Effectiveness of combined modulated ultrasound and electric current stimulation to treat diabetic foot ulcers

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Title A pilot randomised control trial to measure the effectiveness of combined modulate ultrasound and electric current stimulation in treating diabetic foot ulcers

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Abstract (100-250 words)

Objective

The use of combined ultrasound and electrostimulation (CUSECS) as an adjunct therapy for diabetic foot ulcers (DFU) is a relatively new concept. This study aims to investigate if

CUSECS is an effective adjunctive treatment for chronic DFUs when compared with

standard wound care (SWC).

Method

A randomised controlled pilot study design was employed. Eleven chronic DFUs from two centres were sequentially randomised. For eight weeks the experimental group (n=6)

received CUSECS and SWC treatment twice a week; the control group (n=5) received SWC treatment once a week. The CUSECS device delivers ultrasound at a modulating frequency (1.0-3.0 MHz) and intensity (0.0- 2.0 W/cm^2) via a probe and electrostimulation at varying intensity (4000Hz–4250Hz) via electrodes. Wound size percentage was documented via photograph and measured for size. Self-efficacy, economic cost, and quality of life (QOL) and reoccurrence rates were analysed as secondary objectives.

Results

The experimental group achieved a higher rate of mean wound healing at 77% compared to -109% decrease in wound healing in the control group. Two participants completed full

healing in the experimental group and one in the control group. There were no statistically significant findings due to small sample size. There were no direct adverse reactions to this therapy. QOL scores improved in the treatment group. There was no significant change in self-efficacy scores. Experimental group costs were higher however healing rate was quicker which could be extrapolated to cost reductions over time.

Conclusion

Results suggest that CUSECS may be useful adjunctive therapy for treatment of chronic DFUs. Further large-scale studies are needed to ascertain the effectiveness of CUSECS.

The findings here are inconclusive but indicate that CUSECS may offer promise as a treatment.

Declaration of interest:

The authors have no conflict of interest to declare.

The treatment device utilised in this study was supplied on loan by Jagmed Ltd.

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Keywords: (5/6)

1. Adjunctive therapy
2. Diabetic foot ulcers
3. Chronic wound
4. Combined ultrasound and electric current stimulation
5. Ultrasound
6. Electric current stimulation

Paper

Introduction

Diabetic foot ulcers (DFU) result in a major global burden for patients and the health care system. It is one of the most serious complications of diabetes mellitus and responsible for major suffering and financial cost for the patient along with placing a considerable burden on family, health care professionals and facilities and society in general [1]. It is estimated that 25% of those diagnosed with diabetes will develop a foot ulceration in their lifetime [2]. Research indicates that the developments of DFUs and their reoccurrence might be correlated to an individual's self-efficacy and preventative behaviour [3, 4]. The complexity of DFUs and the reality that globally they have no single recognised treatment regime, creates a major challenge for clinicians resulting in the consumption of significant clinical time and hospital resources [5]. The use of adjunctive therapies when standard treatment for DFU fails is increasing in popularity with numerous adjunctive treatments widely available [6, 7].

Combined ultrasound and electrostimulation (CUSECS) is a relatively new adjunctive therapy which implements two therapeutic modalities ultrasound and electrostimulation [8]. Through acoustical cavitation and microstreaming, ultrasound has been found to promote wound healing by increasing angiogenesis, nitric oxide levels, stimulating fibroblasts and collagen production along with increasing macrophage responsiveness [9-13]. The rationale of using electric stimulation in wound healing is based on the theory of the endogenous bio-electric system [14, 15]. It has been found that when the low amperage electrical current that is found within the skin is disrupted e.g. due to a wound, a temporary electric field is generated. This activates key contributors to the wound healing process such as macrophages, neutrophils and fibroblasts [16]. Electrostimulation stimulates this electric field that ceases to exist in chronic wounds.

Individually both ultrasound and electric current stimulation therapies have portrayed positive results in previous studies [6, 10, 17-21]. Despite the type of current, dosage and duration of

ultrasound and electrostimulation differing in many studies, a significant improvement in wound healing has been found in previous trials [6, 10, 17-21]. Their respective benefits in wound healing complement and supplement each other and therefore, it seems reasonable to combine both therapies as done and justified by four published studies. Studies to date combined these treatments have shown some promise with regard to wound healing [8, 22-24]. The current study aimed to further investigate and validate these findings.

Aims and Objectives

The aim of this study is to investigate if CUSECS is an effective adjunctive treatment in treating DFUs when compared with standard wound care treatment.

The specific objectives were; to compare the wound healing percentage rate between the control and experimental group and to assess wound bed condition, QOL, self-efficacy, economic cost and DFU reoccurrence rates between those in the control group and in the experimental group.

Ethical approval

Ethical approval was granted by Hospital Research ethics committee and the Royal College of Surgeons in Ireland Research Ethics Committee for this study. The study was conducted in full accordance with the Declarations of Helsinki 1964 [25]. All data was collected, held and protected in compliance with the Data Protection Acts of 1988 and 2003 and EU General Data Protection Regulation 2018.

Method

This study employed a prospective randomised control trial approach in which data was collected over an eight-week period in a Diabetic foot clinic in a major acute hospital in an urban setting in Ireland. The inclusion and exclusion criteria for this study is illustrated in Table 1.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

· Participants were diagnosed with diabetes. · Participants had the capacity to provide informed consent prior to participation in the study. · Participants were aged 18 or over on the day of the informed consent. · Participants had a DFU that was present for at least 60 and less than 365 days. · Participants and/or caregiver were willing and able to comply with all study procedures and scheduled follow-up visits, for the duration of the study	· Participants without capacity to consent or those who do not provide informed consent. · DFUs that have a total surface area greater than 15 cm^2 as measured by a member of the study staff. DFUs greater than 15cm^2 were not included as chronic ulcers of this size are not common and would require a more intensive intervention should they occur. · Unwilling to continue with their standard wound care therapy for the study duration. · Clinical evidence of infection or gangrene on any part of the affected foot or leg. · Target ulcer involving exposure of tendon, bone or joint capsule, or any tunnelling or sinus tracts. · Target ulcer treatment with a wound dressing containing human growth factors, engineering tissues, or skin substitutes within 30 days of screening visit or planned during the study duration. · History of bone cancer, metastatic disease, radiation or chemotherapy to the affected limb within the 12 months prior to screening visit. · Suspected or confirmed malignancy of the wound. · Participation in another drug or device study for the treatment of DFU within 30 days of screening visit. · Vascular procedures performed within 30 days of screening visit. · Active bleeding tissue or untreated haemorrhagic conditions. · Active or suspected DVT or thrombophlebitis. · Subjects who have a cardiac pacemaker, implanted defibrillator, or other implanted metallic or electronic device. · Conditions which, in the judgment of the treating researcher, may severely compromise the subject's ability to complete the study.

Chronic wounds are notably difficult to heal and have high recurrence rates. They were included in this study due to their significant economic impact on the health system and negative impact on health-related quality of life (HRQOL). Along with this the incidence of chronic wounds is expected to rise due to the prolonged life expectancy among the elderly population and the rise in complex comorbidities including diabetes, vascular disease and obesity [26]. The author hopes to add further data towards combating the difficulties involved in stimulating healing in non-healing wounds. In this study we defined a chronic wound as having a wound present for 60 days and more with a failure to respond to standard treatment within that time frame. It was felt that this time period was satisfactory as wounds that are present for 60 days and showing a lack of progress, from a clinical perspective, indicate the need to re-evaluate current treatment plan.

We did not omit Ischemic wounds in this study as in previous CUSECS studies by Avrahami et al. [22] and O'Connor et al.[24]ischemic wounds were included. The IWGDF 2019 have stated that peripheral artery disease is present in up to 50% of those with a diabetic foot ulceration [27]. Therefore, the author felt including ischaemic wounds assimilated a true clinical test.

Following participants meeting the study's criteria they were provided with an information leaflet, written in an accessible level of English correlating to a score of ten or below on the FOG index [28]. All participants were reassured that participation was voluntary and that they could decline the invitation to participate in the research or withdraw from the study at any stage without suffering any negative consequences. They were assured that in this case that their usual standard of care for their diabetic foot ulcer would continue. Written consent to participant was then obtained from each participant.

Randomisation occurred through sequential randomisation. The treatment for each participant was determined as per the random allocation sequence following completion of initial podiatric assessment. To ensure selection bias didn't occur, the study researcher provided the attending podiatrist with a list of unique ID's with a corresponding randomised study group. This sequential randomisation list was created by using computer-generated software Random Allocation Software. Participants and treating podiatrists were unable to be blinded to treatment as neither method of treatment could be concealed. However, data analysis was undertaken without knowledge of the treatment allocation.

Treatment

Data for this study was collected from week 1 to week 8 of the trial and at a follow-up appointment four weeks after a participant completed the trial. Upon entering the study all study participants completed a SF-36 questionnaire and PROMIS self-efficacy questionnaire for baseline measurements. Participants were also requested to fill out both questionnaires at week 8 of the trial or sooner if full wound healing occurred.

The CUSECS was delivered via the BRH- A2 device which is CE marked and approved for use in clinical settings. The CUSECS therapy was applied for 15 minutes at each treatment session. The present treatment parameters were set to deliver modulated frequency ultrasound of between 1.0-3.0MHz with a maximum intensity of 2.0W/cm². The BRH-A2 was pre-set to deliver electric stimulation current frequencies of between 4000Hz – 4250Hz ±1 with inferential output waveforms and an interferential beat frequency of PPS 1-250Hz. Exact treatment parameters are described in Table 2. The BRH-A2 was calibrated by an authorised BRH technician. This was carried out before the study commenced. Recalibration is recommended every 6 months and the system alerts the operator if calibration is needed prior to this.

Table 2: Parameters for ultrasound therapy and electrostimulation

Ultrasound	
Frequency	1.0-3.0MHz
Wave Type	Continuous
Intensity	2.0W/cm^2
Duration	15-minute treatment twice a week for 8 weeks or until full epithelisation has occurred
Electrical Stimulation	
Current frequency	4000Hz – 4250Hz ±1 4 Pole Interferential mode
Electrode properties	Adhesive, round in shape, 5cm in diameter
Shape of electric pulse	Inferential output waveforms and an interferential beat frequency of PPS 1-250Hz.
Current Intensity	Max Output Current (mA): 0-65±10% mA RMS, max 1Kohm load Maximum current density: 3.2 mA/cm2 at 1kΩ
Duration	15-minute treatment twice a week for 8 weeks or until full epithelisation has occurred

Treatments were performed in the diabetic foot clinic for eight weeks or until wound closure occurred or patients withdrew from the study. Previous studies by Avrahami et al. [22] Toscanella et al. [23] Rosenblum et al. [8] O'Connor et al. [24] administered CUSEC therapy twice a week. Therefore, in this study, the experimental group received standard treatment and CUSECS therapy twice weekly for comparison of methodologies. The control group were treated once a week in accordance with their current standard treatment regime for their DFU by their podiatrist. Standard treatment provided to both groups involved sharp debridement of necrotic tissue, infection control, pressure offloading, management of blood glucose levels and patient education.

During the treatment period a photograph was taken of all study participants' DFU at each treatment session by a camera with an attached standard ruler, after any necessary sharp debridement had occurred. From these photographs, the investigator manually traced the wound edges and the BRH-A2 integrated digital planimetry system software calculated the wound surface area through algorithms. The measuring of the wound was carried out by a single individual to ensure a standardisation of measurements across all wounds. The wound bed condition was evaluated using photograph wound assessment tool (PWAT).

Costs were calculated over the period of the trial to provide an estimate of the economic burden of DFU to the health care system and to the participant. A cost analysis of the direct and indirect cost of both groups was carried out separately and compared to see if one was more favourable than the other. Indirect cost factors included missed working days and transportation cost while direct cost assessed dressing cost, clinician time and cost of CUSECS treatment.

Four weeks after each participant completed the trial participants returned for a follow up appointment in which DFU was measured to document DFU healing or reoccurrence rates. Adverse events and clinical observations were recorded on participants' case report forms. Throughout the study and at the follow-up no wounds included had secondary wound closure. NPWT was not used in any wounds in this study as it is seen as another adjunctive therapy and we wanted to solely test CUSECS.

Statistical analysis

Data from each group was analysed with descriptive statistics and regression analysis according to subjects' age, gender and ulcer duration. Wound healing rate between the control and experimental group was analysed through the percentage difference in the wound size surface area from baseline measurements to week 8 (or sooner if complete wound healing occurs). The mean changes were compared through independent samples t test. Statistical significance was set at $p<0.05$ [(29)]. Secondary outcomes were assessed through Pearson correlation co-efficient test, one-way analysis of variance (ANOVA) and an independent sample t-test. All participants who were randomised into the study following the pre-treatment period were analysed by intent-to-treat. All data was analysed using SPSS version 20 statistical package.

In this pilot study, there was no accurate power calculation of sample size available as this was the first study design of its kind. Billingham et al.[(30)] carried out an audit on the sample sizes of pilot and feasibility clinical trials in the U.K. They found that the median sample size was thirty participants with a range of eight to one-hundred and fourteen study participants [(30)]. Therefore, this study aimed to be within this range.

Results

In total, eleven participants were recruited for this pilot randomised control trial and their demographics are detailed in Table 3.

Table 3: Participant Demographics

	Experimental group (n[1]=6)	Control group (n=5)
Age (Years)		
Mean (SD[2])	68 (11.5)	76 (16.6)
Range	54-82	58-91
Gender		
Male	5	5
Female	1	0
Wound duration (months)		
Mean (SD)	4.3 (1.4)	5.6 (3.2)
Range	3 -6	3-11

[1] Number

[2]Standard deviation

Primary Outcome: Wound Healing Rates

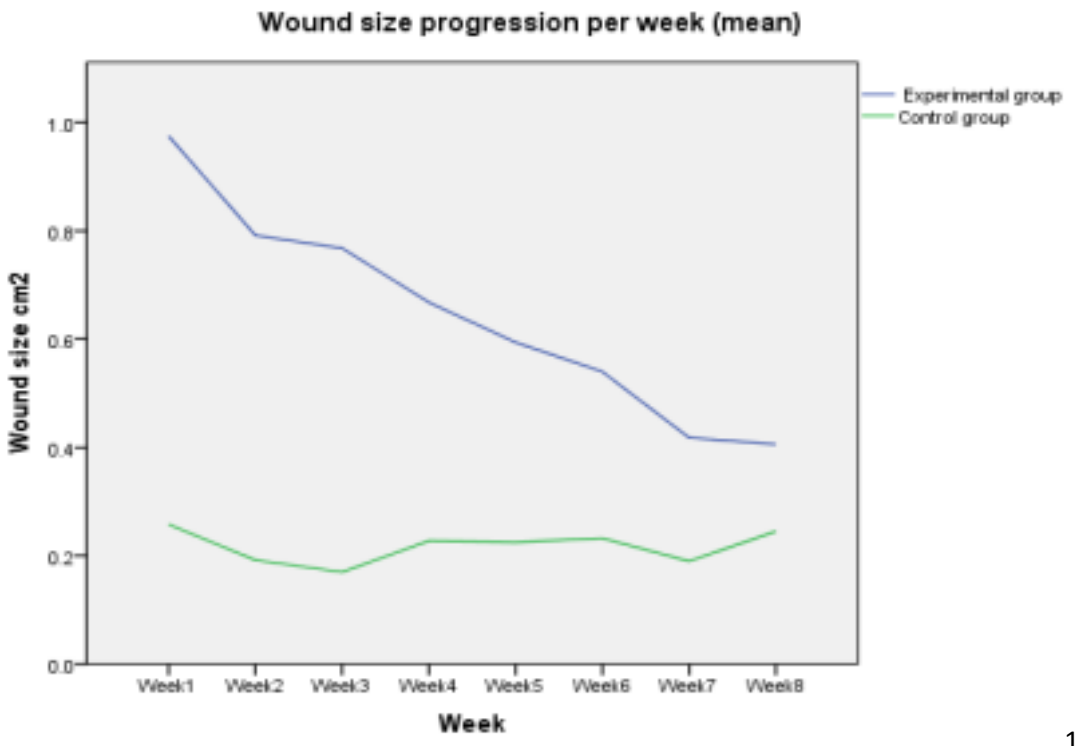
In the experimental group two participants achieved 100% wound closure while one participant had 100% wound closure by week 8 of the trial.

As shown in table 4 there was a larger difference in the mean wound size from the baseline to the last treatment measurements for the experimental group compared to the control group. There was a greater healing rate seen in the experimental group who had a larger mean percentage of wound closure at the end of the trial when compared with the control group. The mean wound size progression throughout the trial is illustrated in figure 1. However, no significant difference in the mean wound surface area between both groups at baseline (p=0.096) or week 8 (p=0.188) was found.

Table 4: Wound size measurements and percentage change

	Experimental group (n=6)	**Control Group (n=5)**	**Significance (p<0.05)**
Baseline wound size Mean (SD) Min-max	0.98cm^2(1.63cm^2) 0.06cm^2 – 4.26cm^2	0.26cm^2(0.21cm^2) 0.02cm^2 –0.57cm^2	p=0.096
Last treatment wound size Mean (SD) Min-max	0.49 cm^2 (0.73 cm^2) 0 cm^2-1.55 cm^2	0.25 cm^2(0.21cm^2) 0.0 cm^2–0.5 cm^2	p=0.188
Wound percentage change (last observed-baseline) Mean (SD) Min-max	77%, SD 18% (54-100%)	(-) 109%, SD 262% (-550-100%)	

Figure 1: Mean wound size progression



Secondary Outcome: Photographic wound assessment

The experimental had a greater mean difference in PWAT scores from the baseline to the last treatment when compared to the control group. The wound tissue, wound size, wound depth, wound edges and the peri ulcer tissue were assessed. Healing is indicated when PWAT scores are decreasing towards 0 over the time period examined. There was a lower mean score seen in the experimental group at the end of the trial however, there was also no significance found in photographic wound assessment scores between both groups with baseline scores at week 1 (p=0.054) or week 8 scores (p=0.614) as depicted on Table 5.

Table 5: Photographic wound assessment (PWA) score data

	Experimental group (n=6)	**Control Group (n=5)**	**Significance (p<0.05)**
PWA baseline Mean (SD) Min-max	12.17 (5.85) 7-21	8.8 (2.9) 5-12	p=0.054
PWA week 8/last treatment Mean (SD) Min-max	7 (6.5) 1-14	8.5 (9) 1-15	p=0.614

Secondary Outcome: Self-efficacy

In the experimental group, 5 out of 6 participants completed the PROMIS questionnaire and in the control group 4 out of 5 participants completed the questionnaire. As shown in Table 6, at the end of the trial self-efficacy scores in the control group 47±3.9 were closer to the general population score of 50 when compared to the experimental group 54±6.3. Self efficacy scores increased slightly across both groups between week 1 and 8 however, changes were not statistically significant (experimental group p=0.691; control group p=0.684).

Table 6: Self-efficacy data

Experimental group **Control group** (n=6) (n=5)		
Self-efficacy baseline Mean (SD) Min-max	49 (12) 32-69	45 (3.8) 42 – 52
Self-efficacy week 8/ full healing Mean (SD) Min-max	54 (6.3) 47-64	47 (3.9) 42-51
Sig. wound healing & self-efficacy week 8/full healing ($p < 0.05$)	0.691	0.684

Secondary Outcome: Quality of life

The eight scales of the SF-36 form were analysed. All patients completed the SF-36 questionnaire at week 1 of the trial. In the control group 4 out of 5 participants completed the questionnaire at week 8; in the experimental group 5 out of 6 completed the questionnaire at week 8 at the trial. As portrayed in Table 7, the mean and correlation for all subsets were analysed and significance was assessed with wound size. Statistical significance was found between limitations due to physical health and wound size ($p=0.028$) only.

Table 7: SF-36 Subscale data and Economic costings

	Experimental group Mean (SD) (n=6)		**Control group Mean (SD)** (n=5)		**Sig[3]. Wk[4] 8 & wound size difference p<0.05**
Health domain	Wk 1	Wk 8	Wk 1	Wk 8	
Physical Health	62.5 (27.3)	43.8 (37.2)	69 (16.4)	67.5 (20.2)	0.305
Limitation due to physical health	18.3 (40.2)	12.5 (25)	97.5 (5.5)	75 (35.4)	0.028
Vitality	47.8 (24.8)	73.8 (20.2)	45 (9.35)	57.5 (16.6)	0.259
Emotional well being	75.2 (22.2)	84 (8.7)	85.6 (3.6)	83 (6.8)	0.862
Limitation due to emotional problems	35 (50.5)	12.5 (25)	86 (31.3)	75 (35.4)	0.213
Social functioning	33.3 (33.2)	31.3 (14.1)	85 (22.4)	65.6 (23.7)	0.053
Pain	47.9 (50)	43.8 (37.9)	65 (42.7)	66.9 (26.7)	0.357
General Health	63.3 (13.7)	57.5 (28.7)	42 (11)	43.8 (24.6)	0.495

Economic cost Indirect	€996.05	€1868.30	
Direct	€444.56	€52.02	

[3]Significance

[4] Week

Secondary Outcome: Economic impact

The average overall cost for participants in this 8-week trial was €1658.66. As illustrated in Table 7, the control group experienced a greater personal economic cost as depicted through the indirect cost however the experimental group had a larger direct costing on the healthcare system when compared to the control group.

Secondary outcome: Reoccurrence rates

The wound size difference was calculated between the end trial measurement and the follow-up measurement for each participant who attended their follow-up appointment. In the experimental group 3 out of 6 participants were followed up and in the control group, 3 out of the 5 participants were followed up.

One of the week-8 healed ulcers in the experimental group remained healed at the four-week review. The other healed ulcer failed to follow-up. Similarly, in the control group the ulcer that achieved full closure remained so at follow-up. As displayed in

Table 8, the experimental group continued to have a greater percentage of wound closure 4-weeks after the trail ended when compared to the control group.

Table 8: Follow up mean wound size percentage

	Experimental group (n=3)	**Control Group (n=3)**
Wound percentage change Mean (SD) Min-max	29% (±50%) (0-86%)	4% (±43%) (-37- (+)48%)

Compliance

All participants were compliant during the eight-week trial. Four weeks after the trial was finished all efforts were made to complete a follow-up analyses of each participants' wound size. Despite this, four failed to return, two from each group.

Adverse events

During the trial one patient was excluded for developing a severe diabetic foot infection. He was administered with intravenous antibiotics with the end result of having an amputation. This did not appear to be connected with the CUSECS as the DFU had improved by 71%. The participant had mentioned having increased weight-bearing activity in his removable cast walker which may have contributed to the development of the diabetic foot infection. However, it is important to note that this correlation is only the author's own speculations. One patient in the control group was treated with oral antibiotic for minor soft tissue infection for seven days. This patient was not excluded as the infection cleared within less than a two week period. Data was not collected from the swab test of the two infected wounds or the type of antibiotics administered. No direct adverse events to the CUSECS were reported throughout the study.

Discussion

There was a higher mean wound size change for the experimental group with an improvement of 77% compared to the control group, where the mean wound size disimproved by -109%. While the DFUs in the experimental group had a greater healing percentage than those in the control group receiving standard care, the sample size was too small to determine if these findings were statistically significant. Despite this, the size measurements for the experimental group are consistent with three previous non comparable studies conducted with CUSECS. Avrahami et al.[22]reported that 59.7% of the 26 DFUs in its trial achieved a 50% closure rate and O'Connor et al. [24]recorded a 71% increase in healing in a case series of seven participants. Toscanella et al. [23] also found an improvement in wound closure rate by 20.97% in a cohort of eighteen participants. Despite the author not mentioning how many of the eighteen participants had a DFU, CUSECS had a beneficial effect on wound healing rates.

The mean wound healing size of the control group in this study was much lower than the experimental group. This is comparable to previous randomised control trials testing the effectiveness of electrostimulation on wound healing, such as a trial conducted by Peters et al. [31]. In the study Peters et al. [31]found that the sham group had a healing rate of 35% when compared to the experimental group who had a healing rate of 65%. Likewise, there was a lower healing rate for the control group in a study by Lundeberg et al. [32] when compared to the experimental group (control 15%; experimental 45%). The control group results are also similar to a RCT carried out by Ennis et al. [13]. This study assessed the effectiveness of ultrasound on wound healing and found that the control group had a 14.3% increase in wound healing, while in the experimental group a 40.7% improvement was seen [13].

Of the five participants in the experimental group, 50% of patients (n=2) achieved full healing and 25% (n=1) of the four participants in the control group fully healed. Overall, when participants' wound size differences were compared, all ulcerations in the experimental group had a healing rate of over 54%, whereas the healing rate of those in the control group was much slower at 12% and over.

The complexity of DFU was highlighted in this small cohort of participants with two participants not fully completing the trial. One participant contracted a stage three infection as classified by the Infectious Diseases Society of America [33], in his foot which had the DFU. This infection progressed resulting in the participant having an amputation of the affected foot. Although this did not appear to be related to the CUSECS treatment, it portrays how quickly the status of this group of patients can change. Indeed, it provides a true representation of the population with DFU in which 56% can

progress to an infected ulcer, and one in five of these will undergo either a minor or major amputation [34].

Over the eight-week trial the wound healing trajectory amongst the experimental group was in more representative of a linear gradient of improvement when compared to the control group. In the control group wound healing disimproved from week three onwards resulting in an increase in wound size. The unpredictable pathway portrayed in the wound size and wound appearance data from week one to week eight in the control group illustrates the stagnant state of healing that chronic wounds are in, creating an uncoordinated healing trajectory, with frequent relapses in progression [35].

Self-Efficacy

Overall, there were no statistically significant associations between DFU healing rates and self-efficacy scores ($p= 0.660$, $r= 0.250$). These findings support those of Perrin et al. [36] and Wendling and Beadle [37] who found there to be no difference in self-efficacy beliefs between those with and without a history of foot pathology. However, it is necessary to mention that in the study conducted by Wendling and Beadle [37] the majority of the study population were healthy which may have influenced the high scorings. Nevertheless, the results from our study agree with Perrin et al. [36] in stating that self-efficacy is not a useful predictive variable for foot-care behaviour.

It is important to note that there is a potential that those who participated in the study were more confident individuals and for that reason agreed to be part of the trial. Along with this, the scores reflect the participants' perceived self-efficacy levels and as they do not reflect actual behaviours, do not necessarily mean that people are confident in carrying out foot management activities. The tool used to evaluate self-efficacy in this study was a general self-efficacy tool. Although overall the results indicate that participants' self-efficacy was within a normal range, the tool does not specifically look at management of foot care.

Therefore, the self-efficacy results from this study must be reviewed with caution and it is suggested that future studies should use tools which focus specifically on individuals with DFU.

HRQOL

The burden of a chronic ulcer on a patient's HRQOL encompassing physical and mental health were analysed between both groups. Previously published studies have found a strong correlation between foot problems and mental health issues [38], with Ismail et al. [39] reporting one-third of those with DFU being diagnosed with depression. This was not exactly the case within the experimental group in this study. This group's emotional wellbeing scores improved by a mean of 9, as did vitality scores by a mean of 26. However, participants in this group still felt their emotional problems had a limitation on their health as the mean increased by 22.5. Social functioning scores also decreased by a small mean of 2. Although the majority of participants in the experimental group still had a DFU, some aspects of mental health may have improved due to the increased wound healing rate. The control group's mental health scores followed more of the pathway described by Hoban et al. [38]. Their emotional wellbeing dis-improved by a small mean of 2 and social functioning decreased by 19.4 despite this overall vitality increased by 8 and role of limitation due to emotional problems decreased by 9.

The physical health components evaluated were made up of physical functioning, limitation to physical health, bodily pain and general health [40]. In a 3.1 year study which included 331 veterans with diabetes, Ahroni and Boyko [41] found that changes in physical functioning and limitations to

physical health were significantly related to changes in the status of individual's foot ulceration. In two separate studies Nabuurs-Franssen et al.[42] and Goodridge et al. [43] reported that those with non-healing ulcers have a greater decline in HRQOL scores with the most significant difference found in physical health of individuals. Our study presented with contrasting findings as those whose ulcerations were improving had a greater mean decline in physical health subscales.

From baseline scores to the end of the trial, both groups' physical health scores decreased however, there was a much larger decrease in the experimental group's scores when compared to the control group (19 vs 2). This decrease suggests impairments in physical activity such as walking and climbing stairs. However, it is important to note that continuous amounts of pressure on a DFU, along with repetitive trauma are two of the main reasons for non-healing wounds [44]. Therefore, pressure mitigation through, for example, rest, total contact casts, removable cast walkers, help create an optimal wound healing environment for DFU [45]. Thus, one would expect those with a DFU to have lower physical health scores in this study. It is possible that the experimental group were more adherent to offloading instructions compared to the control group, providing reasoning for their greater mean difference in physical health scores. However, the author does not have data to prove this.

Overall, in our study the physical health components scores were worse in those with ulcers healing than those with non-healing ulcers. There is no definite explanation for these results however they might be related to participants in the experimental group with healing ulcers being more compliant to reducing pressure on their DFU and therefore reducing their physical exercise. It is also important to note that given the small sample size in this study it is difficult to have full confidence in the small amount of data on a complex scale.

Contributing Factors

There are number of contributing factors which may have influenced the clinical course of the DFUs in the experimental group in this study.

The increase healing rates in the experimental group may be associated with effect of CUSECS on biofilms. Biofilms have been identified in 60-80% of wounds and are known to contribute to reduce healing in chronic wounds such as DFUs [46-48]. Evidence from research has found that a wound care regimen involving the debridement of slough and devitalised tissue is a critical element to disturb a biofilm [49-52]. A recent study conducted by Ashrafi et al. [53]found a significant reduction in bacterial viability and metabolic activity *in vitro* and in human cutaneous wound biofilm models when treated with electrostimulation treatment. Thus, indicating that electrostimulation treatment is a possible antimicrobial management of biofilms. However, it is worthy to note that electrostimulation was not as effective when compared to the antibiotic, ciprofloxacin in reducing biofilms [53].

It is important to highlight that participants in the experimental group attended the trial one extra day a week. Along with receiving CUSECS therapy, they also were provided with one extra wound debridement, when compared with the control group. Due to it not being feasible to have the control group using a sham device, it therefore is not fully clear from the study if electrostimulation or debridement caused a reduction in biofilm, thus contributing to the increase in healing rates.

Despite the presented confounding factors within this study, the wound sizes improved in the experimental group when compared to the control group and the analysis of the healing trajectory between both groups emphasised the complexity of the healing process of chronic DFUs. This study found mental health scores to improve and physical health scores decrease in wounds which portrayed an increase in healing rates. Thus, adding to the

body of evidence supporting the importance of viewing the burden of a DFU from a patient perspective and not solely from a clinical point of view [54]. Interestingly self-efficacy scores in the present study were within the range of the general population. Despite this, the study still supports that ensuring that patients are provided with foot care education and taught self care activities, can increase patient's foot care confidence with the hope of reducing foot complications [37].

The study was consistent in providing more data to the growing body of evidence highlighting the major costs of care and resource utilisation connected with DFU treatment. Experimental group direct costings on the healthcare system were higher due to the addition of the CUSECS therapy however, healing rate was quicker which could be extrapolated to cost reductions over time. Overall, this study provides further evidence-based research which can be used for future research and in which clinicians can take in to consideration in practice.

Limitations and further research

The sample size was much smaller than anticipated and therefore the results must be interpreted with caution. Despite this, the present pilot study offers an insight into this area of adjunctive therapy and builds on previous case study carried out by Avrahami et al. [22], Toscanella et al. [23], O'Connor et al. [24] and Rosenblum et al [8].

A larger longitudinal study would provide more evidence on the effectiveness of CUSECS. A greater cohort would also enable a further investigation into the economic analysis of DFU. It would enable the use of a health economic model such as the Markov model approach to predict probabilities of transition of DFU health states. Further to this, a RCT conducted with a sham device would reduce bias and increase the reliability of the findings. We also recommend the use of disease specific questionnaires to provide a more accurate representation of patients' QOL and self-efficacy. Lastly, we suggest that amount of patient's weight-bearing to be quantified via a stepometer to assess its effect of wound healing and to evaluate patient's compliance.

Conclusion

Overall, this pilot study's results suggest that CUSECS may be a useful adjunctive therapy for treatment of chronic DFUs. The findings of this study aim to promote awareness among clinicians and researchers on the use of an adjunctive treatment for chronic DFUs and its associated impact from a healthcare and patient perspective. It provides researchers with an insight into the recruitment and retention of participant for future research. Further large scale longitudinal studies are needed to ascertain the effectiveness of CUSECS.

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