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Report of the evaluation of the BRH-A2 Wound healing device on Chronic Diabetic Foot Ulcers

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Title:

Report of the evaluation of the BRH-A2 Wound healing device on Chronic Diabetic Foot Ulcers

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Background

Diabetic foot ulcers

Diabetes is predicted to be one of the greatest challenges for individuals and society as a whole into the future. Persons with diabetes are 50 times more likely to develop a foot ulcer than their non-diabetic counterparts (Monteiro-Soares et al., 2012). The prevalence of foot ulceration in this patient group is suggested to range from 3-10% (Monteiro-Soares et al., 2012). These wounds are difficult to heal and this is often compounded by the presence of multiple co-morbidities. Furthermore, diabetes is the leading cause of non-traumatic limb amputation in the world (Dubský et al., 2012). Within 18 months following amputation, almost 50 percent of these people will develop ulceration on the other limb and of these, 58% will have further amputations within three to five years (Apelqvist, 2012). It is worthy of note that the three-year mortality rate after the first amputation is between 20 and 50 percent (Apelqvist and Larsson, 2000, Kuehn, 2012). Having diabetes impacts negatively on the individuals' heath related quality of life when compared to the general population (Winkley et al., 2012). The most important variable influencing changes in HRQOL is the presence of complications of diabetes. Having a foot ulcer causes a loss of mobility for the individual thereby decreasing social functioning. Furthermore almost 50% of people will suffer with intractable pain (Winkley et al., 2012).

The International Working Group of the Diabetic Foot (IWGDF) highlight the continuing difficulties in selecting clinically effective treatments for diabetic foot infection and ulceration. In two commissioned systematic reviews they point to the large number of treatment options available while at the same time the relative weakness of evidence to support the use of many of these options (Game et al., 2016, Peters et al., 2016). Two of these treatments, electrostimulation and ultrasound, were utilised in this study. While both these technologies have been shown to be effective in chronic wound healing, the use of combined modulated ultrasound and electric field stimulation (CUSEFS) is a new and not widely studied treatment (Avrahami et al., 2015). The merits of each treatment individually will be explored below.

Electrostimulation as a therapy

The potential of electrostimulation as a therapy for wounds was first recognised in the mid-19th century and is based on the differing electrical charges which can be detected at skin surface and deeper layers and also between wounded and non-wounded skin (Hess et al., 2003). Widespread interest and research into the use of electrostimulation is evident since the 1960s (Junger et al., 2008). Electrostimulation has been shown to have an effect on a range of mechanisms which are beneficial to wound healing including;

- Improvement of blood flow
- Improvement in tensile strength
- Stimulation of protein and DNA synthesis
- Reductions in oedema
- Decreased bacterial growth
- Promotion of epithelial, fibroblast, neutrophil and macrophage cells
- Reduction in pain

(Kloth, 2014, Kloth, 2005).

Studies in the area have pointed to some promising outcomes for the use of electrostimulation in practice for a range of wound types. For example, Wirsing et al. (2015), in a prospective case series of 47 patients with chronic wounds of various types, found a mean reduction of 95% in wounds surface areas after 8 weeks of treatment applying 45-60 mins of a 1·5μA current intensity to the wound area. Treatments were applied 2 or 3 times weekly using wireless technology and no adverse events were recorded during the course of the study. They concluded that the electrostimulation significantly accelerated wound healing in their sample. Similarly Herberger et al. (2012) in a study with patients with various wound types found that wound size decreased by 44.7%,exudate, fibrin, necrosis, and wound odour decreased and no adverse events occurred when they applied an electrical current to wounds twice daily for 30 mins and 7 days with varying polarities. They also determined that the treatment was well tolerated

by patients. In both these studies the lack of a control however weakens the claims somewhat.

Junger et al. (2008) carried out a placebo controlled double blinded trial with a sample of 39 patients with venous leg ulcers and applied low-frequency pulsed current of 128 Hz with protocoled alternating polarities for the intervention group via electrodes. Both the intervention group and the placebo group also received compression therapy as usual care. Results show wound size reduction in both groups with no significant difference between the groups. The treatment group did however have statistically significant less pain than the control group.

Specifically in relation to DFUs, Peters et al. (2001) carried out an RCT to assess the impact of a 50 V current being applied to the wounds of those in the intervention group overnight (8 hours) using a microcomputer. Both groups also received usual care. Results indicate that 65% healed in the treatment group treated vs 35% in the control group ($p = 0.058$). Wound size reduction was not statistically different between the groups and in both groups the more compliant patients had better outcomes.

Systematic reviews of treatments with electrostimulation have also pointed to its potential and value. Thakral et al. (2013) assessed the value of electrostimulation for plastic surgery and included 17 RCTs in their systematic review. They including all types of wounds and found that electrical stimulation was associated with faster wound area reduction or a higher proportion of wounds that healed in 14 out of 16 RCTs. Like other authors in the area (see e.g. Hess et al. (2003) they caution that the variety of methods and disparity in how electrostimulation is applied, in relation to current, dosage and duration, makes it somewhat difficult to aggregate findings in this regard. Kloth (2005) looking specifically at lower extremity wounds concluded that the 22 studies reviewed provide a rationale for electrostimulation being used adjunctively with standard care to

enhance the healing of lower extremity wounds of venous, arterial, and neuropathic aetiologies. Significantly for the present study he found that electrically induced acceleration of the closure of wounds caused by non-ischemic diabetic neuropathy has been demonstrated in 4 studies, including 2 RCTs. There is therefore a large body of evidence to support the use of electrostimulation for wound healing.

Ultrasound as a therapy

Ultrasound is defined as sound waves, as a result of electrical energy, which are beyond the range of human hearing (>20,000 Hz) (Hess et al., 2003). Ultrasound has been in use both as a therapy and in diagnostics for some time in healthcare. Its utility in wound healing is however a more recent focus of research and clinical interest.

Ultrasound is used for both its heat generating mechanism and for its non-thermal related properties. At intensities of 1-1.5 Watts/cm^2 the thermal properties of ultrasound are used for soft tissues injuries and for scar improvement (Hess et al., 2003). For therapeutic use in wound healing however other intensities have been shown to have a positive effect on the inflammatory process, angiogenesis and reduction in bacteria (Lai and Pittelkow, 2007, Reher et al., 1999, Yao et al., 2014).

Kavros et al. (2008) studied the use of low frequency ultrasound in the treatment of below-knee lower extremity wounds. Two groups had either ultrasound at an intensity 0.1-0.8 W/cm^3 on 3 occasions per week for 6 months or until healed or usual care. In the intervention group 53% healed over an average of 147 days vs 32% in the control in 134 days (p=.009). When evaluated by aetiology the treatment was most effective in venous ulcers. In a study also addressing venous leg ulcers Samuels et al. (2013) demonstrated a clinically though non-statistically significant effect of low frequency (<100kHz), low intensity (<100mW/cm^2) ultrasound. In a 3 arm study involving both in vitro and in vivo

samples the patients who were exposed to 15 min treatments with 20 kHz of ultrasound had accelerated wound closure.

In relation to DFU specifically, Ennis et al. (2005) with a sample of 133 patients treated the intervention group with 40 KHz of ultrasound at an intensity of 0.1 -0.5 W/cm^2 as well as usual care. The treatment was administered 3 times a week for 4 minutes over 12 weeks or until healed. Results indicate a better healing rate in the intervention group than the control (40.7% vs 14.3% p = 0.0366) and the treatment was found to be well tolerated and had no ill effects. In a 3 armed study also with DFU patients Yao et al. (2014) also applied treatments with low-frequency ultrasound. The three groups had differing amounts of ultrasound per week (Group 1: 3 x week, Group 2: 1 x week, Group 3: placebo). The 3 times per week group showed the greatest amount of wound size reduction compared with baseline (86% p < 0·05) leading the authors to conclude that the treatment applied when applied 3 times per week led to better wound outcomes.

The use of ultrasound as a wound healing treatment has also been subject to systematic review. Baba-Akbari Sari et al. (2006) carried out a Cochrane review to ascertain the usefulness of ultrasound for the treatment of pressure ulcers. They found 3 RCTs which had a significant degree of heterogeneity and demonstrated no evidence of benefit of ultrasound in the treatment of pressure ulcers. The small amount of studies included however leads to the possibility of as yet undiscovered benefits. In their Cochrane review Cullum et al. (2010) studied the effectiveness of ultrasound on venous leg ulcers. Eight trials met the inclusion criteria and they found that more patients healed with ultrasound than without it at 7 - 8 weeks (pooled RR 1.4, 95% CI 1.0 to 1.96). The longer term benefits of ultrasound treatment (at 12 weeks) were however less clear (pooled RR 1.47, 95% CI 0.99 to 2.20). Thus as is the case with electrostimulation there is an underlying evidence base for the use of ultrasound in wound healing even though neither could be described as mainstream therapies and both as seen as adjunct therapies.

Combining Electrostimulation and Ultrasound

The combination of these two treatments is not widely studied but given their potential and documented efficacy as outlined above the proposition to combine them would appear to be reasonable. One published study to date (Avrahami et al., 2015) has looked at the combination of these therapies. The authors approach the study with the premise that there is a value in combining the therapies particularly in relation to the effect that both therapies individually have been shown to have on strengthening collagen build-up in wound healing. They postulate that the evidence that ultrasound stimulates fibroblast growth when combined with the evidence that electrostimulation pulls fibroblasts together in a tighter collagen weave is likely to be complimentary.

Avrahami et al. (2015) carried out a retrospective analysis of 300 wounds which were treated with CUSEFS. They looked specifically at 65 wounds both DFUs (n=27) and venous leg ulcers (n= 38). Patients all had at least 8 treatments in a minimum of 4 weeks, twice weekly with CUSEFS using the BRH-A2 device (BRH Medical). The device delivers modulated frequency (1.0-3.0 MHz) and intensity (0.0- 2.0 W/cm^2) of ultrasound and varying electrostimulation intensity (0-250 Hz). Results indicate that 59.3% achieved 50% closure within 4 weeks. This was further broken down as 71.1% of the venous leg ulcers and 59.3% of the DFUs treated having 50% closure within 4 weeks. The authors found no significant association between gender, wound size on presentation or the longevity of the wound on the outcomes. In the venous leg ulcer group age was significantly associated with the outcome. The authors conclude that CUSEFS offers a useful adjunct therapy for chronic hard to heal wounds.

The evaluation

Aims

The aim of this evaluation was to investigate if CUSEFS is an effective treatment for patients with chronic ‘hard to heal’ wounds.

Methodology

Design

This evaluation employed a prospective, non-comparative, case series design.

Population and sample

This evaluation was undertaken in a Podiatry Led diabetic foot clinic in an acute hospital setting in an urban location in Ireland.

Inclusion criteria

- Patients with chronic wounds, including diabetic and venous ulcers and pressure ulcers.
- Patients who had been treated prior to affiliation for at least 2 months with systemic and local treatments such as debridement, antibiotics, hyperbaric oxygenation and vacuum systems, with little or no improvement in the three weeks prior to their assessment.
- Patients who could commit to twice weekly treatment for at least four weeks

Exclusion criteria

- Patients who could not attend on a twice weekly basis

Procedures

CUSEFS treatments were applied twice weekly on participating patients using the BRH-A2 wound healing device. The device is CE marked and approved for use in clinical settings. It delivered the treatment of ultrasound at modulating frequency (1.0-3.0 MHz) and intensity (0.0- 2.0 W/cm2) via a probe which was applied to the wound by the operator. Electrostimulation was delivered at varying intensity (0-250 Hz) via electrodes which were placed at the wound boundaries. Treatments were performed twice a week in the Diabetic foot clinic for 4 weeks or until wound closure occurred or patients needed to withdraw for other reasons. Normal treatment and care were maintained for all patients alongside the treatment for the duration of the study

Data Collection

The following demographics were recorded at the commencement of the study (these were recorded on the BRH-A2 software):

- Age
- Gender
- Wound type
- Wound duration
- Treatments to date
- Complications

During the treatment period wound sizes were measured and recorded using the camera, a standard ruler and calculated using the BRH-A2 wound area measurement software. Adverse events and clinical observations by the team were also recorded. Data were analysed using Excel spreadsheets and analysis of wound measurements using the bespoke BRH-A2 software which is an integral part of the system.

Ethical Issues

Full Institutional review processes were followed prior to commencement. Prior to commencing the evaluation participants were given an information leaflet which was written to the level of education associated with a FOG index of 10 or below. This explained the treatment and advised of the patients' right to withdraw at any time during the study. Written consent to participate was then obtained from each patient.

Results

Sample

In total 7 patients (Labelled Patients A to E) were recruited for this case series. The demographic are detailed in table 1.

Table1: Demographic data

Number of participants	**7**
Gender	
Male	**6 (85%)**
Female	**1 (15%)**
Age	
Range	**42-83**
Mean	**63 ±16.6**
No. of Wounds treated	**8**

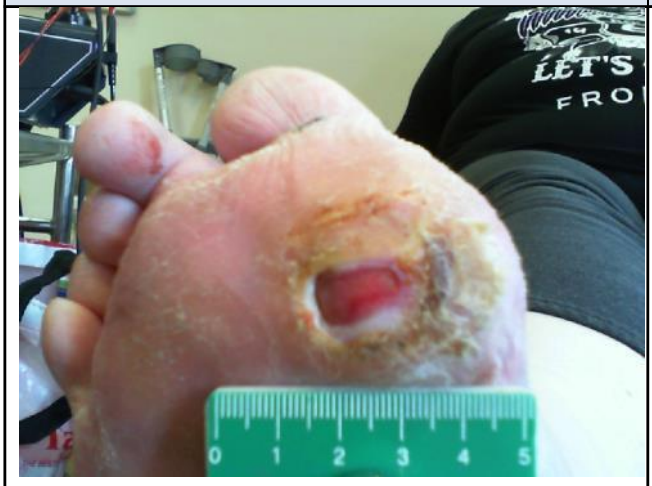
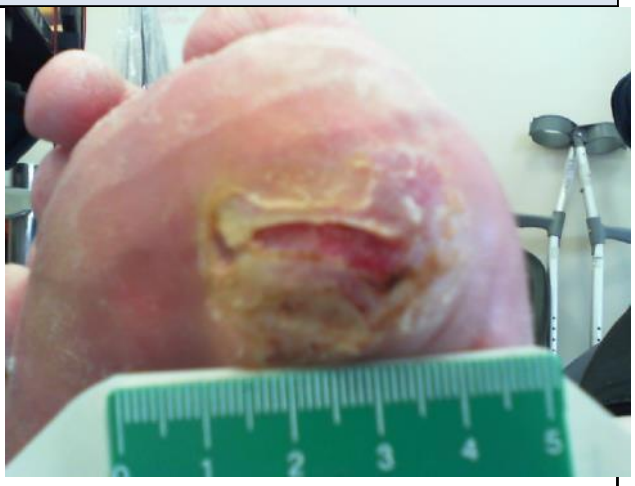
During the initial recruitment phase it was decided that patients with neuropathic diabetic foot ulcers only would be targeted, as they were the most prevalent type of patient in this particular clinic and it was considered that this would provide more comparable data.

Subsequent recruitment was then widened to include all diabetic foot ulcers. Neuroischaemic ulcers are the most prevalent in developed countries.

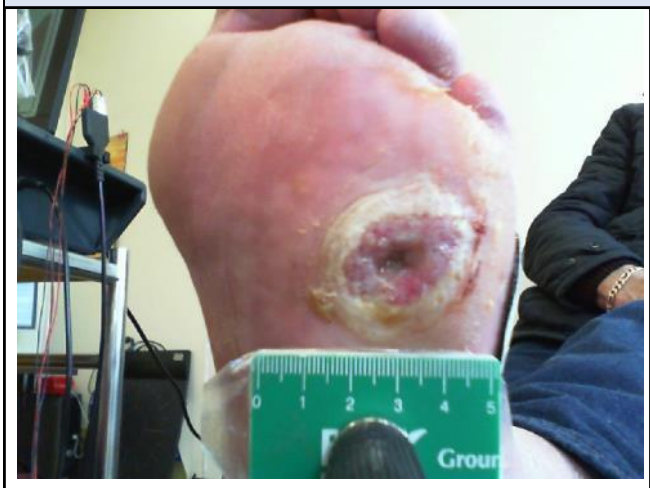
- One patient (Patient E) had 2 wounds (one each on the first and second toe of the left foot) and these were treated as separate wounds.
- One patient (Patient B) was unable to complete the course of treatment as he developed complications unrelated to the treatment.

Individual Patient Outcomes

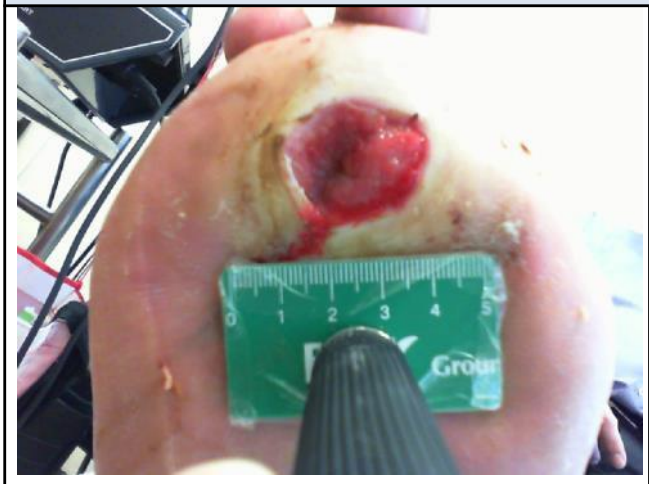
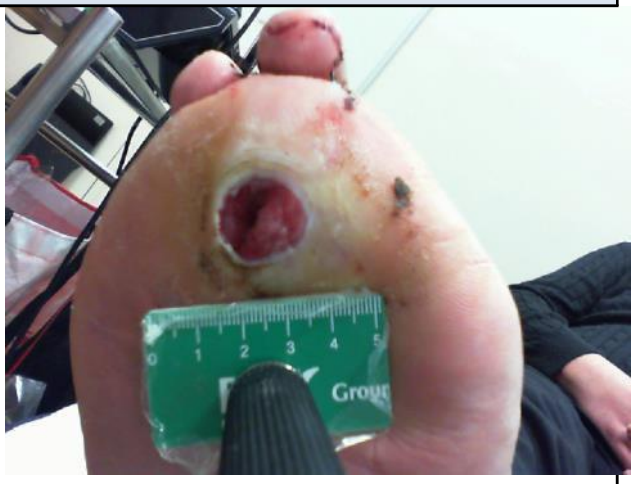
Patient A

Wound type:	Neuropathic Diabetic Foot Ulcer
Wound duration:	9 Months
Treatments to date:	Antibiotics, Debridement, Dressings
Past complications:	Osteomyelitis
Treatment duration	25 days
Number of treatments	8
Wound Size on commencement	143.01 mm^2
Wound Size at completion of treatment	49.72 mm^2
% Difference	65%
Adverse Events	None
Before	**After**
	
Clinical Comments	Full closure not achieved but wound improved over the course of the treatment

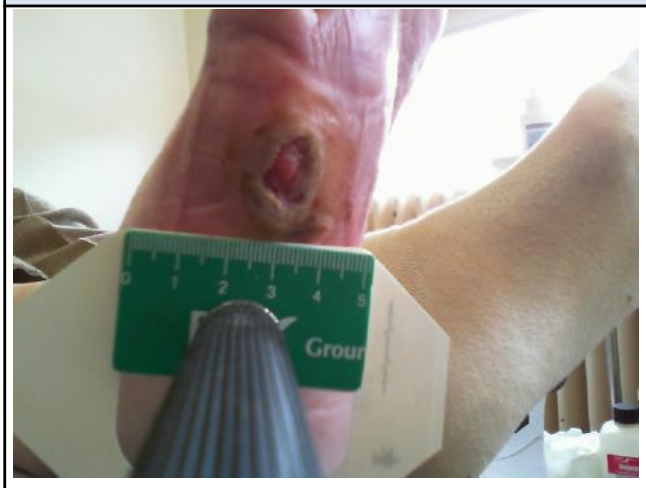
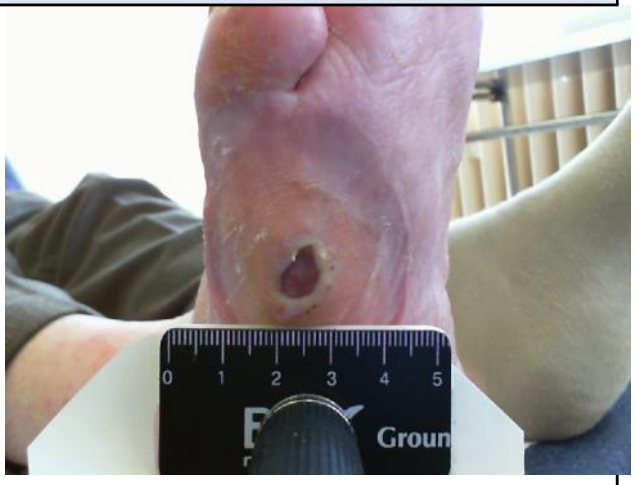
Patient B

Wound type:	Neuropathic Diabetic Foot Ulcer
Wound duration:	20 Months
Treatments to date:	Debridement, Dressings
Past complications:	Osteomyelitis, Cellulites
Treatment duration	8 days
Number of treatments	2
Wound Size on commencement	913.00 mm^2
Wound Size at completion of treatment	Unknown
% Difference	N/A
Adverse Events	None
Before	**After**
	
Clinical Comments	This patient had to withdraw due to a severe cellulitis which was unrelated to the treatment and which he had on a number of occasions in his past history. He was subsequently treated with IV antibiotics for cellulitis and osteomyelitis and was casted for 8 weeks.

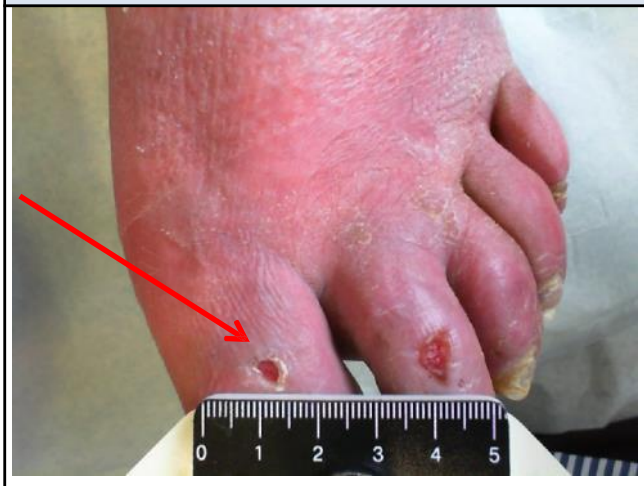
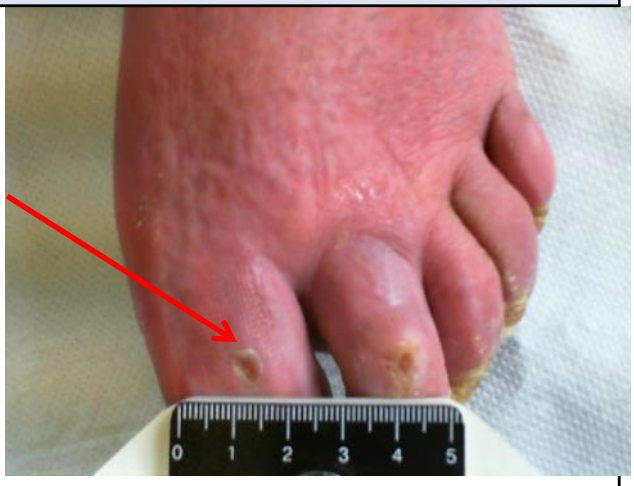
Patient C

Wound type:	Neuropathic Diabetic Foot Ulcer
Wound duration:	6 Months
Treatments to date:	Antibiotics, Debridement, Dressings, TNP
Past Complications:	Osteomyelitis
Treatment duration	27 days
Number of treatments	8
Wound Size on commencement	527.95 mm^2
Wound Size at completion of treatment	264.05 mm^2
% Difference	50%
Adverse Events	None
Before	**After**
	
Clinical Comments	Full closure not achieved but wound improved over the course of the treatment. There was a noticeable improvement in the skin area around the wound.

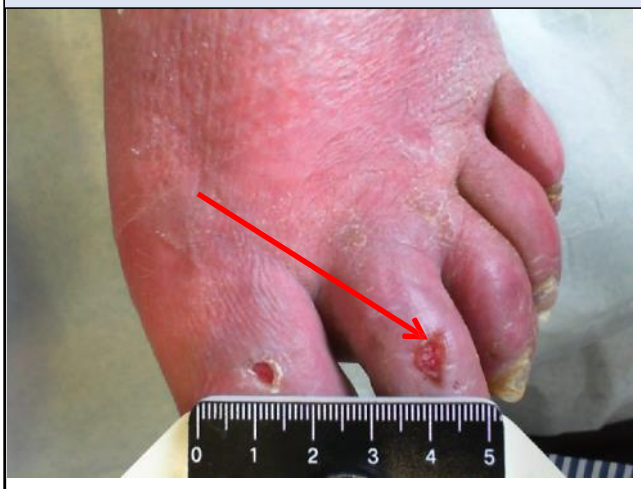
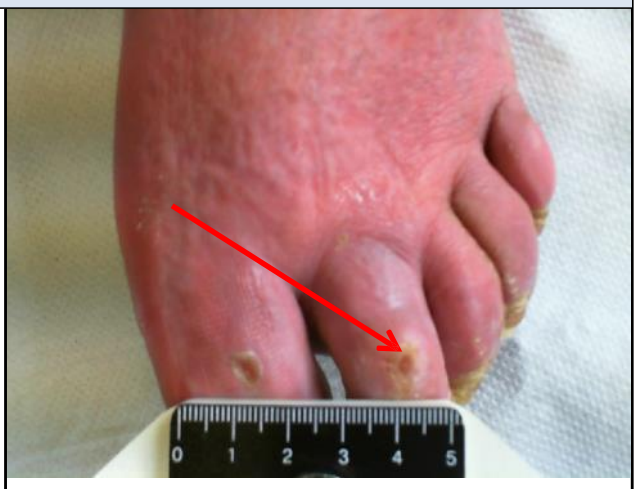
Patient D

Wound type:	Neuropathic Diabetic Foot Ulcer
Wound duration:	9 Months
Treatments to date:	Antibiotics, Debridement, Dressings
Past complications:	Osteomyelitis
Treatment duration	25 days
Number of treatments	8
Wound Size on commencement	118.5 mm^2
Wound Size at completion of treatment	48.4 mm^2
% Difference	84%
Adverse Events	None
Before	**After**
	
Clinical Comments	We saw a good response in relation to wound size reduction. The overall clinical picture however deteriorated severely. The patient had a reoccurrence of osteomyelitis (unrelated to this treatment) and as a result entered limb salvage modalities.

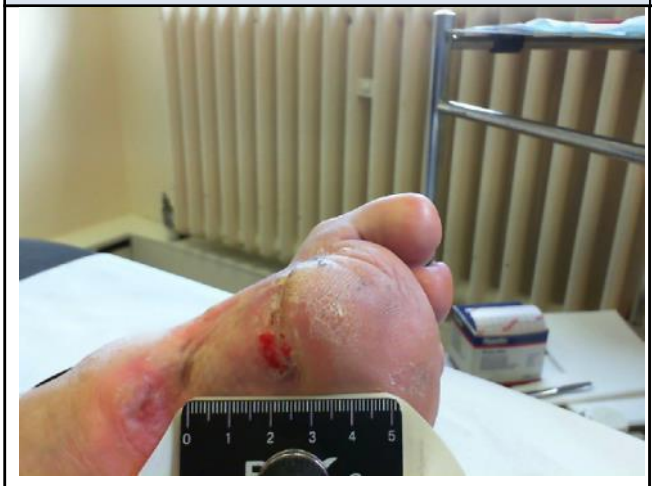
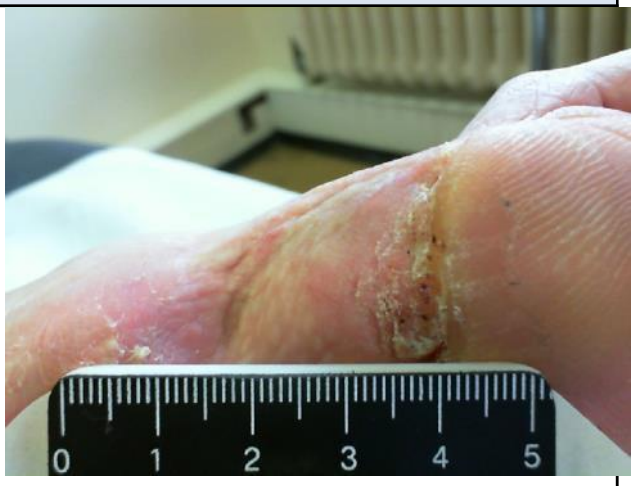
Patient E (Wound 1)

Wound type:	Neuroischaemic Diabetic Foot Ulcer
Wound duration:	3 Months
Treatments to date:	Debridement, Dressings
Past complications:	Osteomyelitis
Treatment duration	28 days
Number of treatments	8
Wound Size on commencement	23.12 mm^2
Wound Size at completion of treatment	14.34 mm^2
% Difference	38%
Adverse Events	None
Before	**After**
	
Clinical Comments	Wounds on both the first and second toe were treated, both responded well. There was a noticeable improvment in surrounding skin

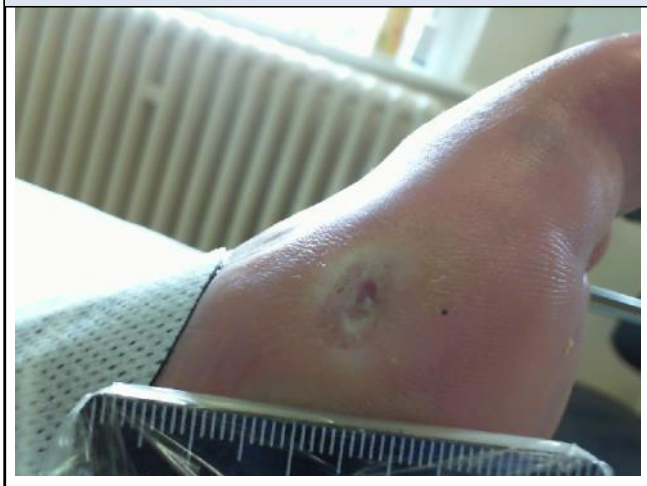
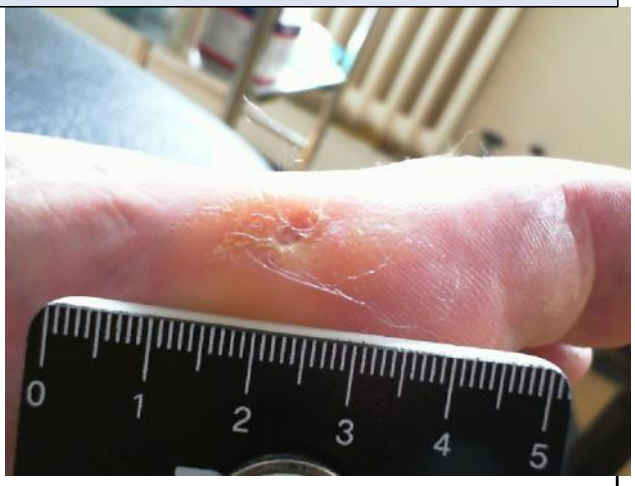
Patient E (Wound 2)

Wound type:	Neuroischaemic Diabetic Foot Ulcer
Wound duration:	3 Months
Treatments to date:	Debridement, Dressings
Past complications:	Osteomyelitis
Treatment duration	28 days
Number of treatments	8
Wound Size on commencement	27.71 mm^2
Wound Size at completion of treatment	2.03 mm^2
% Difference	93 %
Adverse Events	None
Before	**After**
	
Clinical Comments	Wounds on both the first and second toe were treated, both responded well. There was a noticeable improvement in surrounding skin

Patient F

Wound type:	Neuropathic Diabetic Foot Ulcer
Wound duration:	2 Months
Treatments to date:	Debridement, Dressings
Past complications:	Osteomyelitis
Treatment duration	16 days
Number of treatments	5
Wound Size on commencement	104.98mm^2
Wound Size at completion of treatment	Wound closed
% Difference	100%
Adverse Events	None
Before	**After**
	
Clinical Comments	Wound closure was achieved after 5 treatments. Skin around the wound edges was also improved

Patient G

Wound type:	Neuroischaemic Diabetic Foot Ulcer
Wound duration:	17 Months
Treatments to date:	Dressings
Past complications:	Osteomyelitis
Treatment duration	24 days
Number of treatments	8
Wound Size on commencement	22.22 mm^2
Wound Size at completion of treatment	1.57 mm^2
% Difference	93%
Adverse Events	None
Before	**After**
	
Clinical Comments	The wound improved as did the surrounding skin. Full closure was not quite achieved.

Summary and Conclusion

During the course of this clinical case series 8 neuropathic DFUs were treated with CUSEFS over a 4 weeks period. As can be seen from the data above, in all cases that were able to continue with the treatment there was wound size reduction in all the wounds involved. Table 2 summarizes the wound size reduction figures for all of the wounds treated.

Patient A	143.01	49.72	65%
Patient B	913.00	N/A	N/A
Patient C	527.95	264.05	50%
Patient D	118.5	48.49	59%
Patient E (Wound 1)	23.12	14.34	38%
Patient E (Wound 2)	27.71	2.03	93%
Patient F	104.98	0	100%
Patient G	22.22	1.57	93%
		Mean	**71%**
		Range	**38-100%**

All of the wounds treated on the protocoled 8 occasions or until closure show a decrease in wound size with 2 wounds completely healing. The mean wound size reduction across all wounds is 72%. This represents a good outcome in terms of wound size reduction. When compared with the data from the only other study on the use of CUSEFS, Avrahami et al. (2015), 75% of the wounds show a closure rate of 50% or more as compared to 59.3% for DFU in their study. Thus, while this case series has a smaller sample size, it offers further confirmation of the findings of Avrahami et al. (2015).

As per the protocol for this study the patients in this case series had treatment for a maximum of 4 weeks at which point their usual care continued. All of the wounds treated exhibited wound size reduction within the treatment period. While it is not possible to say

definitively that all wounds would have closed had the treatment continued, the trajectory suggests that this may be the case. Some of the patents involved went on to have further problems with their wounds not related to this study or treatment. This is not unusual in this area of care as these types of chronic wounds are notoriously difficult to treat and often reoccur. The addition of an adjunct therapy like CUSEFS on a longer term basis may have been beneficial in preventing some of these issues however. A notable benefit of the treatment as captured by the clinical observations during the treatment was that they were in many cases noticeable improvement in skin surrounding the wound area. This indicates that the treatment may play a role in improving the wound border tissue.

The results of this case series evaluation must be considered in the light of the small sample size. The result indicates that the application of CUSEFS offers a useful adjunct therapy in the treatment of DFUs. Further, larger scale studies involving control groups are now needed to gather further evidence in this regard. The finding here are promising and support the use of CUSEFS as a treatment.

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