Exploring the effectiveness of topical haemoglobin therapy in the acute care setting on diabetic foot ulceration

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Article points

1. Overcoming diabetic foot ulceration challenges
2. Addressing oxygen deficiency in chronic wounds
3. Topical haemoglobin therapy as an adjunct to gold standard care.

Key words

- Diabetic foot ulceration
- Haemoglobin therapy
- Oxygen deficiency

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Diabetic foot ulceration (DFU) is a particularly challenging wound group in today's healthcare arena, occurring across primary and secondary care settings, resulting in physical, psychological and financial burden to the patient and healthcare provider. According to Edmonds (2007), the most common occurrences that clinicians and patients experience are infection, tissue trauma and deterioration, amputation and resulting disability. Clinicians, healthcare stakeholders and industry, alongside patient focus groups, are constantly seeking new ways of preventing, managing and improving DFU outcomes through exploring new and exciting innovations, such as topical oxygenation therapy as an adjunct to standard care (Norris, 2014; Bateman, 2015; Tickle, 2015). This article will discuss the positive outcomes in relation to wound healing, pain reduction, slough reduction and exudate levels within an acute setting of 20 patients who presented with chronic DFU and who received topical haemoglobin therapy via a spray device, compared with a similar group who received standard care only by the same clinical teams in the same ward environment.

The diabetic phenomenon is global in scope with an arguably underestimated 2.8% of the world's population being diagnosed with this condition anticipated to reach figures of above 4.4% by the year 2030 (Wild et al, 2000). Diabetes is a lifelong condition and patients will experience both acute and chronic complications, often multiple and complex, affecting all of the major organs of the body, increasing mortality rates as the patient ages (NICE, 2015). Patients with diabetes are cared for across all clinical arenas due to the nature of the disease and its secondary causes, which often results in inconsistencies of care delivery and management for this group, according to Wild et al (2000). Many centres now have diabetes specialists that through referral processes follow up this patient group to ensure gold standards of care are initiated, and national guidelines and policy are adhered to in order to ensure patient safety, positive outcomes and optimisation of care occurs.

DFU injury and tissue destruction is common and difficult to manage and ultimately heal. It often results in tissue loss, infection, pain and an overall negative impact upon the patient socially, physically and psychologically, according to Bateman (2015). It is estimated that around 7% of people with diabetes will develop at least one DFU over their lifetime (Hunt et al, 1969) and it represents one of the most common reasons for admission to a healthcare setting in the UK, stated Dow (2001). A report published by NHS Diabetes states that £650 million is spent in the UK alone on treatment of DFU and associated amputations each year (Arenberger et al, 2011).

Oxygen within the wound-healing process

Oxygen is a vital element within the wound-healing process; it is required at all stages of inflammation through to eventual healing and scar formation (Petri et al, 2016). Within normal cellular function, an O^2 tension range of 30 mmHg is required to enable normal cellular division when the body is not in the inflammatory stage. However, when the inflammatory phase of wound healing has been instigated, this oxygen tension range is increased to 50–100 mmHg, automatically placing the tissues in a

Page points

1. Diabetic foot ulceration (DFU) poses clinical challenges across all healthcare specialities, despite gold-standard care intervention
2. Oxygenation of all wounds within the phases of wound healing is essential for optimal outcome achievement
3. Topical haemoglobin therapy demonstrates positive outcomes when treating DFU as an adjunct to standard therapy in respect of wound healing, exudate reduction and pain reduction.

hypoxic state; this relates to all tissue injury, be it acute or chronic in nature (Gordillo et al, 2008). In 2016, work carried out by Petri et al, using photoacoustic imaging of real-time tissue oxygen changes in chronic leg ulcers pre- and post-application of topical haemoglobin therapy, found increased oxygenation of tissues from 56% pre-application to 69% at five minutes and 78.8% at 20 minutes post-application. Although a pilot study in its early stages, it highlights the theory behind hypoxia and its related impact upon the wound healing stages, particularly as it is already known that tissue oxygenation needs to be at a range of 50–100 mmHg for optimisation of cellular division.

Wound healing and oxygenation of cells and tissues is, therefore, essential for progress through the stages of inflammation to wound maturation (Dissemond et al, 2015), within the diabetic patient population. However, their biological capacity is generally greatly reduced due to multiple factors, such as related cardiovascular insufficiencies, macro and micro angiopathy, obesity, reduced immobility and altered gait (NICE, 2015). Temporary hypoxia after injury triggers wound healing by stimulating the release of growth factors and angiogenesis, but persistent hypoxia delays wound healing by increasing the levels of oxygen free-radicals (O'Loughlin et al, 2010; Braun et al, 2014). The resulting chronically oxygen-depleted cells in these patients have devastating effects on vulnerable tissue, often resulting in infection, wound deterioration, death of tissue and amputation (Winfeld, 2014).

Topical haemoglobin therapy

A topical haemoglobin contact spray (Granulox®, Infirst Healthcare) is a novel treatment that accelerates healing in slow-healing wounds, including DFU, and it was first approved for use in chronic wounds in 2012. The active ingredient is pure haemoglobin of porcine origin and its mode of action is to bind oxygen from the atmosphere and then release it into the wound bed by facilitating diffusion (Feldmeier et al, 2005; Timmons, 2006; Sen, 2009; Schreml et al, 2010; Arenbergerova et al, 2013).

Methodology

The evaluation was conducted in an acute ward environment in a large UK acute hospital, with patients recruited in February 2015 and monitored for a 6-month period (28 weeks). The comparison control group was retrospectively selected from the same clinic and period in February 2014 from admission records. It must be stressed that comparison control group analysis is not ideal, but does provide an insight into current practice within the same environment with the same clinicians outside of Granulox application.

The evaluation was not conducted as a formal clinical study, but data on the use of the haemoglobin spray and the outcome of the wounds were collected by the wound care specialist as part of standard care and then compared retrospectively to a similar cohort of patients, using the same inclusion and exclusion criteria, during the same period the previous year. Ethics Committee approval was not required in line with the NHS Trust's policy on clinical evaluations of CE-marked products used within their licensed indications without randomisation — if this had been a randomised controlled trial, approval by the Ethics Committee would have been required. Patients were required to give verbal consent following an explanation and review of the product and information leaflet prior to receiving the haemoglobin spray. This procedure was documented by the clinician in the patient notes.

The same inclusion and exclusion criteria applied to both patient cohorts. Inclusion criteria comprised patients aged >18 years with a DFU that had failed to heal substantially, defined as <40% reduction, in the past 12 weeks. The DFU had to be located below the ankle and have a Site, Ischaemia, Neuropathy, Bacterial Infection, Area and Depth (SINBAD) score of a maximum of 2. The SINBAD classification system encompasses variables that are recognised to contribute to ulcer outcome. The maximum SINBAD score of 2 was selected for this evaluation, since patients scoring ≥3 usually have vascular insufficiency and other wound healing issues that would impair the effectiveness of any wound-healing product. It is well recognised that any tissue injury is hypoxic, whether the patient has any comorbidities or not. Petri et al (2016) found up to a 30% reduction of oxygen in wounds.

Patients were excluded if they presented with infected ulcers, were receiving systemic antibiotic therapy or corticosteroids, were pregnant or lactating, had an ankle-brachial pressure index (ABPI) <0.5 or toe pressure <70 mmHg, or an HbA_{1c} measurement >10% (13.3 mmol/L), in line with

the recommendations for use on the product label, where underlying conditions should be treated and all alternative options for revascularisation of arterial insufficiency should have been exhausted.

A total of 20 patients who presented within the ward with a chronic DFU for ≥12 weeks who met the inclusion criteria and who verbally consented to participation were treated with standard wound care plus haemoglobin spray and were thus monitored over the full 28-week period. Both cohorts of patients were cared for in the same clinical setting by the same medical team, following gold standard practice, such as offloading, formulary and guidelines. The patients in the haemoglobin spray group were also maintained on the same dressing type they were using prior to the evaluation. Debridement was carried out in both groups based on medical need. The haemoglobin spray was applied in the clinical environment by the usual clinician twice a week until complete wound closure occurred, with dressings changed each time the haemoglobin spray was applied. If required for appropriate wound management, additional dressing changes were permitted as usual practice. Granulox was only applied twice a week (*Table 1*).

All clinical data regarding wound size, exudate levels, slough and pain levels were collected by the author at each dressing change using the standard assessment documentation based upon Applied Wound Management (Gray et al, 2005). Wound size was measured using a sterile disposable paper ruler as part of the author's dressing pack for consistency. Pain management and scoring was evaluated using the usual format of the McGill pain index tool (0 being pain free to 10 being the worst experience of pain). Data from the comparison control group were collected retrospectively from electronic and paper records by the author; this represented patients from the same clinical area, cared for by the same team, using the same policies and care plans at the same period exactly a year prior. The same exclusion and inclusion criteria were applied to minimise sampling bias.

Statistical analysis

Statistics are reported using a chi-square test for group level (nominal) data and unpaired two-tailed t-test for numeric (parametric) values. Statistical significance was defined as $p<0.05$. No adjustment for multiple statistical analysis was made. The primary outcome was defined as wound closure after 28 weeks.

Table 1. Baseline data.

Category	Haemoglobin spray group (n=20)	Control group (n=20)	P-value
Mean age (range), years	55.0 (18-89)	54.4 (28-85)	0.92
Gender (male/female), n	10/10	11/9	0.75
Mean HbA1c at week 0, %	7.0	6.9	0.84
Mean wound size at week 0, cm2	5.1	6.6	0.45
Mean SINBAD score (score 1/ score 2)	8/12	8/12	1.0
Duration of wound at week 0 (range), months**	5.8 (3-18)	5.4 (3-12)	0.69
Neuropathy present (Yes/No)	10/10	9/11	0.75
Ischaemia*** present (Yes/No)	9/11	8/12	0.75

Key:
*p> for difference between the two groups, using chi-square for group level data and independent two-tail t-test for numeric variables
**Based on oval of L*W
***Vascular deficiency to foot

Results

A total of 40 patients were included in this evaluation: 20 patients in the haemoglobin spray group, and 20 in the retrospective control group. The mean age of the patients was 55.0 years in the haemoglobin spray group and 54.4 years in the control group (range was 18 to 89 years). In the haemoglobin spray group, 50% of the patients were male and in the control group 55% were male. The mean HbA_{1c} was 7.0%/8.6 mmol/L in the haemoglobin spray group and 6.9%/8.4 mmol/L in the control group (*Table 2*). Anatomical sites for the DFU represented the common sites, according to Edmonds (2007), with the most common being the plantar (haemoglobin group 40%, control group 50%).

The mean time for wounds being present prior to the application of haemoglobin spray was 5.8 months compared with 5.4 months in the control group. The mean baseline wound size was slightly larger in the control group (6.6 cm^2 versus 5.1 cm^2 in the haemoglobin spray group (p=0.45)). Eleven patients in each group utilised various methods of off-loading which equated to 55% of each group, the most common device was that of surgical footwear.

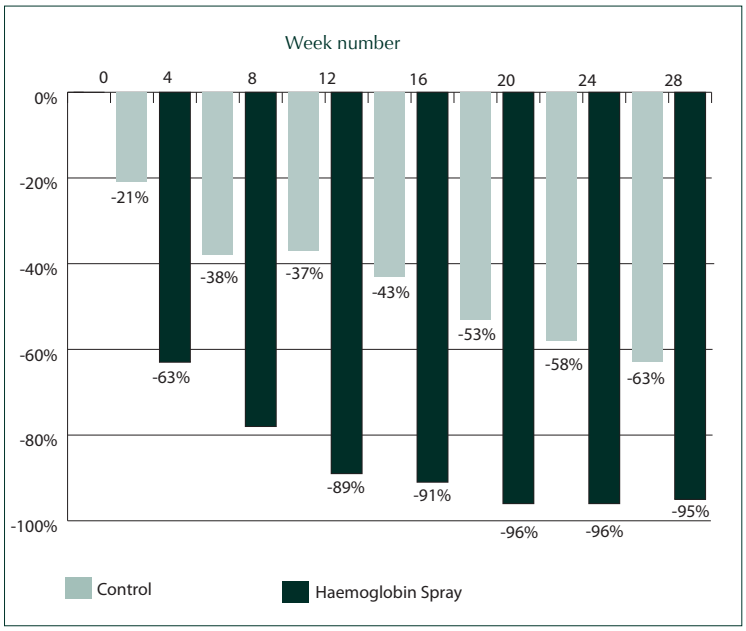

Figure 1. % wound size reduction weekly.

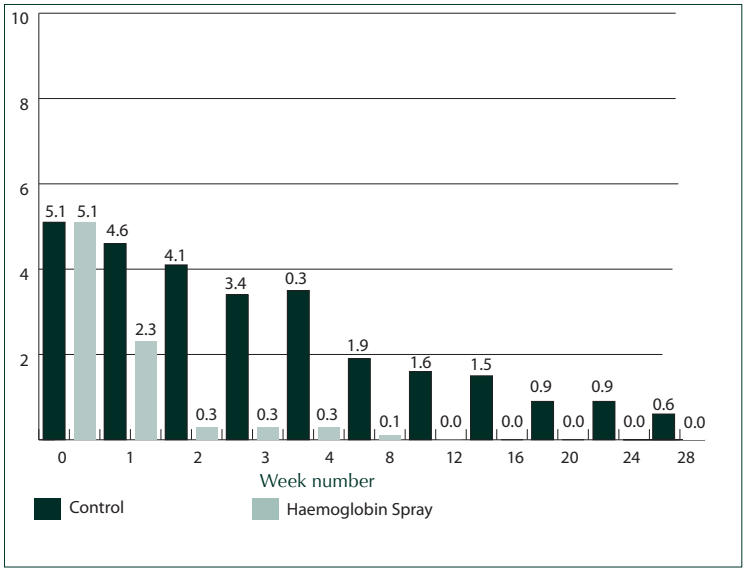

Figure 2. Pain scores – (0 = no pain, 10 = worst pain).

Overall, there were no statistically significant differences between the two groups at baseline for any of these parameters.

Wound healing

All of the patients in the haemoglobin spray group had some degree of wound healing by week 4, ranging from a reduction of 18% to 100%, with a mean reduction of 63%, and five patients (25%) had complete wound healing by week 4. In the control group, 15 patients (75%) had some degree of wound healing by week 4, with wound size reduction ranging from 4% to 100%, with a mean reduction of 26%, but only one patient achieved complete healing at this time, and five patients actually had an increase in wound size (increase ranging from 10% to 108%).

All of the healed wounds in the haemoglobin spray-treated group at week 4 were of the smallest wound size category (0–2cm^2). These patients also had a shorter duration of wound pre evaluation, were in a lower age range (except for one patient), were free of neuropathy and vascular deficiency, and had a HbA_{1c} of 8% (10.1mmol/L) or lower. Similarly, the patient in the control group whose wound healed within 4 weeks was non-neuropathic, had no ischaemia, was young (28 years of age), the wound had been present for only 3 months and was of the smallest wound size category (2cm^2) at baseline. None of the wounds that were healed by week 4 recurred over the course of the 28-week evaluation period.

After 28 weeks' treatment, a total of 15 patients had their wounds completely healed in the haemoglobin spray group. Of the remaining five patients whose wounds had not healed at this point, one patient had died due to a non-wound-related cause, and three of the remaining four patients had stopped the haemoglobin spray treatment prematurely and then became static or worsened again after achieving reductions in wound size of 68%, 79% and 91% respectively, with the haemoglobin spray treatment.

The remaining patient, a 76-year old with poorly controlled diabetes, had achieved 95% wound size reduction at 28 weeks despite a relatively large foot ulcer measuring 3.8 x 1.8 cm at baseline and suffering from both neuropathy and limb ischaemia. In the control group at week 28, a total of eight patients had their wounds completely healed. One patient in this group also died due to a non-wound-related cause, one patient underwent an amputation, six patients had notably reduced wound sizes (65%, 98%, 96%, 90%, 56% and 37%), one patient's wound had not changed, and three patients had an increase in wound size (50%, 33% and 33%).

A rapid reduction in overall wound size was seen in the haemoglobin spray group compared with the control group. By week 4, there was an average wound size reduction of 63% in the haemoglobin spray group versus 26% in the control group (p=0.03). By week 16, this had increased to 91% in the haemoglobin spray group compared with 43% in the control

group (p=0.01), and this increased further to a 95% reduction in wound size at week 28 in the haemoglobin spray group compared to a 63% reduction in the control group (p=0.02)

The number of wounds that had not healed by completion of the evaluation, i.e. had not achieved full epithelialisation by week 28 are shown in *Table 2*. A significant difference was seen between the two groups at week 9 (12 patients in the haemoglobin spray group with a wound that had not healed — on intent-to-treat basis — compared with 18 patients in the control group) (p=0.04) and by week 16 there was a 50% difference between the groups in favour of haemoglobin spray (nine patients in the haemoglobin spray group with a wound that had not healed compared with 18 patients in the control group) (p<0.01). By week 28, only five wounds in patients treated with haemoglobin spray had not fully healed (one of whom had died), compared with 12 in the control group (including one death and one amputation) (p=0.04).

Pain assessment

Pain levels were evaluated for all patients who reported experiencing pain at baseline (16 patients in haemoglobin spray group, 14 control patients). As some patients were unable to feel any pain at all due to loss of sensation in the feet, patients without any pain at baseline were not included in the pain evaluation. Mean pain scores were similar between the two groups at baseline (5.1 for both groups). Haemoglobin spray treatment was associated with substantially lower pain scores throughout the evaluation period. By week 4, mean pain score in the haemoglobin spray group was 0.3 and all patients were completely pain free from week 12 through to week 28. In the control group, mean pain score was 3.5 at 4 weeks (p<0.001 compared to the haemoglobin spray group), at week 12, six patients still suffered from pain and these patients had a mean pain score of 3.7. By week 28, two patients still had a mean pain score of 4.0

Slough levels

All wounds in both groups had a similar degree of slough present at baseline, with an average level of slough coverage of 50% in both groups (p=0.99). Wounds in the haemoglobin spray group rapidly achieved slough elimination over the course of treatment. After 4 weeks, all patients treated with haemoglobin spray achieved complete slough elimination, compared with only a 10% reduction in the control group (p<0.001). After 24 weeks of treatment, one patient in the haemoglobin spray group had recurrence of slough in the wound, however, this patient had stopped using haemoglobin spray prematurely, which may have contributed to the slough recurrence, while in the control group, presence of slough was still evident in four wounds, with an average remaining slough coverage of 43%. As a result of the superior wound healing, there was no debridement required in the haemoglobin spray group, with only basic wound cleaning with saline needed, versus the requirement for three cases of theatre surgery and three cases of bedside debridement in the control group.

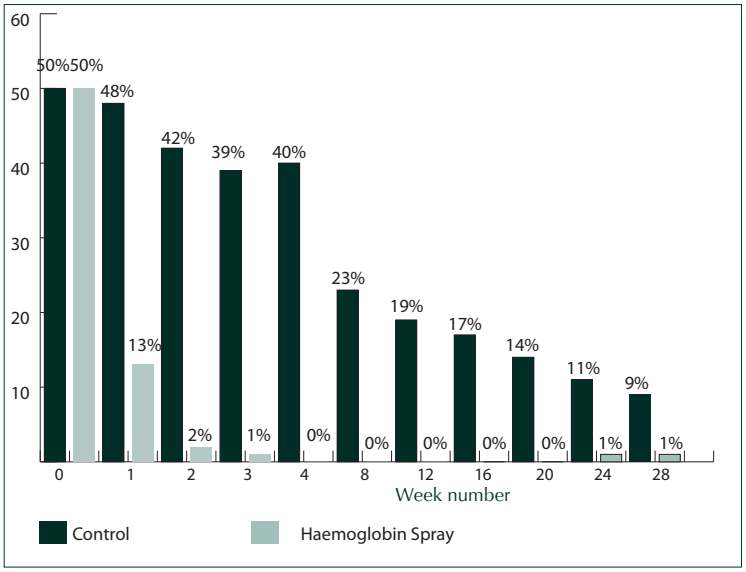

Figure 3. Slough percentage.

Table 2. Levels of exudate by number of patients.

	Week number	High	Moderate	Low	None/healed
Haemoglobin Spray	Week 0	12	8	0	0
	Week 4	0	4	10	6
	Week 8	0	3	8	9
	Week 28	0	2	1	17
Control	Week 0	9	5	6	0
	Week 4	5	8	5	2
	Week 8	2	8	5	5
	Week 28	1	5	4	10

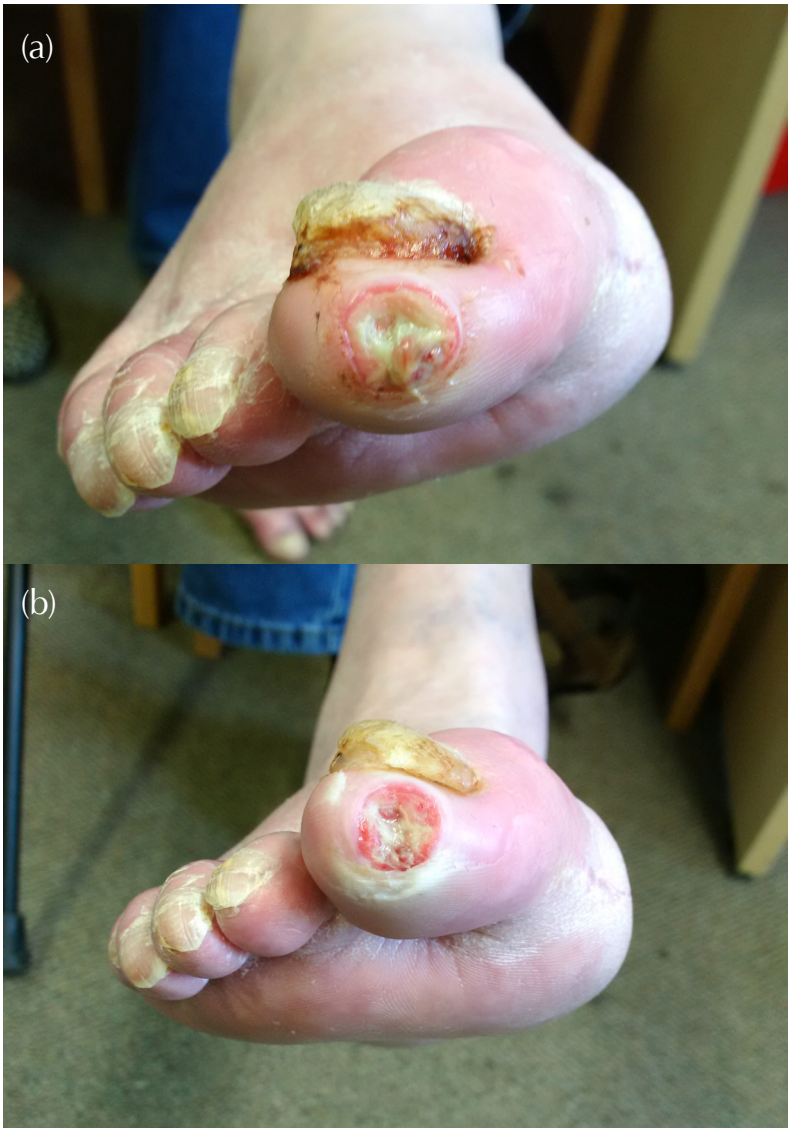

Figure 4. (a) Case study one, diabetic foot ulcer at day 0. (b) Case study one, diabetic foot ulcer at day 7, following treatment with Granulox and Softpore dressing.

Exudate levels

At baseline, 12 patients had a high level of exudate, eight patients had a moderate level and 0 patients had a low level of exudate in the haemoglobin spray group; while nine patients had a high level, five patients had a moderate level and six patients had a low level of exudate in the control group. By week 4, exudate levels demonstrated a significant reduction across all patients in the haemoglobin spray group, with all 12 patients with high levels of exudate at baseline being reduced (100%), versus four out of nine patients (44%) in the control group. After 28 weeks of treatment, zero patients had high levels of exudate, two patients had moderate exudate levels, one patient had low exudate levels, and six patients had no exudate or were healed in the haemoglobin spray group, whereas in the control group, one patient had persistent high-exudate levels, five had moderate and four had low levels, and eight patients had no exudate or were healed.

Adverse events

One patient in each group died; however, neither of the deaths was related to the wounds or to use of haemoglobin spray. There were an additional nine events in the control group, but no further events in the haemoglobin spray group. The events in the control group comprised one amputation, three unplanned surgeries for wound debridement requiring treatment in a surgical theatre, and five cases of wounds that were infected and required antibiotic treatment (in four of the patients). There were no reported allergic reactions, refusal on religious or dietary choices within the 28-week period.

Case study

A 78-year-old male with type 2 diabetes, who was stable with HBA_{1c} 6.8 mmols, a smoker of 10 cigarettes a day, with no neuropathy presented to the podiatrist and district nurse with a left great toe hallux ulceration of 3 months duration and no boney injury on X-ray. The patient declined any debridement or offloading therapies. Negative swab results were obtained at the time of review at the GP clinic. At day 0 prior to Granulox application, the wound was sloughy with malodour, moderate levels of serous exudate, macerated peri-skin and toe nail bed (*Figure 4a*), and a pain score of 7/10 on the McGill pain index. The ulcer was dressed with Softpore® (Richardson Healthcare) adhesive dressing and Granulox was applied twice a week.

At day 7 after two applications of Granulox (*Figure 4b*), pain levels were 2/10 on the McGill pain index, there were low levels of serous exudate, no malodour, and the nail bed was clean and suitable for reduction by the podiatrist. The wound went on to heal at week 6 and offloading declined by the patient throughout care delivery.

Conclusion

As clinicians, we are aware of the importance of oxygenation at a cellular level in the support of

wounds healing through the normal channels of inflammation, granulation and maturation. Within the diabetic patient population, as a result of multiple complexities, hypoxia to both circulation and at a cellular level is even more apparent with devastating consequences, such as infection, tissue destruction, amputation and resulting disability.

This article demonstrates the positive results of a 28-week evaluation of DFU who have had topical haemoglobin therapy deployed alongside their usual standard of care within an acute setting, compared with a similar group of patients under the same care environment who received standard care alone. Topical haemoglobin therapy as an adjunct to standard care has demonstrated positive outcomes in regards to wound reduction, wound closure, slough and exudate-level reduction, alongside improvement in pain scores over the 28-week monitoring period compared with those patients who did not receive the therapy. It is recommended that pilot work such as this is develops further into robust research studies, such as randomised control trials, to continue to test theory, build evidence to enable clinicians to make informed choices in regards to adjunct tools, and to apply its merits in relation to improvement in clinical practice. ■

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