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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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 promotes a rapid treatment for chronic leg ulcers. Previous reports have shown exponential improvement in healing rates with haemoglobin spray as soon as intended randomization of the drug was achieved. However, the exact potential benefit of haemoglobin spray is not yet known. Method: Further analysis of data from the post hoc analysis of the 4-week study shows the healing rates of patients treated with haemoglobin spray. Results: Patients in the haemoglobin spray spray arm showed a significantly higher healing rate (p<0.0001) after 13 weeks compared to patients treated with standard care alone. As illustrated in Figure 1, a significant 53% average wound-size reduction in the haemoglobin spray spray arm was achieved. The results in the haemoglobin spray spray arm showed a significant healing rate of 97% at 13 weeks compared to 47.1% in the standard care alone group.

Discussion

These findings achieve benefits across a large range of outcomes, from rates of wound closure to the size of wounds at the end of the treatment. The combination of haemoglobin spray and standard care is likely to enhance the real-life benefit of wound healing, which is evidenced by the positive changes in the clinical parameters. Further research should be conducted to explore the underlying mechanisms of haemoglobin spray in wound healing, which may contribute to a more effective treatment strategy for chronic venous leg ulcers.

Keywords: haemoglobin, chronic venous leg ulcers, healing outcomes, post hoc analysis.

References

2. Granix® (granulocyte colony-stimulating factor) [prescribing information].

Image of the page with the abstract and discussion.
The role of Granulox® in chronic wound healing
Two case studies

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**The role of Granulox® in chronic wound healing**

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**Annexure A**

**The importance of oxygen in wound healing**

Throughout the decades, the importance of oxygen in wound healing has been well researched. This research shows tissue perfusion and oxygenation are crucial factors for optimal healing.

This case report presents two different patients whose wounds were not healing due to lack of oxygen. The importance of oxygen in wound healing was demonstrated through the use of Granulox®, a hydrogel medication that can be used as an adjuvant therapy to improve wound healing.

**Case report 1**

**Chronic venous insufficiency from DVT**

A 40 yr old male patient was diagnosed with chronic venous insufficiency following an episode of deep vein thrombosis (DVT). He also had continuous DVT. The patient developed a sternal wound of six years duration which due to recurrent infection had failed to heal. Despite having several evidence-based wound care therapies, the sternal wound still had not healed and the patient’s quality of life is disrupted.

Both wounds had a lack of oxygen supply which had resulted in necrosis due to the lack of oxygen in wound healing phases. Using topical haemoglobin to both wounds provided an improved 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.

**Case report 2**

**Sternotomy secondary healing wound**

A 57 year old lady had an emergency sternotomy 6 years ago. Due to her recurrent B.8 health, the wound has had several episodes of infection requiring IV ABX.

She had a debossed 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.

**Observations, conclusions & discussion**

Oxygen plays a major role in wound healing, and 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 eventual dressing change on the patients quality of life. After a thorough examination of the wound and constant treatment updates made on the evidence base of wound healing, a slight adjustment was made to the dressings and healing regime.

A topical oxygen adjunct therapy was applied to the wound bed (Fig 6). This stimulated the healing process once again and corrected the hypoxic state to an oxygenated state. Granulox® has demonstrated 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 apply before any new dressing (if 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.

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**References**

7. GMS Krankenh营养 Interdiszipl; 2011 6(1).
Granulox® in practice: 4 patient case studies

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Granulox® in practice: 4 patient case studies

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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 and guideline inclusions in the UK, Birmingham Community Healthcare NHS Trust decided to evaluate Granulox® for inclusion, as an add-on to standard care for a minimum of 12 months.

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.

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 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. Wound size 24mm length x 77 mm width.

Treatment response

- Patient was initiated on Granulox® in March 2014, applied 2 times per week.
- Ulcer decreased in size from 4mm x 5mm to 2mm x 3mm (80%).
- Pain level decreased from 7 > 4. Wound is still ongoing. He has currently used 11.08.14 had 41 applications of Granulox®.
- Continuing with Granulox® as substantial improvement was noticed.

Ulcer resolved 27.06.14 after 12 applications of Granulox®.

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.

Ulcus present since December 2013. Commedicated 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.

Ulcer resolved 15.05.14, after 12 applications of Granulox®.

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 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).

Commedicated Granulox® 24.03.14. Wound size of the wound on the medial side of hallux 16mm 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.
- Ulcer of right hallux 6mm x 9mm wound resolved 27.06.14 after 27 applications of Granulox®.

Case study 4

Right and left heel wound

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

Wound treatment started 16.05.2014. She received tramadol, paracetamol and ibuprofen (8 of each taken 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 20mm 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 a reduction from 24mm length x 78 mm width (16.06.14) to 12.07.14 and 16 applications of Granulox®.
- Pain level decreased from 11 to 4.

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

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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 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 inclusions in the UK, the Salford Royal Hospital NHS Foundation Trust decided to evaluate Granulox®.

This paper presents the results from this product evaluation in non-healing diabetic foot ulcers. 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.

Method

Over a seven month period, from 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.

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.

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

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

Patient 1
Neuropathic diabetic foot ulcer after amputation

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

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

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 4

(A) Baseline

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 hydrofibre but 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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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 arterial 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.

Case Study One: Female, 51 years of age

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.

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 aut amputation of distal right long toe. Seborrhoeic dermatitis Protein S deficiency.

Medication: Losartan, Omeprazole, Ferrous sulphate, Clopidogrel, Sterneum, Doprost 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, Isadine, 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.

References


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