of TGF-β1 in human dermal fibroblasts.[1,2]

Injury leads to the oxygen-dependent release of certain cytokines such as TNF by parenchymal cells which stimulate epidermal cells at wound edges to restructure their cytoskeleton and induce re-epithelialisation.[3,4]

Localised hypoxia in foot wounds may occur due to macro and microvascular disease processes.
These reduce availability of oxygen to the wound bed and may be a cause of chronicity in the wound and increased pain. In these cases, use of Granulox was limited due to its use only following weekly sharp debridement and redressing.

Increased application of Granulox over the prescribed period of 4 weeks may also promote better wound outcomes by restarting the healing process more quickly and this requires further investigation.

Results & Conclusion

In both cases, the patient's wounds improved, one went on to heal completely, and there was reduction in pain score.

These case studies suggest that facilitating an increase in oxygen concentration at the surface of a chronic wound using Granulox can help to reduce pain and restart wound healing in hypoxic wounds.

A future randomised control trial with increased application of Granulox would establish the efficacy of this treatment in chronic foot wounds.

Acknowledgements
We appreciate the help of Infirst Healthcare who supplied Granulox.

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