Evaluating the use of a topical haemoglobin spray as adjunctive therapy in non-healing chronic wounds – a pilot study

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Abstract

Chronic wounds are a major financial burden across the globe and South Africa is no different. Wounds cannot heal without oxygen and chronic wounds are often featuring delayed healing not only due to vascular issues but often due to chronic inflammation associated with a prolonged inflammatory phase. The purpose of this pilot study was to evaluate the use of a topical porcine Haemoglobin spray (Granulox® provided by ReDermis) as an adjunctive therapy in the treatment of non-healing chronic wounds such as diabetic foot ulcers, venous leg ulcers, arterial ulcers and pressure ulcers. Patients selected were all complicated cases with a number of co-morbidities influencing the normal wound healing cascade.

Introduction

It is no secret that chronic wounds are a major financial burden across the globe and South Africa is no different. With the global rise of diabetes as well as obesity we have seen a significant increase in diabetic foot ulcers leading to amputation as well as an increase in the number of patients suffering from venous and or arterial insufficiency with leg ulceration. We also know that key to the wound healing cascade is sufficient blood supply and therefor also tissue oxygenation. Mild hypoxia is a normal biological process following the initial wound injury, followed by a series of initial responses such as seen within the inflammatory phase. During the inflammatory phase oxygenated plasma diffuses from the surrounding intact tissue to the hypoxic wound area, to facilitate healing (Bishop, 2008). Without a sustainable amount of oxygen the overlapping wound healing phases (hemostasis, inflammation, proliferation and maturation) cannot take place. In the case of extreme hypoxia and local ischaemia insufficient oxygen reaches the wound; this is a common feature associated with chronic wounds or non-healing wounds (Sen, 2009). In this type of environment Reactive oxygen species (ROS) thrive resulting in more tissue damage, other cellular processes also kicks in and stall wound healing keeping the wound trapped in the inflammatory phase.

If the vascular system is compromised and sufficient oxygen cannot be delivered naturally, supplemental oxygen has been shown to aid healing (Gottrup, 2004). Supplemental oxygen delivery through topical haemoglobin seems to be a more practical solution than other existing oxygen therapies. The topical haemoglobin has the ability to bind atmospheric oxygen and transporting it directly in to the wound bed where it is released within the wound bed tissue (Arenbergerova, et al., 2013).

The purpose of this pilot study was to evaluate the use of a topical porcine Haemoglobin spray (Granulox® provided by ReDermis) as an adjunctive therapy in the treatment of non-healing chronic wounds such as

diabetic foot ulcers, venous leg ulcers, arterial ulcers and pressure ulcers. Patients selected were all complicated cases with a number of co-morbidities influencing the normal wound healing cascade.

Granulox® (ReDermis) is a noval haemoglobin spray produced from porcine blood products, the haemoglobin binds atmospheric oxygen and carries it to the wound bed, where it is then released. Haemoglobin does not get used up or dissipate it facilitates diffusion and can create a cycle of continuous oxygen support (Arenbergerova, et al., 2013). At the start of this South African pilot study limited information on the use of Granulox were available other than the examples of a few other pilot case studies across the globe. Findings in this study correlates with the consensus recommendations from Chadwick et al 2015 (Chadwick, et al., 2015).

Method

A total number of 11 patients with a wide variety of chronic wounds were selected. All patients had a history of non- healing wounds for longer than 8 weeks. Informed consent were obtained from all participants for the treatment. All patients were informed about the porcine origin of the product. See Inclusion and exclusion criteria as summarized in Table 1.

In all these patients the basic principles of wound bed preparation was followed according to the international Wound Bed Preparation Guideline (Sibbald RG, 2006) (Sibbald R.G., 2011).

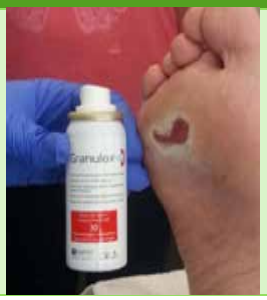
All wounds were required to have visible granulation tissue present with no clinical signs of infection present at the start of the study, as recommended by the Working Group on the use of topical haemoglobin in chronic wound management consensus recommendation. (Chadwick, et al., 2015). See *Figure 1* illustrating the pathway suggested by the Consensus group in 2015.

Frequency of haemoglobin application was initially 2-3 times per week and then reduced to once a week.

Wounds and surrounding skin were washed with a diluted antisepticum soap to decrease bio load from surrounding tissue. Sharp debridement was done where necessary to remove slough and debris before application. All wounds were cleaned with a combination Polihexanide and Betaine solution prior to application. Granulox® (ReDermis) were uniformly sprayed form about 5-10cm above the wound *(See Granulox® (ReDermis) practical application.)* Wound dressings used were all breathable non-occlusive dressings.

Photographs were taken at each dressing change and wound bed described according to TIME. Longest length and width were measured and recorded.

Granulox® (ReDermis) were stored in the refrigerator at (2˚C - 8˚C)

Granulox® (ReDermis) applied in practice			
			
Wound cleansed with PHMB and Betaine solution	Application of Granulox spray 5-10cm away from the wound		Hydropolymer foam dressing
			
Wound cleansed with PHMB and Betaine solution. Fibrin debrided via sharp debridement		Application of Granulox spray 5-10cm away from the wound	Patients are educated about the look and colour of the product
			
Application of Granulox® (ReDermis) during the pilot study			Using hydrophobic dressing as contact layer

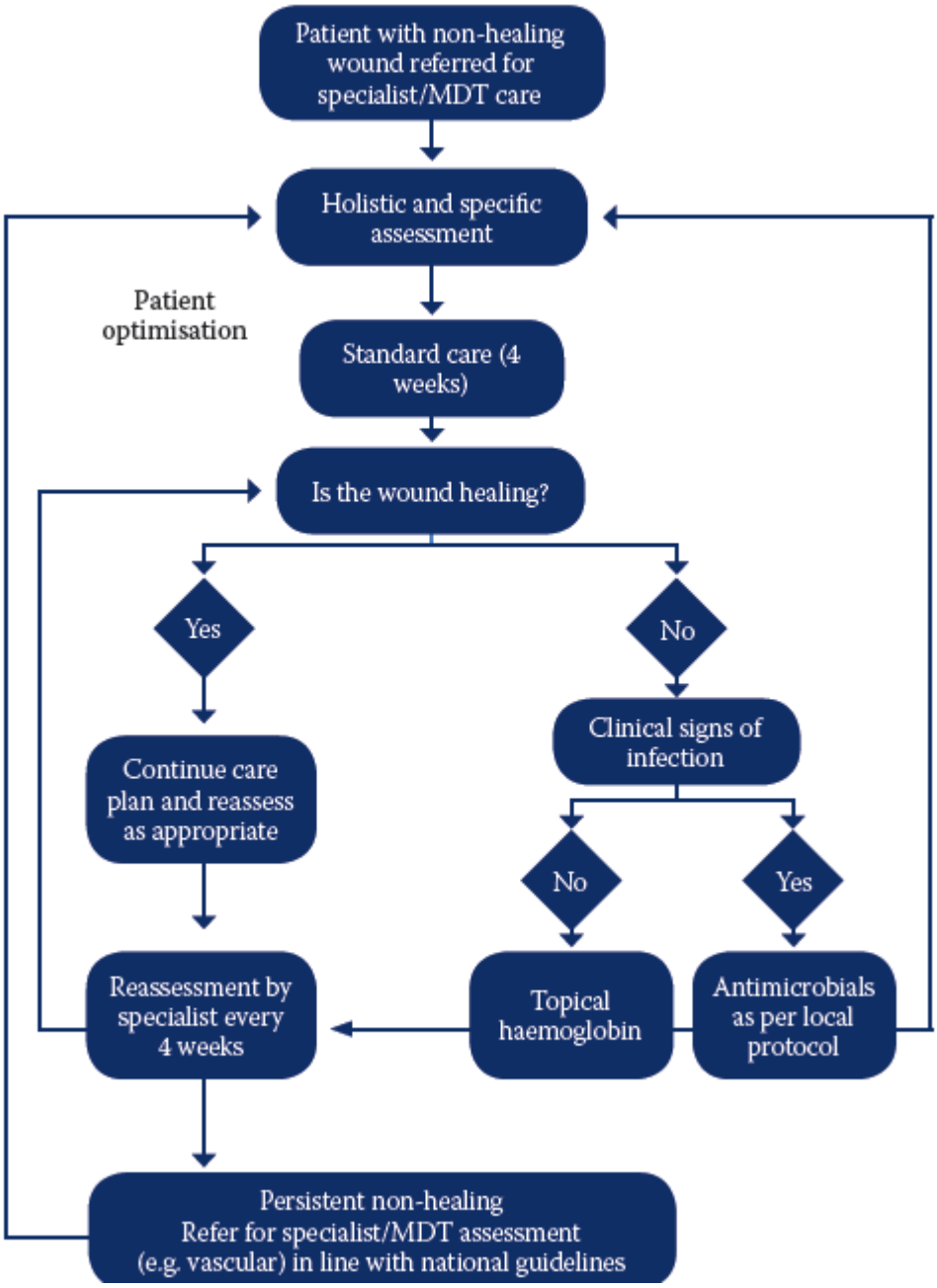


Figure 1: Practical advice for Granulox in clinical practice. (Chadwick et al 2015)

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Non-healing or slow healing wound duration longer than 8 weeks	• Clinical signs of deep tissue infection
• No clinical signs of deep tissue infection	• Patient declined consent
• Clean wound bed	• Patient unable to follow up at the Centre
• Informed consent	• Religious, cultural or dietary objections from the patient
• Patient to be able to visit Centre for follow up and data capturing	• Non-compliant patient with care regime
• Superficial slough or fibrin present with granulation tissue	

Table 1: Pilot study inclusion and exclusion criteria

Patient demographics are shown in *Table 2*. All patients who met the inclusion criteria were enrolled in the pilot study also patient with little slough and fibrin that was easily debrided. 63% of Patients treated had chronic leg ulcers which varied in origin as displayed in *Table 2*.

PATIENTS (*n*=11)	DESCRIPTION	% or MEAN
GENDER	Male Female	*n* = 6 *n* = 5
AGE (years)	50 - 83	Mean = 70.2
WOUND DURATION PRIOR TO APPLICATION (weeks)	24 - 72	Mean = 35.2
WOUND DURATION STUDY (weeks)	3 – 9	Mean = 5.4
WOUND TYPE	Venous ulcer Mixed venous arterial ulcer Rheumatoid venous ulcer Diabetic foot ulcer Pressure ulcer Surgical	n = 3 (27.2%) n = 2 (18.2%) n = 2 (18.2%) n = 2 (18.2%) n = 1 (9.1%) n = 1 (9.1%)
WOUND SIZE (mm)	Length (10-125) Width (9 – 75) Depth (1-5)	Mean = 52.5 Mean = 27.1 Mean = 2.5
WOUND DESCRIPTION	Slough or fibrin with granulation Granulation	n = 5 n = 6

Table 2: Patient demographics of pilot group *n* = 11

Results

The outcomes of the pilot study is summarized in *Table 3*. All wounds showed a significant decrease in wound size especially during the first two weeks of application. The average reduction in wound size irrespective or the original size of the wound was 12% within 1 week of application. Wounds also showed a reduction of more than 43% on average after 4 weeks of treatment. 18% of the patients in the study were healed by 4 weeks. 45% of the patients had to discontinue treatment with Granulox due to infection. 36% of the patient in the study discontinued with using Granulox and continued to heal thereafter. All patients experienced a reduction in wound pain and verbalized that the progression of healing was improving their quality of life. It was also evident during the study that fibrin formation delays wound

healing especially when Granulox were applied at longer intervals. See summary of cases and treatment response in *Table 3-14*.

PATIENT	WOUND TYPE	PRIOR WOUND DURATION	TREATMENT DURATION	TREATMENT RESPONSE
Patient 1 (NEL003) Table 4	Mixed arterial and venous ulcer	28 weeks	4 weeks	Wound decreased from 32mm x 24mm to 16mm x 11 mm. More than 50% reduction in size. Also very good improvement in tissue quality.
Patient 2 (JAN010) Table 5	Diabetic foot ulcer	72 weeks	9 weeks	Wound decreased from 37mm x 18mm to 9mm x 4mm. More than 70% reduction in wound size. Very significant difference in size within the first 3 weeks with very good quality epithelialization. Granulox® was discontinued after 9 weeks due to infection and increased pressure
Patient 3 (PEL003) Table 6	Pressure ulcer	24 weeks	4 weeks	Wound initially increased in size by 2mm. then decreased from 12mm x 10mm to 7mm x 3 mm. More than 25% reduction in size. Significant decrease of fibrinious layer within 1st week.
Patient 4 (MOG001) Table 7	Venous leg ulcer	48 weeks	3 weeks	Wound decreased from 48mm x 42mm to 26mm x23mm within 3 weeks. A reduction of close to 50%. Granulox® was discontinued to clinical signs of infection and wound continued to heal on its own.
Patient 5 (SMI013) Table 8	Venous leg ulcer	24 weeks	8 weeks	Wound decreased from 23mm x 17mm to 3mm x 6mm. Granulox® discontinued because patient could not follow up at Centre anymore. Wound healed on its own further
Patient 6 (KEK002) Table 9	Diabetic foot ulcer	36 weeks	8 weeks	Wound decreased from 86mm x 32mm to 70mm x 25mm. Slow but steadily improvement in spite of continues fibrin formation on top of the wound bed. Fibrinious layer removed via sharp debridement. Granulox® discontinued due to Pseudomona infection
Patient 7 (JOS001)	Venous leg ulcer	36 weeks	4 weeks	Wound healed
Patient 8 (VAN070)	Rheumatoid venous ulcer	24 weeks	3 weeks	Wound initially decreased from 20mm x 20mm to 16mm x 12mm within 3 weeks. Granulox® were discontinued due to infection.
Patient 9 (PIE010)	Venous leg ulcer	48 weeks	6 weeks	Patient responded positively during the first two weeks. There after seemed to be a struggle and treatment was discontinued at 6 weeks
Patient 10 (LIE006)	Surgical	30 weeks	3 weeks	Wound decreased from 63mm x 9mm to 30mm x 3mm within 3weeks. More than a 50% reduction in size. Granulox® discontinued because patient is going on holiday
Patient 11 (DEA001)	Rheumatoid venous ulcer	72 weeks	8 weeks	Wound decreased from 125mm x 42mm to 87mm x 25mm. Almost 40% reduction in size. Granulox® had to be discontinued

				due to infection

Table 3: Outcomes from pilot study n=11

PATIENT 1 (NEL003) PHOTO REPORT

		
Baseline photo **L=32mm, W=24mm**	**Week 1 photo** **L=26mm, W=20mm**	**Week 4 photo** **L=16mm, W=11mm**

Table 4: Patient 1 (NEL003)

PATIENT 2 (JAN010) PHOTO REPORT

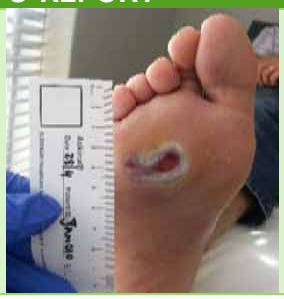
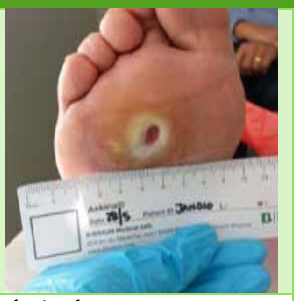
			
Baseline photo **L=37mm, W=18mm, D=3mm**	**Week 1 photo** **L=33mm, W=18mm, D=2mm**	**Week 4 photo** **L=12mm, W=6mm, D=1mm**	**Week 6 photo** **L=9mm, W=4mm, D=1mm**

Table 5: Patient 2 (JAN010)

PATIENT 3 (PEL003) PHOTO REPORT

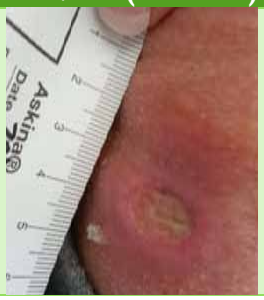
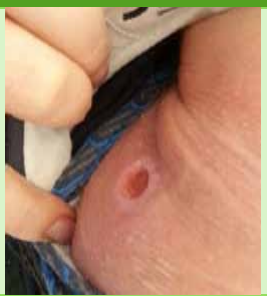
			
Day 5 **L=12mm, W=10mm, D=2mm**	**Week 2 photo** **L=9mm, W=6mm, D=1mm**	**Week 3 photo** **L=6mm, W=5mm, D=0mm**	**Week 4 photo** **L=7mm, W=3mm, D=0mm**

Table 6: Patient 3 (PEL003)

PATIENT 4 (MOG001) PHOTO REPORT

			
Baseline **L=48mm, W=42mm, D=3mm**	**Week 1 photo** **L=35mm, W=33mm, D=2mm**	**Week 3 photo** **L=26mm, W=23mm, D=1mm** **Granulox discontinued**	**Week 4 photo** **L=6mm, W=3mm, D=0mm**

Table 7: Patient 4 (MOG001)

PATIENT 5 (SMI013) PHOTO REPORT

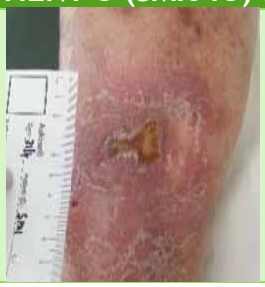
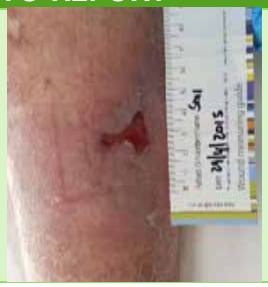
			
Baseline **L=23mm, W=17mm, D=1mm**	**Week 1 photo** **L=21mm, W=16mm, D=1mm**	**Week 4 photo** **L=8mm, W=14mm, D=1mm**	**Week 8 photo** **L=3mm, W=6mm, D=0mm** **Granulox discontinued**

Table 8: Patient 5 (SMI013)

PATIENT 6 (KEK002) PHOTO REPORT

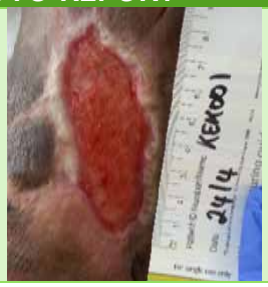
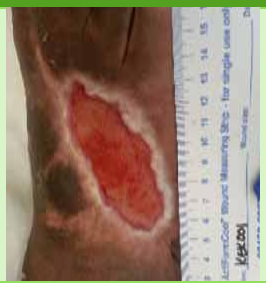
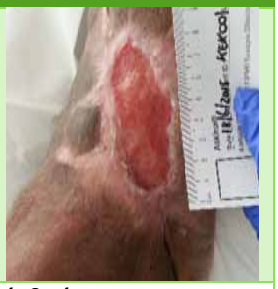
			
Baseline **L=86mm, W=32mm, D=3mm**	**Week 1 photo** **L=80mm, W=30mm, D=2mm**	**Week 4 photo** **L=80mm, W=28mm, D=2mm**	**Week 8 photo** **L=70mm, W=25mm, D=2mm** **Granulox discontinued**

Table 9: Patient 6 (KEK001)

PATIENT 7 (JOS001) PHOTO REPORT

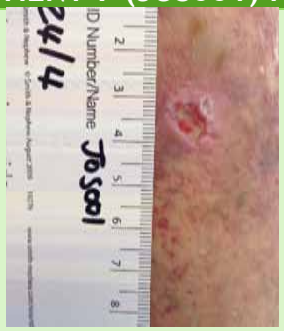
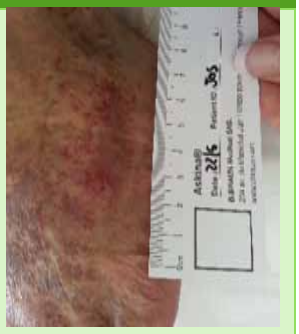
			
Baseline **L=13mm, W=9mm, D=2mm**	**Week 1 photo** **L=13mm, W=7mm, D=2mm**	**Week 2 photo** **L=10mm, W=5mm, D=2mm**	**Week 4 photo** **Healed** **Granulox discontinued**

Table 10: Patient 7 (JOS001) PHOTO REPORT

PATIENT 8 (VAN070) PHOTO REPORT

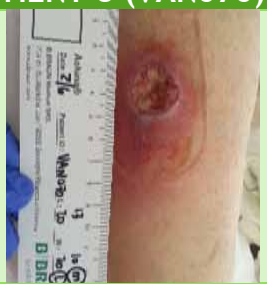
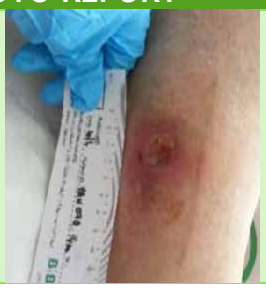
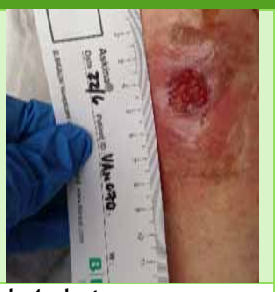
			
Baseline **L=20mm, W=20mm, D=3mm** **Localised infection and chronic inflammation**	**Week 1 photo** **L=16mm, W=16mm, D=2mm**	**Week 3 photo** **L=12mm, W=16mm, D=2mm** **Inflammation flare up due to arthrites**	**Week 4 photo** **L=16mm, W=18mm, D=1mm** **Granulox discontinued due to infection**

Table 11: Patient 8 (VAN070) PHOTO REPORT

PATIENT 9 (PIE010) PHOTO REPORT

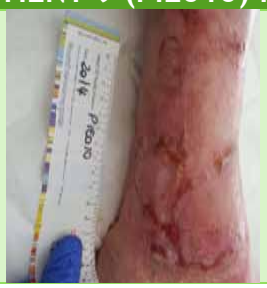
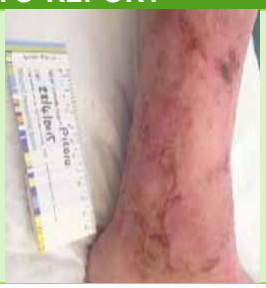
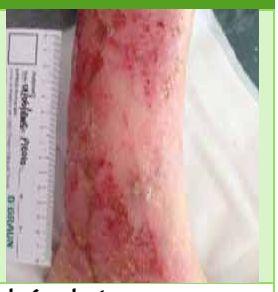
			
Baseline **L=120mm, W=75mm, D=2mm** **Chronic inflammation**	**Week 1 photo** **Over all decreae in size of all ulcers**	**Week 5 photo** **Inflammation flaring up also new satelite wounds**	**Week 6 photo** **Granulox discontinued due infection and skin erythema**

Table 12: Patient 9 (PIE010) PHOTO REPORT

PATIENT 10 (LIE006) PHOTO REPORT			
			
Baseline **L=63mm, W=9mm,** **D=5mm**	**Week 1 Photo** **L=50mm, W=6mm,** **D=3mm**	**Week 2 Photo** **L=40mm, W=5mm,** **D=2mm**	**Week 3 Photo** **L=30mm, W=3mm,** **D=2mm** **Granulox discontinued patient going on holiday**

Table 13: Patient 10 (LIE006) PHOTO REPORT

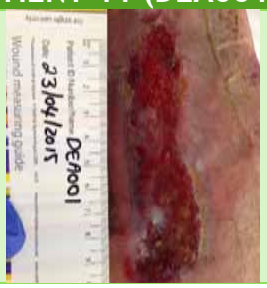
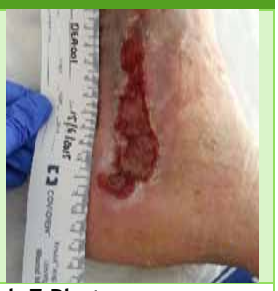
PATIENT 11 (DEA001) PHOTO REPORT			
			
Baseline **L=125mm, W=42mm,** **D=3mm**	**Week 1 Photo** **L=120mm, W=36mm,** **D=2mm**	**Week 4 Photo** **L=110mm, W=32mm,** **D=2mm**	**Week 7 Photo** **L=87mm, W=25mm,** **D=1mm** **Granulox discontinued due to infection**

Table 14: Patient 11 (DEA001) PHOTO REPORT

Conclusions

All patients showed an increase in wound healing and improvement in granulation tissue and epithelialization within 7 days of treatment. In 4 of the patients topical application of Haemoglobin was halted for a limited time period following increased fibrin formation and clinical signs of infection were noted. This was very significant in Patient KEK001 with a history of chronic Pseudomona infections.

Overall no adverse effects were noted nor any allergic reactions. The topical Haemoglobin can be applied during all phases of wound healing, but we noted improved results when wounds were clean with no slough nor signs of infection present.

This pilot study and the evidence provided certainly shows that there is great potential for the use of Granulox® (ReDermis) in the treatment of chronic wounds or wounds that show signs of tissue hypoxia. This novel porcine haemoglobin spray delivers vital oxygen to the wound bed and has a direct impact on the quality of tissue formation as well as the speed of healing. Patient compliance is essential and the recommended application time is every 2-3 days to ensure the best possible result. Some of the cases treated had delayed healing for more than 72 weeks with a mean of 52 weeks between the 11 cases. On average there was a 43% reduction in wound size within 4 weeks of treatment.

The wound healing results from this study is very similar to the pilot study done by Chadwick (Chadwick, 2014) even though the treatment duration was much shorter for the purpose of this study.

The results with regards to decrease in superficial slough and fibrin in this study were also very similar to a study done by Hunt in 2015 on 100 outpatients with sloughy wounds (Hunt, 2015).

We do need more randomized control trails to further evaluate this product especially with regards to its mode of action and the level of oxygen available in the wound bed.

Recommendation as to which wound dressing as secondary dressing would be best suitable with the use of Granulox® (ReDermis) will also be very beneficial. From the pilot study it seems that silicone foam dressings work best, but composite wound dressings can also be beneficial when exudate is a factor.

Monitoring the clinical signs of infection is essential in the use of Granulox® (ReDermis) and it is recommended that a qualified Health Professional be involved in the treatment plan including a qualified Wound Care Practitioner.

Within the South African environment I am not convinced that Granulox® (ReDermis) should be used by the general public without the supervision of a qualified Health Professional. Even though there were no side effects, wounds that did develop infection and also subsequent fibrin formation increased in size.

Declaration of interest

All products for the evaluation were provided by ReDermis, which had no control over or involvement within this data or any previous data collections, analysis or article submissions

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