

Topical haemoglobin spray for diabetic foot ulceration

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Abstract

The development and subsequent deterioration of diabetic foot ulceration (DFU) is a common occurrence across all healthcare divides, concerning all patient groups, age, gender and social environments. It increases demand on clinical resources and creates unnecessary hardship for patients. Chronic DFU is challenging to prevent and notoriously difficult to manage owing to the complex nature of the patient and the disease itself. The improvement of oxygenation to many chronic wound groups is gaining momentum across wound care; particularly in those wounds such as DFU that present with circulatory, oxygen-deficient scenarios. *Method:* a descriptive evaluation was undertaken in an acute clinical setting where a spray solution containing purified haemoglobin was used in a cohort of 20 patients who presented with chronic (>12 weeks) DFU. Standard wound care was undertaken by 18 health professionals with no changes to products, devices or practice before evaluation. All wounds received the addition of the product on eight set occasions over a 4-week period and the resulting data correlated in regards to the set outcomes of wound surface area reduction, ease of use, adverse events and patient acceptability. *Results:* at 4 weeks all wounds had demonstrated positive wound reduction, there were no adverse events, all patients and clinicians found the product acceptable and easy to use. Interestingly, although not a set outcome, all wounds commenced the evaluation with wound-bed slough present and at 4 weeks 100% were deemed slough free. At a further 4-week review no patients wounds had regressed. *Conclusion:* the incorporation of a haemoglobin spray solution within this cohort of DFU resulted in a positive improvement in wound healing and slough elimination. Further work in this area is recommended to increase the evidence.

Key words: Topical oxygen therapy ■ Wound healing ■ Diabetes ■ Diabetic foot ■ Foot ulcer

It is estimated that 1 in 20 people had been diagnosed with diabetes in the UK up to 2012, though this figure does not acknowledge those patients yet to be identified (Diabetes UK, 2012). Hex et al (2012) suggested an annual healthcare spend of £1 billion for people with type 1 diabetes and £8.8 billion for those with type 2 diabetes, expected to rise year-on-year across the UK.

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In association with diabetes, there is also an ongoing increase in the incidence of foot lesions/ulcers, which affect one in 10 patients and, according to Sharp (2013), represent one of the most common reasons for admission to a healthcare setting. Diabetic foot ulceration (DFU) presents a significant financial burden for the NHS with an estimated spend of up to £661 million annually, representing 0.7% of the total NHS healthcare allocation (Kerr, 2011).

With regard to DFU aetiology, Boulton et al (2005) suggested prevalence rates of up to 42% for neuropathic disease, up to 23% for vascular insufficiency and up to 77% for those patients who would progress to surgical amputation. Patients with diabetes account for up to 50% of all amputations (Ahmad et al, 2014) with the majority of these patients, around 6000 annually, presenting with foot ulceration according to the National Diabetes Support Team (2008). Surgical amputation is estimated to cost the NHS up to £76 million (Kerr, 2011), representing 0.06% of the NHS annual budget of £121 billion (Harker, 2012) with many operations deemed preventable and therefore avoidable (Diabetes UK, 2012).

Clinicians encounter DFU in the diabetic population on a daily basis with ulceration proving notoriously difficult to heal, resulting in infection, extensive tissue damage, amputation and long-term disability (Edmonds, 2007). Evaluation and review of new and innovative products or interventions is therefore essential if clinicians are to keep abreast of managing this wound group effectively.

DFU and oxygenation

Diabetes occurs when there is inadequate uptake of glucose by the cells of the body resulting in raised blood glucose levels (Pocock and Richards, 2006). Insulin, the hormone produced in the pancreas, regulates the release and storage of energy from food. High plasma glucose levels caused by diabetes can damage blood vessels and nerves resulting in ineffective reduction in circulating oxygen and deranged sensation (Vuolo, 2009).

Type 1 diabetes primarily affects the younger population, often diagnosed in childhood or in some cases in adults up to 35 years, and is thought to be a genetically predisposed auto-immune disease that results in the body destroying insulin-producing cells, increasing glucose levels in the bloodstream. Type 2 diabetes usually occurs later in life (over 40 years of age), where insulin-producing cells are not able to produce adequate amounts of insulin or there is a degree of insulin resistance, through a lack in the body's response to increasing circulating glucose levels (National

Institute for Health and Care Excellence (NICE), 2004)

Diabetes increases the risk of foot ulceration, which is often chronic in nature, due to macro and micro-angiopathy; ischaemia alone or in conjunction with varying levels of neuropathic nerve damage. Impairment and dys-regulation occur within the wound-healing process at both cellular and molecular stages (Rafehi et al, 2011).

Oxygen is an essential component of the wound-healing process. (Norris, 2014). Tissue that has had an insult and begins the wound healing process will automatically have an increased demand in the tissues for their oxygen delivery capacity and rely on this process to enable tissue to travel through the key stages of inflammation, proliferation and maturation (Flanagan, 2000). The body's tissues have no capacity for retaining oxygen molecules and therefore require a consistent delivery along with nutrients and other agents at varying levels on demand if wound healing is to occur effectively (Timmons, 2006). Consequently, chronically oxygen-depleted cells at micro and macro levels have devastating effects on vulnerable tissue, often resulting in deterioration, disfigurement and disability, particularly within the population of patients with diabetes (Dow, 2001). Oxygenation is therefore imperative, either systemically or topically, in the wound-healing process.

Topical oxygenation of tissues is not a new practice, with clinicians recognising across many specialities the benefits and effectiveness of this therapy (Ladizinsky and Roe, 2010; Norris, 2014; Winfeld, 2014; Tickle, 2015). Both hyperbaric oxygen therapy (HBOT) and topical oxygen therapy are interventions that can be implemented to support and aid wound healing (Tickle, 2015). Topical haemoglobin treatments are designed to permit haemoglobin-mediated oxygen diffusion in the wound bed as an aqueous medium, improving wound healing states (Arenbergerova et al, 2013).

Granulox

Granulox is a topical oxygen therapy comprising a haemoglobin spray for use on those wounds that are deemed chronic in nature. Its action purports to the binding and releasing of oxygen from the normal atmosphere onto the wound-bed surface, improving the oxygenation of the wound tissues through the process of diffusion, consequentially improving and supporting wound healing (Norris, 2014; Tickle, 2015). The therapy requires very little training for its use, has no reported negative side effects to date and can be used by both clinicians and patients alike. The product is approved for multi-use as a non-wound-contact spray, to be applied at least every 72 hours on all wounds deemed chronic in nature, present for 12 weeks or more (Arenbergerova et al, 2013).

Granulox is deemed unsuitable for use with certain disinfectants (such as hydrogen peroxide or chlorhexide), or proteolytics as these can impair its effectiveness, where infection is present, and in those patients who are pregnant or lactating owing to a lack of significant data in these areas. Wound beds must be clean and void of infection before application if the product is to be applied to the optimum environment.

Notable positive outcomes have emerged from work undertaken by Arenberger et al (2011) and Arenbergerova

Table 1. The SINBAD system for classifying and scoring foot ulcers

Category	Definition	SINBAD Score
Site	Forefoot	0
	Midfoot and hindfoot	1
Ischaemia	Pedal blood flow intact, one pulse palpable	0
	Clinical evidence reduced pedal blood flow	1
Neuropathy	Protective sensation intact	0
	Protective sensation lost	1
Bacterial Infection	None	0
	Present	1
Area	Ulcer <1cm ²	0
	Ulcer >1cm ²	1
Depth	Ulcer confined to skin and subcutaneous tissue	0
	Ulcer reaching muscle, tendon or deeper	1
Total possible score		6

Source: Adapted from Ince et al (2008)

et al (2013) exploring topical haemoglobin oxygenation of chronic wounds (general) and chronic leg ulcers respectively. A published case study by Babadagi-Hardt et al (2014) on chronic wounds/compression and Budd-Chiari syndrome and recent clinical pilots using topical haemoglobin spray therapy on leg ulcers (Norris, 2014) and pressure ulcers (Tickle, 2015) and showed distinctly positive results. All of the authors promote the positive outcomes of increased healing potential, wound reduction and no negative reactions, building up the evidence across the chronic wound arena.

Methodology

A single acute centre descriptive evaluation was undertaken to explore the efficacy of Granulox spray, with the primary outcome set as percentage reduction in wound surface area after 4 weeks' treatment with Granulox and secondary outcomes of patient acceptability, adverse events and ease of use.

Inclusion criteria were age over 18 years, a Site, Ischemia, Neuropathy, Bacterial Infection, Area and Depth (SINBAD) score maximum of 2 (Table 1), and diabetic foot ulcer located below the ankle. The SINBAD score of 2 was chosen as patients scoring 2 and below have fewer risk factors to inhibit healing, those scoring 3 or over usually have vascular insufficiency and one or two other wound-healing issues that would impair the effectiveness of any product that is placed on the wound bed. Exclusion criteria related to those patients that presented with infected ulcers, who were receiving systemic antibiotic therapy and/or corticosteroids, that were pregnant or actively lactating, that had an ankle-brachial pressure index (ABPI) below 0.5 or toe pressure below 70 mmHg or HbA1c (glycated haemoglobin) measurement over 10 or 86 mmol/litre and a SINBAD score of 3 or more.

In the course of the evaluation, 20 patients who presented to the department with chronic DFU for 12 weeks or more who met the inclusion criteria, and who verbally consented following verbal explanation and review of the product and information leaflet, were treated with Granulox and

Table 2. Patient demographics

	Gender	Age	HbA1c	BMI	Diabetes type	Ulcer	Wound present	SINBAD score	Offload device	Neuropathy	Vascular*
1	Male	50	6	38	2	Plantar	6 months	2	Yes	Yes	No
2	Female	69	7	40	2	Plantar	3 months	2	Yes	Yes	No
3	Female	54	5	<30	1	Hallux	4 months	1	No	No	No
4	Male	18	7	<30	1	Hallux	3 months	1	No	No	No
5	Male	54	5	38	2	Pedal	4 months	1	No	No	No
6	Male	61	7	15	2	Plantar	5 months	2	Yes	No	Yes
7	Male	58	8	36	2	Calcaneus	3 months	1	No	No	No
8	Female	71	8	36	2	Plantar	9 months	2	Yes	Yes	Yes
9	Female	62	4	<30	2	Pedal	3 months	1	No	No	No
10	Male	89	9	<30	2	Plantar	18 months	2	Yes	Yes	Yes
11	Female	84	9	39	2	Plantar	12 months	2	Yes	Yes	Yes
12	Female	79	6	36	2	Phalanges	4 months	1	No	Yes	No
13	Male	32	8	40	1	Plantar	12 months	2	Yes	No	Yes
14	Male	24	6	<30	2	Calcaneus	3 months	2	No	No	No
15	Female	41	8	<30	1	Plantar	3 months	2	Yes	Yes	Yes
16	Female	65	9	38	2	Calcaneus	4 months	2	No	Yes	Yes
17	Male	76	8	36	1	Calcaneus	8 months	2	Yes	Yes	Yes
18	Male	66	6	38	2	Hallux	5 months	2	Yes	Yes	Yes
19	Female	28	6	<30	1	Hallux	3 months	1	Yes	No	No
20	Female	19	8	<30	1	Pedal	3 months	1	No	No	No

*Vascular deficiency to foot

Table 3. Exudate levels pre and post evaluation*

Exudate pre Granulox	Patients	Exudate post Granulox	Patients
None	0%	None	70%
Mild	35%	Mild	25%
Moderate	35%	Moderate	5%
Severe	30%	Severe	0%

*Assessed according to wound exudate continuum from Gray et al (2005)

monitored over a 4-week period. Each patient received the same standard of care that they entered the evaluation with, so that the only variable was the addition of the spray product. Pre-evaluation care included soft silicone foams (adhesive/non-adhesive) hydrofibre adhesive foams, gentle adhesive foams, retention bandage, and the continuation of off-loading boots and shoes. The wound data was collated using the recognised Applied Wound Management Assessment documentation (Gray et al, 2005; Wounds UK, 2009) which is the standard wound care documentation used in the trust.

During the evaluation period all patients continued to have their dressings changed twice a week with the Granulox administered each time. Data collected related to wound size, exudate levels, consistency of same standards of care, percentage of slough, granulation and epithelium present. The products were applied either by the patient independently (75%) under clinical observation (following a visual demonstration in simple terms by the nurse or healthcare assistant) or the clinician (25%), with the clinician

documenting the relevant data sets at each dressing change in the same designated treatment area (all dressing changes occurred in the acute setting). The author observed the dressing changes weekly and cross-checked the data for accuracy and to enable collection of both patient and clinician's experience throughout the process. At weeks 1 and 3, each patient and clinician was asked verbally, on a scale of 1 being difficult to 5 being easy, how they felt the product was to use and on acceptability to the patient, a scale of 1 not acceptable to 5 very acceptable. Ethical approval was not required, in line with trust policy with regard to clinical review of CE-marked products. Informed verbal consent was documented by the clinician in relevant notes.

Results

The setting was one single acute site with 20 patients who presented with chronic DFU of 12 weeks' standing or more over the period of February to March 2015. All 20 patients who met the criteria were recruited and underwent the addition of Granulox to their care regimen over a 4-week period. *Table 2* details the patient's pre-evaluation information.

Table 2 summarises the wide spectrum of patients and their individual complex DFU and comorbidities status; mean age 54 years, 1:1 male to female ratio, HbA1c mean rating 6.5 with 3 patients only just meeting the criteria at 9%, body mass index (BMI) ranged from a cachectic 15 to a high-risk 40 with 55% classified obese range of 30–40. Regarding type of diabetes, 35% were type 1 and the majority were type 2. Anatomical sites for the DFU represent the common sites for these ulcers to occur (O'Loughlin et al, 2010): plantar 40%, hallux and calcaneus

20%, pedal 15%, and distal phalanges 5%. The mean time for wounds being present prior to the application of Granulox was 10 months (range: 3 months to 18 months). With regard to off-loading devices used before and continuing throughout the evaluation period, 5% had a fibreglass heel cast, 5% Cascade foam boot, 15% Air Cast boot, 15% Darco shoe, 15% ProCare shoe, totalling 11 patients (55%) using off-loading equipment.

At 4 weeks the DFU exudate levels demonstrated a significant reduction across all patients with an endpoint of 70% increase in patients with no exuding wounds, a 10% reduction in wounds with mild exudate, a 30% reduction in moderate exuding wounds and a complete resolution of all wounds that commenced the therapy within the severe group (Table 3). Although not a preset objective, it is interesting to note that all of the 20 patients had presented with varying levels of wound bed slough, ranging from 10% to 100%, at day 1 and at week 4 all 20 patients' wounds were slough free (Figure 1). No debridement process at all occurred during the evaluation, only basic wound cleaning with saline where needed.

Wound reduction was positive in all of the recruits with 5 of the patients (25%) going on to full epithelialisation at the last wound assessment (Table 4). This is not surprising clinically within this patient group as each of these 5 patients had a shorter duration of wound pre-evaluation, were in the lower age bracket (except patient 9) and all

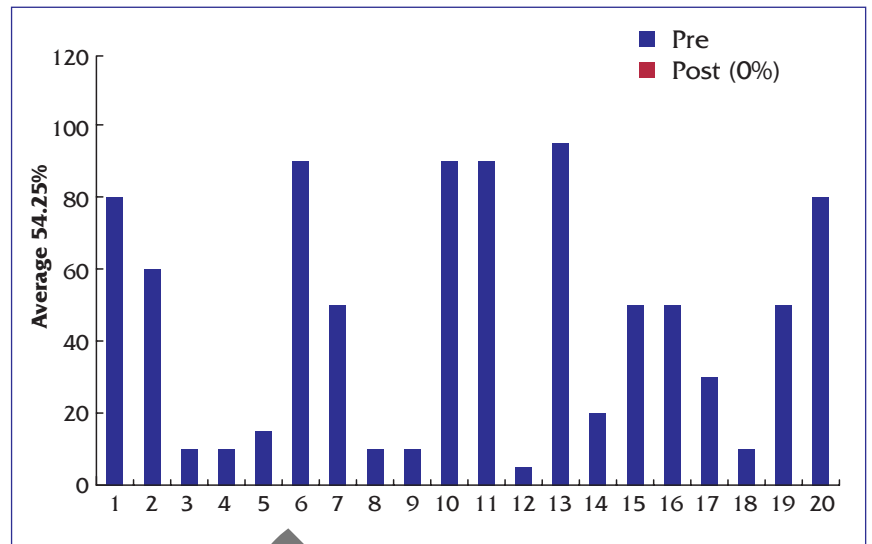


Figure 1. All 20 patients started the evaluation with some level of slough being present and at 4 weeks all wounds were slough free.

were free of neuropathy and vascular deficiency. Only one patient (Patient 19) of the group who had reached full epithelialisation at week 4 had used an off-loading device while others with devices had varying levels of wound closure, suggesting the benefits cannot be solely related to dressing products or off-loading equipment.

Table 4. Wound reduction at 4 weeks				
Patient	Wound size at start (width x length)*	Wound size at end (width x length)	Approximate wound size reduction† (%)	Off-loading device used
1	2 cm x 1 cm	1.5 cm x 0.3 cm	78%	Fibreglass heel cast
2	3 cm x 2.8 cm	2.6 cm x 2.6 cm	20%	Air Cast boot
3	0.5 cm x 0.4 cm	0.2 cm x 0.2 cm	80%	None
4	0.4 cm x 0.5 cm	0 cm x 0 cm	100%	None
5	2.1 cm x 1 cm	1 cm x 0.5 cm	76%	None
6	3 cm x 2.5 cm	2 cm x 2.1 cm	44%	Air Cast boot
7	3 cm x 2.8 cm	2.5 cm x 2.5 cm	26%	None
8	4 cm x 3.1 cm	3 cm x 2.5 cm	40%	Darco Shoe
9	1 cm x 1 cm	0 cm x 0 cm	100%	None
10	4.5 cm x 5 cm	4.1 cm x 4.5 cm	18%	ProCare shoe
11	6 cm x 5.5 cm	5.2 cm x 4.5 cm	29%	Cascade Foam boot
12	0.8 cm x 0.4 cm	0.2 cm x 0.1 cm	94%	None
13	1.8 cm x 3 cm	1.6 cm x 2.5 cm	26%	Darco Shoe
14	1 cm x 1.2 cm	0 cm x 0 cm	100%	None
15	4.2 cm x 3 cm	3.8 cm x 2 cm	40%	Air Cast boot
16	3 cm x 1.5 cm	2.1 cm x 1.2 cm	44%	None
17	3.8 cm x 1.5 cm	2.5 cm x 1 cm	56%	ProCare shoe
18	1 cm x 1 cm	0.5 cm x 0.5 cm	75%	Darco Shoe
19	0.4 cm x 0.3 cm	0 cm x 0 cm	100%	ProCare shoe
20	1 cm x 0.8 cm	0 cm x 0 cm	100%	None
			Mean: 62.3% Median: 56%	
*Width may be the larger measurement owing to the standard way measurements were recorded i.e. plantar ulcer width measured across the foot				
†Reduction estimated using wound surface area calculated from width and length measurements				

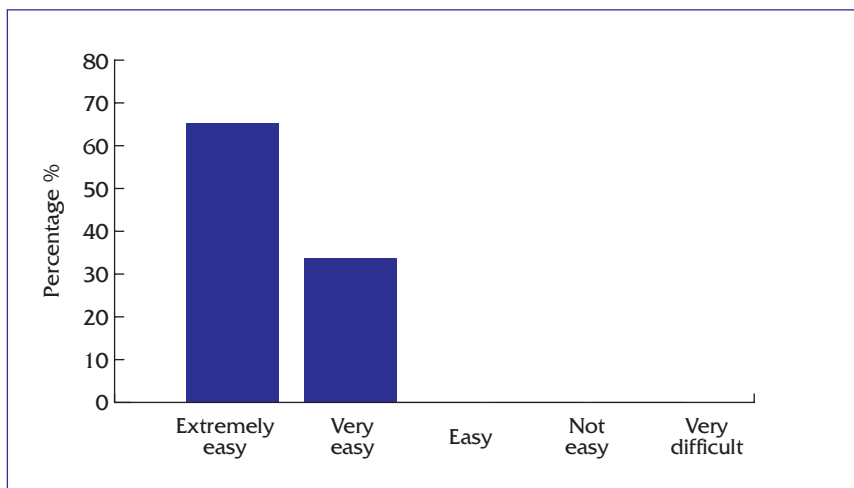


Figure 2. Acceptability: 15 patients found the product easy to use with 10 stating extremely and 5 very easy, 5 patients within the cohort did not use the product as the clinician had applied the spray.

Patient and clinician satisfaction

Of the 20 patients, 75% after limited demonstration were able to apply Granulox independently as part of their own dressing regimen within the clinical area observed by the clinician, 25% of patients had either a mental health or physical disability that prevented them from using the spray and so clinicians applied the spray—three patients out of the five had a confirmed diagnosis of dementia with cognitive disfunction of understanding, memory loss etc, while the other two patients had end-stage rheumatoid arthritis and could not hold the spray with their fingers or press the button to release product. All the clinicians involved in the evaluation, 18 in total, both healthcare assistants and registered nurses, were satisfied with the use and ease of the product scoring a 5 stating it was extremely easy to use. Of the 15 patients who administered their own Granulox, 10 found the product extremely easy to use grading it as a 5 patients while 5 found the product easy to use grading it as a 4. (Figure 2) A total of 4 out of the 18 clinicians were slightly nervous at first in using the product:

‘I am wary a little, as it doesn’t look like a dressing or wound care product’ (Registered nurse)

Despite this all 18 clinicians were happy to continue to use the product throughout the evaluation.

Regarding the written document provided to the groups, two patients highlighted that the information leaflet in the pack was small in print and a larger print specifically for them would have been useful. This was also emphasised by three of the clinicians who felt a simple diagrammatic leaflet for patients would aid understanding of the product’s function and benefits over the detailed version available. Overall, all of the clinicians and patients praised the product and wished to continue with it throughout the 4-week evaluation period.

**‘Simple—I didn’t think it would work as it’s just clear water to me, and it’s so easy to spray on’
Patient 9, who went on to full epithelialisation.**

Discussion

Wound tissue is dependent on a consistent influx of oxygenation to enable the process of healing to occur

(Flanagan, 2000). Hypoxic tissue will fail to regenerate, stay fixed in the inflammatory stage, and be prevented from moving along the wound-healing continuum increasing the risk of bacterial infection and tissue disfiguration (Sen, 2009).

This small evaluation explored the application of Granulox haemoglobin spray within the acute setting over a 4-week period for those patients who presented with chronic diabetic foot ulcers despite clinicians using best practice according to NICE (2011) guidelines. All 20 patients demonstrated varying levels of progressive wound healing, wound reduction, elimination of slough and a positive reduction in exudate levels. The results of this study supports the European work carried out on lower limb extremities by Arenberger et al (2011) who found encouraging healing rates of 93% with topical oxygenation therapy versus 7% without at 6 months in a single-site, randomised controlled trial) and Arenbergerova et al (2013) who found 53% average improvement with haemoglobin vs 21% average worsening without, in a prospective randomised control study in 72 non-healing or worsening venous leg ulcers receiving standard care with compression. Work in the UK carried out by Norris (2014) on venous leg ulcers and Tickle (2015) on pressure ulcers, agreed with other studies in showing positive benefits in wound size reduction, exudate minimisation and the improvement in visible presence of slough with the use of topical oxygenation donation on chronic wounds.

As an adjunct to the clinical benefits of Granulox, this evaluation touched on the clinicians’ and patients’ experience of the product’s use over a 4-week period. Due to physical or mental health issues not all of the patients were able to use the product independently and required clinical input in the dressing regimens. The actual product container itself would therefore require modifying if its use across all patient groups is to be maximised. Patients with arthritis found the container and button difficult to manipulate due to restricted movement in their fingers—perhaps a larger nozzle or button could be adapted for their use.

Despite this, all recruited patients and participating clinicians found the product easy to use and were happy to continue its application over the evaluation duration. Patients continued to use the product in the clinical area after the 4-week period; the author monitored them at 2-week intervals for another 4 weeks and no patients regressed with regard to wound healing.

Strengths and limitations of evaluation

The evaluation cohort group represented only a small sample of patients who presented with chronic DFU that had been present for 3 months or more in an acute setting. The product’s effects over a longer period of time, with increased applications, and on patients with a SINBAD score of 3 or more have not been addressed and so the benefits to the wider population are not known. However, the data collected acknowledge various ages, equal gender numbers, the most common anatomical sites for DFU, and varying comorbidities, which enriches and strengthens the evidence. There were no patient drop-outs, the data were collected and cross-checked by the author; the results demonstrated a

positive set of outcomes adding to and mirroring results from current available literature. Although clinical efficacy and patient/clinician experience have been basically explored with positive outcomes, addressing a more in-depth experiential aspect alongside the economic and strategic elements would expand the knowledge of this product's benefit within health care, gaining increased credibility of oxygen therapy within the DFU population.

Conclusion

Emphasis on DFU prevention and management 'gold standard' of care must incorporate a full multidisciplinary approach that includes effective patient education, accurate assessment by the appropriate clinician and subsequent correct diagnosis, effective management planning and re-evaluation (O'Loughlin et al, 2010). The patient and carer are absolutely vital to this team approach if prevention of ulceration is to be maintained and any management strategies put in place are consistent and complied with (Sign, 2013). Wound management using innovative therapies is one key part of that holistic care package for those patients who have developed DFU. This evaluation, although only small in sample size, is worthy of consideration by clinicians in management of those DFUs that are deemed chronic despite 'gold standard' interventions being in place. Further comprehensive evidence gathering is required in moving forward to ensure clinicians are fully informed as to the benefits across all wound groups of this innovative oxygen-delivery therapy.

BJN

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KEY POINTS

- Chronic diabetic ulceration to the heel and ankle is challenging to prevent and difficult to manage
- Oxygen is an essential component of the wound-healing process, but high plasma glucose levels caused by diabetes can lead to angiopathy and ischaemia and a decrease in circulating oxygen
- This article discusses the evaluation of a topical oxygenation therapy for diabetic foot ulceration
- Within a patient population with an average 10-month duration of wound, within 4 weeks 100% were slough free, 25% had complete wound closure and 100% had a reduction in wound size
- The patient and clinician experience were reported to be positive

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