Combined use of modulated ultrasound and electric current stimulation for diabetic foot ulcers: a case series

Objective: Diabetic foot ulcers (DFUs) are a significant challenge in wound care practice. Our aim was to evaluate the combined use of of two therapies, ultrasound and electrostimulation, in the treatment of DFUs.
Method: This study employed a prospective, non-comparative, case series design, undertaken in a podiatry-led diabetic foot clinic, in an acute hospital setting, in an urban location in Ireland. We recruited patinets with hard-to-heal DFUs who were treated twice a week with combined modulated ultrasound and electric current stimulation.
Results: We recruited seven patients with eight chronic DFUs. A mean wound size reduction of 71% was achieved and there were no adverse reactions to the therapy.
Conclusion: The results of this small case series indicate that combined modulated ultrasound and electric current stimulation offers promise as an adjunct therapy for DFUs. Further large scale trials are now warranted.
Declaration of interest: The authors have no conflict of interest to declare.

diabetic foot • electric current stimulation • electrostimulation • ultrasound

People with diabetes are 50 times more likely to develop a foot ulcer than their non-diabetic counterparts.[1] The prevalence of foot ulceration in this patient group is suggested to range from 3–10%,[1] and these wounds are difficult to heal, and often compounded by the presence of multiple comorbidities. Diabetes is the leading cause of non-traumatic limb amputation in the world.[2] Within 18 months following amputation, almost 50% of these people will develop ulceration on the other limb and 58% of these will have further amputations within three to five years.[3] It is worthy to note that the three-year mortality rate after the first amputation is between 20% and 50%.[4,5] Having diabetes impacts negatively on the individual's health-related quality of life (HRQoL) when compared with the general population.[6] 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.[6]

The International Working Group of the Diabetic Foot (IWGDF) highlights the continuing difficulties in selecting clinically effective treatments for diabetic foot infection and ulceration. In two commissioned systematic reviews it points to the large number of treatment options available, while at the same time highlighting the relative weakness of evidence to support the use of many of these options.[7,8] In this study we used treatments – electrostimulation and ultrasound. While both of these technologies have been shown to be effective in chronic wound healing, the use of combined modulated ultrasound and electric current stimulation (CUSECS) is a new and not widely studied treatment.[9] The merits of each treatment will be explored below.

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.[10] Widespread interest and research into the use of electrostimulation is evident since the 1960s.[11] 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.[12,13]

Studies have pointed to some promising outcomes for the use of electrostimulation in practice for a range of wound types. For example, Wirsing et al.,[14] in a prospective case series of 47 patients with chronic

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wounds of various types, found a mean reduction of 95% in wounds surface areas after eight weeks of treatment, applying 45–60 minutes of a 1.5µA current intensity to the wound area. Treatments were applied 2–3 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.,[15] in a study with patients with various wound types, applied an electrical current to wounds twice daily for 30 minutes over seven days with varying polarities. They found that wound size decreased by 44.7%, exudate, fibrin, necrosis and wound odour also decreased, and no adverse events occurred. The authors also determined that the treatment was well tolerated by patients. However, in both these studies the lack of a control group weakens the claims.

In relation to DFUs, Peters et al.[16] carried out an RCT to assess the impact of a 50V current applied to an individual's wounds overnight (eight hours) using a microcomputer. Both the intervention and control groups also received standard care. Results indicate that 65% healed in the treatment group versus 35% in the control group (p=0.058). The wound size reduction was not statistically different between the groups and in both groups the more concordant patients had better outcomes. In other trials, however, statistically significant effects have been demonstrated. Polak et al.[17] note statistically significant wound size reduction at one and six weeks for pressure ulcers (PUs) treated with electrostimulation, and Lawson and Petrofsky[18] demonstrated increased healing rate between control and intervention in a trial using electrostimulation of DFUs.

Systematic reviews of treatments with electrostimulation have also pointed to its potential and value. Thakral et al.[19] assessed the role of electrostimulation for plastic surgery, in all wound types, and included 17 randomised control trials (RCTs) in their systematic review. They found that, in 14 out of 16 RCTs, electrical stimulation was associated with faster wound area reduction and a higher proportion of wounds healed completely. Like other authors in the area (see e.g. Hess et al.)[10] they caution that the variety of methods and disparity in how electrostimulation is applied, in relation to current, dosage and duration, makes it difficult to aggregate findings. However, Kloth,[13] 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. Importantly, for the present study, he found that electrically induced acceleration of the closure of wounds in individuals with non-ischemic diabetic neuropathy, had been demonstrated in four studies, including two RCTs. There is, therefore, an important body of evidence to support the use of electrostimulation for wound healing.

Ultrasound has been in use both as a therapy and as a diagnostic for some time in health care. Its use 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 1–1.5W/cm^2, the thermal properties of ultrasound are used for soft tissues injuries and for scar improvement.[10] For therapeutic use in wound healing, however, high frequency ultrasound with spatial average temporal peak (SATP)=0.5W/cm^2 or lower has been shown to be effective in the treatment of chronic wounds during inflammation and proliferation stages.[17] Also with no thermal effect, pulsed mode ultrasound typically delivered with a duty cycle of 20%, yielding spatial average temporal average (SATA)=0.1W/cm^2 has been shown to benefit wound healing.[20–23]

Kavros et al.[24] studied the use of low frequency ultrasound in the treatment of below-knee lower extremity wounds. The intervention group had ultrasound at an intensity 0.1–0.8W/cm^3, three times per week for six months, or until healed. A control group received standard care. In the intervention group, 53% healed over an average of 147 days, versus 32% over 134 days, in the control group (p=0.009). When evaluated by aetiology the treatment was most effective in venous leg ulcers (VLUs). In a further study, also in VLUs, Samuels et al.[25] demonstrated a clinical, though non-statistically significant, effect of low frequency (<100kHz), low intensity (<100mW/cm^2) ultrasound. In this three-arm study, involving both *in vitro* and *in vivo* samples, the patients who were exposed to a 15 minutes treatment with 20kHz of ultrasound had accelerated wound closure.

In relation to DFU, Ennis et al.,[26] 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, in addition to standard care. The treatment was administered three times a week, for four minutes, over 12 weeks, or until the wound healed. Results indicated a better healing rate in the intervention group than the control (40.7% versus 14.3%, p=0.0366). The treatment was found to be well tolerated and had no ill effects. In a further three armed study, with DFU patients, Yao et al.[22] also employed treatment 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). Group one showed the greatest amount of wound size reduction compared with baseline (86%; p<0.05), leading the authors to conclude that the treatment, when applied three times per week, led to better wound outcomes. Thus, as is the case with electrostimulation, there is an existing evidence base for the use of ultrasound in wound healing, even though both are seen as adjunct therapies and neither could be described as mainstream therapies.

The combination of electrostimulation and ultrasound 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[9] has looked at the combination of these therapies. The authors approach that study from the premise that there is a value in combining the

Table 1. Treatment details and technical specifications

Ultrasound		Electrical stimulation	
Frequency	1.0–3Mhz	**Current frequency**	Synchronous output channels Carrier frequency: 4000Hz Frequency range: Channel 1=4000Hz, Channel 2=4000Hz to 4250Hz ±1 Interferential beat frequency: PPS 1–250Hz in 5Hz increments
Probe Size	4cm^2	**Electrode properties**	Round, 5cm diameter placed around the wound edge at a minimum distance of 5cm.
Wave type	Continuous	**Shape of electric pulse**	Interferential Output waveforms
Intensity	Maximum intensity: 2.0W/cm^2 Continuous wave: 8W with 4cm^2	**Current intensity**	Max Output Current (mA): 0-65±10% mA RMS, max 1Kohm load Maximum current density: 3.2 mA/cm^2 at 1kΩ
Duration	15 minute treatments x 2 per week for a maximum of 4 weeks or until fully healed Maximum intensity: 2.0W/cm^2 BNR: <5 ERA: 4cm^2±10%	**Duration**	15 minute treatments x 2 per week for a maximum of 4 weeks or until fully healed. Maximum power density: ≤0.25 W/cm^2

BNR—beam nonuniformity ratio; ERA—effective radiating area

therapies, particularly in relation to the effect that each individual therapy has been shown to have on strengthening collagen build-up in wound healing, through increasing blood flow to the wounded area. 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.[9] carried out a retrospective analysis of 300 wounds which were treated with CUSECS. They looked specifically at 65 wounds, both DFUs (n=27) and VLUs (n=38). All patients had at least eight treatments, in a minimum of four weeks, twice weekly, with CUSECS, using the BRH-A2 device (BRH Medical). The device delivers modulated frequency (1.0–3.0MHz) and intensity (0.0–2.0W/cm^2) of ultrasound and varying electrostimulation intensity (0–250Hz). Results indicate that 59.3% achieved 50% closure within four weeks. This was further explained as 71.1% of the VLUs and 59.3% of the DFUs treated, having 50% closure within four weeks. The authors found no significant association between gender, wound size on presentation and the longevity of the wound, on the outcomes. The authors conclude that CUSECS offers a useful adjunct therapy for chronic, hard-to-heal wounds.

Aims

The aim of this evaluation was to investigate if CUSECS is a useful treatment for patients with chronic, hard-to-heal DFUs.

Methods

This study employed a prospective, non-comparative, case series design. The study 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 DUFs, VLUs and PUs
- Patients who had been treated before recruitment for at least two months with systemic and local treatments such as debridement, antibiotics, hyperbaric oxygenation (HBOT) and vacuum systems, with little or no improvement in the three weeks before their assessment
- Patients who could commit to twice weekly treatment for at least four weeks.

Exclusion criteria

- Patients who could not attend the clinic on a twice weekly basis.

Treatment

CUSECS 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 is designed to deliver the treatment of ultrasound at modulating frequency (1.0–3.0MHz) and intensity (0.0–2.0W/cm^2) via a probe, which is applied to the wound by the operator, and electrostimulation at varying intensity (0–250Hz) via electrodes which were placed at the wound boundaries. Exact treatment parameters are described in Table 1.

Treatments were performed in the diabetic foot clinic twice a week for four weeks, or until wound closure occurred, or patients needed to withdraw for other reasons. Usual wound treatment and care were

Table 2. Demographic data

Number of participants	**7**
Gender	
Male	6 (85%)
Female	1 (15%)
Age	
Range	42–83 years
Mean	63±16.6 years
Number of wounds treated	**8**

maintained for all patients alongside the additional treatment, for the duration of the study.

During the treatment period wound sizes were measured and recorded using a 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 BRH-A2 software which is an integral part of the system. Full institutional review processes were followed prior to commencement. Before starting the study participants were given an information leaflet, written to the level of education associated with a FOG index (Gunning Fog Index of Readability) of 10 or below.[27] This explained the treatment and advised of the patient's right to withdraw at any time during the study. Written consent to participate was then obtained from each patient.

Fig 1. Case 1, 43-year-old female with neuropathic diabetic foot ulcer on the plantar aspect of her right foot

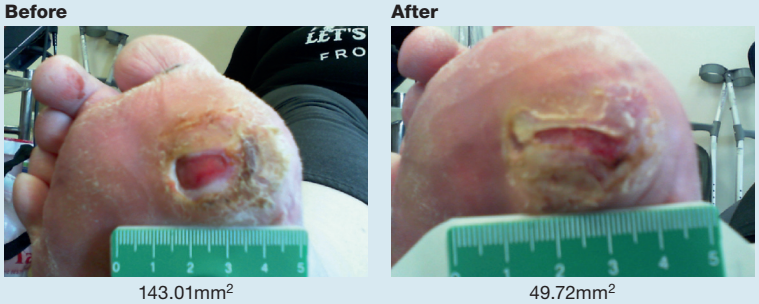
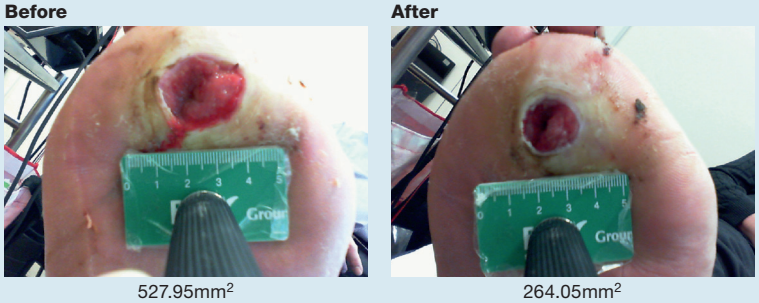


Fig 2. Case 3, a 44-year-old male with neuropathic diabetic foot ulcer on the plantar aspect of his right foot



Results

Sample

In total, seven patients (labelled Case 1 to 7) were recruited for this case series. Demographics are detailed in Table 2.

During the initial recruitment phase it was decided that patients with neuropathic DFUs 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. Patients were considered for inclusion with University of Texas Diabetic Wound Classification[28] scores (UT) of 1A or below.

- One patient (Case 5) had two wounds (one each on the first and second toe of the left foot) and these were treated as separate wounds
- One patient (Case 2) was unable to complete the course of treatment as he developed complications unrelated to the treatment.

Case 1

A 43-year-old female who had neuropathic DFU on the plantar aspect of her right foot for nine months (Fig 1). She had a history of previous osteomyelitis in the foot and had been treated with antibiotics, debridement and dressings. At the start the wound size was 143.01mm^2 and the UT score was 1A (Fig 1). She underwent eight treatments over 25 days and showed significant wound reduction over the course of the treatment. Wound size at completion of treatment was 49.72mm^2, representing a 65% reduction (Fig 1). No adverse reactions were experienced.

Case 2

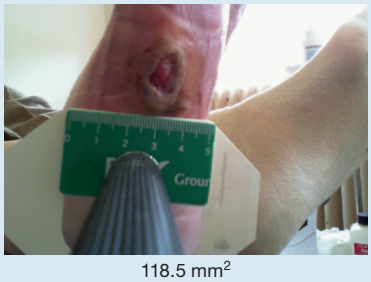
A 83-year-old male who had neuropathic DFUs on the plantar aspect of his left foot for 20 months. He had a history of previous osteomyelitis and cellulitis in the foot, and had been treated with debridement and dressings. At the start of the study the wound size was 91.3mm^2 and the UT score on commencement was 1A. He underwent two treatments in an eight day period. This patient had to withdraw due to a severe cellulitis which was unrelated to the treatment and which he had had on a number of occasions in his past history. He was subsequently treated with IV antibiotics for cellulitis and osteomyelitis and was placed in an offloading cast for eight weeks. No adverse reactions were experienced to his two treatments. However, no determination of effect on wound size could be made.

Case 3

A 44-year-old male who had neuropathic DFU on the plantar aspect of his right foot for six months. He had a history of previous osteomyelitis in the foot and had been treated with antibiotics, debridement and

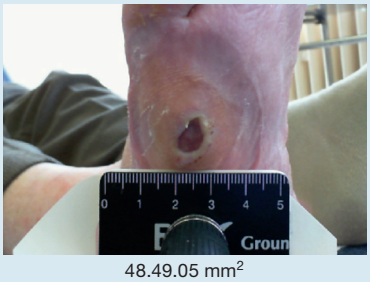
Fig 3. Case 4, a 78-year-old male with a neuropathic diabetic foot ulcer on the lateral/plantar aspect of his right foot

Before



118.5 mm^2

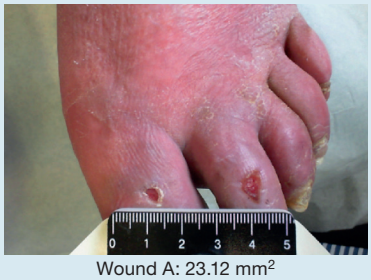
After



48.49.05 mm^2

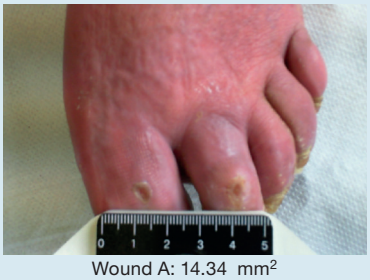
Fig 4. Case 5, 66-year-old male with two neuroischaemic neuropathic diabetic foot ulcers on the toes of his left foot

Before



Wound A: 23.12 mm^2
Wound B: 27.71 mm^2

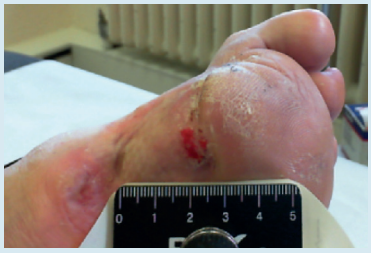
After



Wound A: 14.34 mm^2
Wound B: 2.03 mm^2

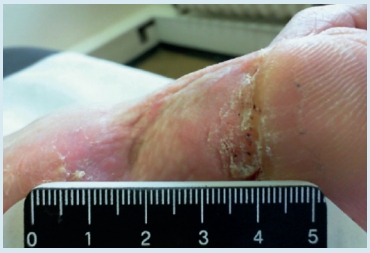
Fig 5. Case 6, a 47-year-old male with a neuropathic diabetic foot ulcer on the plantar/medial aspect of his left foot

Before



104.98 mm^2

After



Wound Closure

dressings. At the start of the study the wound size was 527.95mm^2 (Fig 2) and the UT score was 1A. The patinet underwent eight treatments over 27 days and showed significant wound size reduction over the course of the treatment. Wound size on completion of treatment was 264.05mm^2, representing a 50% reduction (Fig 2). There was also a noticeable improvement in the skin area around the wound. No adverse reactions were experienced.

Case 4

A 78-year-old male who had a neuropathic DFU on the lateral/plantar aspect of his right foot for nine months. He had a history of previous osteomyelitis in the foot and had been treated with antibiotics, debridement and dressings. At the start of the study the wound size was 118.5mm^2 and the UT score was 1C (Fig 3). The patient underwent eight treatments over 25 days and showed wound reduction over the course of the treatment. Wound size on completion of treatment was 48.49mm^2, representing an 59% reduction (Fig 3). No adverse reactions to the treatments were experienced. While we saw a good response in relation to wound size reduction, the overall clinical picture deteriorated. The patient had a reoccurrence of osteomyelitis (unrelated to this treatment) and as a result entered limb salvage modalities.

Case 5

A 66-year-old male who had two neuroischaemic neuropathic DFUs on the toes of his left foot for nine months. Wound A was situated on the large toe and wound B on the second toe. He had a history of previous osteomyelitis and had been treated with debridement and dressings. At the start of the study the wound sizes were 23.12mm^2 (wound A) and 27.71mm^2 (wound B) and the UT score for both wounds was 1C (Fig 4). The patient underwent eight treatments over 28 days and showed significant wound reduction over the course of the treatment. Wound size on completion of treatment was 14.34mm^2 for wound A and 2.03mm^2 for wound B, representing a 38% and 93% reduction respectively (Fig 4). There was also a noticeable improvement in surrounding skin. No adverse reactions to the treatments were experienced.

Case 6

A 47-year-old male who had a neuropathic DFU on the plantar/medial aspect of his left foot for 17 months. He had a history of previous osteomyelitis and had been treated with antibiotics and dressings. At the start of the study the wound size was 104.98mm^2 and the UT score was 1A (Fig 5). The patient underwent five treatments over 16 days and wound closure was achieved (Fig 5). There was also a noticeable improvement in surrounding skin. No adverse reactions to the treatments were experienced.

Case 7

An 80-year-old male who had a neuroischaemic DFU on the plantar/medial aspect of his left foot for 17 months. He had a history of previous osteomyelitis and had been treated with debridement and dressings. At the start of treatment the wound size was 22.22mm^2 and UT score was 1C (Fig 6). The patient underwent eight treatments over 24 days and showed significant wound reduction over the course of the treatment (Fig 6). Full closure was not achieved but wound size on completion of treatment was 1.57mm^2 representing a 93% reduction. There was also a noticeable improvement in surrounding skin. No adverse reactions to the treatments were experienced.

Discussion

During the course of this clinical case series

eight neuropathic DFUs were treated with CUSECS over a four weeks period. As can be seen from the data above, in the cases that were able to continue with the treatment, all showed wound size reduction in all the wounds involved. Table 3 summarises the wound size reduction figures for all of the wounds treated.

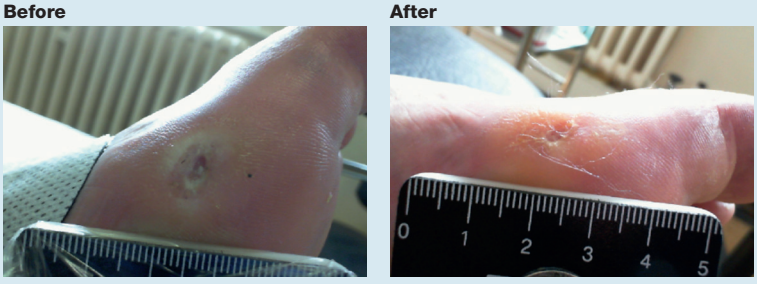
All of the wounds treated on the planned eight occasions, or until closure, showed a decrease in wound size, with two wounds completely healing. The mean wound size reduction across all wounds was 71%. This represents a good outcome in terms of wound size reduction. When compared with the data from the previous study on the use of CUSECS,[9] 75% of the wounds show a closure rate of 50% or more, compared with 59.3% with closure rates of 50% or more in the study by Avrahami et al. Thus, while this case series has a smaller sample size, it offers further confirmation of the findings of Avrahami et al.[9] The findings also support the idea that both of these treatments are useful adjuncts in diabetic foot wound healing for ultrasound[22,26] and for electrostimulation.[8] If these individual therapies tighten collagen weave and stimulate collagen growth respectively, then the promising wound size reductions shown by this study point to a good reason for their combination.

As per the protocol the patients in this case series had treatment for a maximum of four weeks, at which point their standard care continued. All of the wounds treated exhibited wound size reduction within the treatment period. 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 are often recurrent. A notable benefit of the treatment, as captured by the clinical observations during the treatment was, in many cases, the noticeable improvement in skin surrounding the wound area. This indicates that the treatment may play a role in improving the wound border tissue.

Limitations and further research

The results of this case series evaluation must be considered in light of the small sample size. The results indicate that the application of CUSECS offers a useful adjunct therapy in the treatment of DFUs. Further larger scale studies involving control groups are now needed to gather more evidence in this regard.

Fig 6. Case 7, a 80-year-old male with a neuroischaemic diabetic foot ulcer on the plantar/medial aspect of his left foot



22.22 mm^2 1.57 mm^2

Table 3. Summary of wound size reduction

	Wound size at the start of treatment mm^2	Wound size at end of treatment mm^2	% closure
Case 1	143.01	49.72	65%
Case 2	91.3	Not available	Not available
Case 3	527.95	264.05	50%
Case 4	118.5	48.49	59%
Case 5 (Wound 1)	23.12	14.34	38%
Case 5 (Wound 2)	27.71	2.03	93%
Case 6	104.98	0	100%
Case 7	22.22	1.57	93%
Mean			**71%**
Range			**38–100%**

Conclusion

DFUs continue to pose significant problems for patients suffering from them and for health professionals in their treatment. The emergence and testing of new therapies therefore, remains a priority. This case serious offers promising evidence for the use of CUSECS in treating DFUs. Further evidence by way of larger trials is now required. This study provides a basis for further investigation in this field. **JWC**

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