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

Peter Arenberger* | Fredrik Elg§ | Keith Cutting#

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Abstract

Background: Topical haemoglobin provides a suitable treatment for venous leg ulcers. Anecdotally, improved healing, particularly in terms of shorter healing time, is observed when haemoglobin spray is used in addition to standard care. This study is a post-hoc analysis to evaluate the potential to reduce wound closure times through the use of haemoglobin spray in combination with standard care.

Method: Partial analysis of data from the post-marketing phase IIb study, in order to ensure any assumptions are explicit and for case. Three questions were addressed:
1. What overall wound-burden implications can be expected from haemoglobin spray?
2. What overall wound-burden implications can be expected for patients and care?
3. What overall wound-burden implications can be expected from haemoglobin spray for patients and care?

Results: Platelet adsorption is minimal with topical haemoglobin use and produce a sterile product used throughout. No adverse systemic effects or complications were reported. The study included 72 patients, randomly assigned to receive haemoglobin spray or standard care alone, and followed-up at 12 weeks. Plaque healing rates with haemoglobin spray as add-on therapy to standard care was significantly improved (23.1% vs 8.3%, respectively, p=0.0095).

Conclusion: In the present study, topical haemoglobin promises a significantly more rapid healing time than haemoglobin spray alone, but it is noted that ulcers which were used to evaluate the healing trajectory for these patients going forward is driven by assumptions. Although analysis of wound size change vs baseline is not possible, a linear projection for normality of healing trajectories for these patients going forward is driven by assumptions. Although analysis of wound size change vs baseline is not possible, a linear projection is adopted for the purpose of this exercise, a linear projection will under-estimate the expected time to complete wound closure for patients treated with haemoglobin spray.

Introduction

Chronic venous leg ulcers do not heal within a reasonable timescale and results in significant morbidity and disability. One study of patients with chronic venous leg ulcers has shown that wound closure can take 1 years and standard care alone is unlikely to last for more than 60% of patients with chronic venous leg ulcers. Hence, the use of auxiliary therapies is necessary, of which the most common is wound dressings. Although, these studies have been conducted in several countries of Europe, the data from the US are not available, and therefore a similar study in the US would be beneficial. Although, these studies have been conducted in several countries of Europe, the data from the US are not available, and therefore a similar study in the US would be beneficial.

For the purpose of this exercise, a linear projection will under-estimate the expected time to complete wound closure for patients treated with haemoglobin spray. Although, these studies have been conducted in several countries of Europe, the data from the US are not available, and therefore a similar study in the US would be beneficial. Although, these studies have been conducted in several countries of Europe, the data from the US are not available, and therefore a similar study in the US would be beneficial.

Results show a treatment response rates at 28 weeks for the haemoglobin spray treatment group and R²=0.985 for the standard care alone arm.

Discussion

The results show that: uncontrolled haemoglobin spray arm was included in the analysis; clinics, who had high rates of chronic venous leg ulcers. The data from the US are not available, and therefore a similar study in the US would be beneficial. Although, these studies have been conducted in several countries of Europe, the data from the US are not available, and therefore a similar study in the US would be beneficial. Although, these studies have been conducted in several countries of Europe, the data from the US are not available, and therefore a similar study in the US would be beneficial.

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Table 5. Wound size change at 12 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Wound size change (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard care</td>
<td>45</td>
<td>2.5 ± 1.6</td>
</tr>
<tr>
<td>Haemoglobin spray</td>
<td>27</td>
<td>1.5 ± 1.2</td>
</tr>
</tbody>
</table>

*Note: Values are means ± standard deviation

References


Tables

Table 1. Summary of the work of the Arenberger group in 2010 study

<table>
<thead>
<tr>
<th>Product</th>
<th>Standard</th>
<th>Haemoglobin spray</th>
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</thead>
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<tr>
<td>Healing rate (4 weeks)</td>
<td>100%</td>
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</tr>
<tr>
<td>Healing rate (8 weeks)</td>
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<td>100%</td>
</tr>
<tr>
<td>Healing rate (12 weeks)</td>
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Table 2. Differences in healing rates between standard care and haemoglobin spray

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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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Abstract

Throughout the decades, the importance of oxygen in wound healing has been well researched 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 places the burden of wound management which is a vast economic cost to the N.H.S. This poster presents two patients with chronic wounds.

Patient 1 has chronic venous insufficiency due to past history of DVT and ODVT. He has had chronic leg ulcers for more than five years. Although Doppler assessment was done, the ulcer was not covered with the Granulox®. He 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 failed to heal and the patient’s quality of life is drastically reduced.

Both wounds had a lack of oxygen supply which had resulted in necrosis/draining sinuses hence the great impact on wound healing phases. Using topical haemoglobin, to both wounds, is able to improve 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 ulcer 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 the oxygen to the wound healing process has been well researched in recent years. This research shows tissue perfusion and oxygen are crucial factors to optimal healing (Chambers, 2012). However, Bishop (2008) stated that since oxygen is not stored in the tissue, chronic oxygen supply to the wound is paramount for tissue repair to occur completely.

This case report presents the successful management of chronic wounds from two different patients using an adjourned oxygen therapy Granulox®. Granulox® is not yet widely used in the United Kingdom but usage has been internationally. (1,2)

Case report 1
Chronic venous insufficiency from DVT

A 40yr old male patient was diagnosed with chronic venous insufficiency following recurrent skin infections due to continuous ODVT. The patient developed repeated bacterial leg ulcers. The ulcer started 5 years ago with several episodes of wound deterioration.

The patient had a Doppler assessment to determine the ABI prior to starting full two layer compression (K2 system®) 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 DVO and taken a day job in a workshop. Having a painful leg constantly impacts on his day to day job.

Due to an increase in pain, oedema 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 Nurses, the ulcer being cleaned using normal saline solution, antimicrobial impregnated tulle dressing applied to ulcer, sucked out with absorbent pad (high-exudate) and k2 compression applied from knee to toes.

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 maintained with an emollient followed by k2 compression bandaging from toe to knees. The plan included to continue weekly with the new regime. Fig 3 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 oedem is considerably reduced.

Wound margins have reduced further on the 4th week, the patient reports taking less analgesia and is able to sleep on the whole week and no exudate/pain was present.

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

Case report 2
Sternalostomy secondary healing wound

A 57 year old lady had an emergency sternotomy 6 years ago. Due to her recurrent B/H, the wound has had several episodes of infection requiring IV ABX. She had a dehisced sternal wound which has 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 esewate was not contained appropriately and the tissue in the wound bed had a thick, dark yellow brown and an odour.

This patient was then referred to Tissue Viability and on initial inspection it was noted that the wound bed was stenotrophic as described by both the patient and staff.

The patient was started on Granulox® on 22 April 2014, applied daily on the wound bed after being thoroughly cleaned and prepared. The solution followed by the antimicrobial dressing is used) (Fig 5A).

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.

Case report 1
Chronic venous insufficiency from DVT

Fig 2
Wound size, cm²

Fig 3A 13.02.2012

Fig 3B 03.08.2014

Fig 3C 06.08.2014

Fig 3D 16.04.2014

Fig 3E 16.10.2014

Case report 2
Sternalostomy secondary healing wound

Fig 4
Wound size, cm²

Fig 5A 16.04.2014

Fig 5B 12.05.2014

Fig 5C 16.10.2014

Observations, conclusions & discussion

Oxygen plays a major role in wound healing. 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 led to the patients quality of life. After a thorough examination of the wound bed and correct treatment updates made on the evidence base of wound healing, a slight adjustment was made towards their care regimes.

A topical oxygen adjuvant therapy was applied to the wound bed using Granulox®. Granulox® can be applied in any care setting and is easy to use, simply applied over any existing non-adhesive dressing (Fig 6).

Granulox® can be used in different settings and is easy to use and is an easy worldwide dressing (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.
Granulox® in practice: 4 patient case studies

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Minal Padhiar, Diabetes Specialist Podiatrist / minal.padhiar@bhamcommunity.nhs.uk

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Soho Road Health Centre, 247-251 Soho Road, Birmingham
Granulox® in practice: 4 patient case studies

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Minal Padhia, Diabetes Specialist Podiatrist / minal.padhia@bhamcommunity.nhs.uk

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 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 inclusion 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 who have failed to respond to standard care.

Method

Over a six month period, March to July 2014, four patients who 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 regimes, 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 observed, 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.

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

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

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.

Case study 3

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

63 year old Caucasian man with severe associated arthritis deformities affecting both his hands and feet.

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 regimes, 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 observed, or until wound closure. The four patient case profiles are detailed on this poster.

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 Brufenol (8 of each tablet per day, every 4 hours, a large dose of pain killer).

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 24mm length x 77 mm width.

Presentation at Wounds UK Annual Conference 10-12 November 2014 | © The Author. All rights reserved

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.
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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Granulox® product evaluation in non-healing diabetic foot ulcers
Achieving healing in 2 out of 4 cases where standard care failed

Paul Chadwick | Consultant Podiatrist, Salford Royal Hospital NHS Trust, Podiatry & Foot Health | Paul.J.Chadwick@salf.nhs.uk

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.

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 regimes, evaluations and outcomes were monitored at regular patient follow-up.

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.

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).

Figure 2

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 3

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 planter, 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 5 mm (Figure 3A).

Figure 4

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

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

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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 Barco shoe with FP7 insert for offloading. Despite regular debridement and dressing with a range of dressing types (including Acticoat, Inadine, Aquacel), the amputation site remained static 12 months following auto-amputation.

Method:
Granulox was applied weekly, followed 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.

References

Case Study One:

Female, 51 years of age

Previous history:
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 QOD – oesophagitis (2012), Bilateral cataract surgery, peripheral neuropathy.

Medication:
Gliclazide, Aspirin, Folic Acid, Ketorvite, Alfacalcidol, Cholecalciferol, Benereva Sachets, Anaasep, Gabapentin, Oxanduston, Methochromide, Galabentin, Levomepromazine, Movicid, Atorvastatin, Venorer.

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.

Method:
Granulox was applied weekly, following sharp wound debridement, and dressed with Advance, the amputation site remained static 4 weeks post amputation.

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

Case Study Two:

Female, 61 years of age

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, Sebornoctic dermatitis Protein S deficiency.

Medication:
Losartan, Omeprazole, Ferrous sulphate, Clopidogrel, Sternefit, Diproct 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 Barco shoe with FP7 insert for offloading. Despite regular debridement and dressing with a range of dressing types (including Acticoat, Inadine, Aquacel), the amputation site remained static 12 months following auto-amputation.

Method:
Granulox was applied weekly, followed 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.

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