Original Investigation

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Neuromuscular Electrostimulation Increases Microcirculatory Flux in Mixed Etiology Leg Ulcers

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ABSTRACT

OBJECTIVE: To determine if intermittent neuromuscular electrostimulation (NMES) of the common peroneal nerve increases microvascular flow and pulsatility in and around the wound bed of patients with combined venous and arterial etiology.

METHODS: Seven consenting participants presenting with mixed etiology leg ulcers participated in this study. Microvascular flow and pulsatility was measured in the wound bed and in the skin surrounding the wound using laser speckle contrast imaging. Measurements were made at baseline and when the venous pumps of the leg were activated by 1 Hz intermittent neuromuscular stimulation of the common peroneal nerve. The nerve was stimulated transdermally at the head of the fibula.

RESULTS: When activated by NMES, wound bed flux increased by 38% (95% CI, 11%–73%; $P = .023$), and periwound flux increased by 19% (95% CI, 9%–32%; $P = .009$). Pulsatility increased in the wound bed by 214% (95% CI, 51%–985%; $P = .017$) and in the periwound by 122% (95% CI, 38%–299%; $P = .014$).

CONCLUSIONS: The results indicate that NMES is effective in augmenting microvascular flow in leg ulcers with combined venous and arterial etiology.

KEYWORDS: geko, laser speckle contrast imaging, mixed leg ulcer, neuromuscular electrical stimulation, peripheral arterial occlusive disease

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INTRODUCTION

Although the most common cause of leg ulcers is venous insufficiency, the second most common cause is now recognized to be a combined venous and arterial etiology, representing about 13% of all chronic wounds.[1] The arterial component to the etiology has important ramifications for treatment, because the presence of peripheral arterial disease precludes the use of high compression.[2] Meanwhile, although the primary management for purely arterial ulcers is revascularization, studies suggest that the venous component of a mixed etiology ulcer remains the determining factor for healing.[3] This finding has prompted clinicians to seek other modes of intervention to restore perfusion.[4]

Intermittent (1 Hz) neuromuscular electrostimulation (NMES) of the common peroneal nerve has been shown to activate the venous muscle pumps, producing significant hemodynamic effects.[5] Increases have been measured to venous, arterial, and microcirculatory perfusion[6,7] in healthy individuals, as well as in those with vascular disease.[8] Further, research has shown microcirculatory flux and pulsatility to be improved in and around the wound bed of both arterial[9] and venous[10] leg ulcers. Intermittent NMES has been used successfully over an extended period to treat nonhealing ulcers of various etiologies,[11–13] and a self-controlled randomized trial demonstrated an increase in the rate of healing in venous leg ulcers.[14]

In this mechanistic study, the researchers used laser speckle contrast imaging (LSCI) to determine if intermittent NMES of the common peroneal nerve increases microvascular flow and pulsatility in and around the wound bed of patients with combined venous and arterial etiology.

METHODS

This study is reported in accordance with CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines.[15] The study was conducted in accordance

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with the principles of the Declaration of Helsinki (2013) and in compliance with ISO14155:2011. Ethical approval (IRAS 229471) was obtained prior to the study investigation. The study is registered (NCT03186560), and the registered protocol is available to view. The supplementary data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients attending outpatient clinics at the Aneurin Bevan University Health Board and Cardiff and Vale University Health Board were screened over an 8-month period. Inclusion criteria were as follows: 18 years or older, intact healthy skin at the site of device application, able to understand the patient information sheet, willing and able to give informed consent, willing and able to follow the requirements of the protocol, and diagnosis of a mixed arterial and venous leg ulcer. Mixed leg ulcers were diagnosed by a wound healing expert, using a combination of ankle brachial pressure index (ABPI; 0.5–0.8) and the presence of peripheral vascular disease on an arterial duplex scanning. Exclusion criteria were as follows: significant wound infection (not colonization), either acute or chronic; history of significant hematologic disorders or deep vein thrombosis within the preceding 6 months; pregnancy; presence of a pacemaker or implantable defibrillator; current use of any other NMES; use of an investigational drug or device within the past 4 weeks that may interfere with this study; recent surgery that may affect the study in the opinion of the chief investigator (eg, abdominopelvic or lower limb surgery); recent trauma to the lower limbs that would prevent stimulation of the leg with NMES; and obesity (body mass index >35 kg/m^2).

NMES Device

Activation of the leg venous muscle pumps was achieved using the geko device (Firstkind Ltd), a UKCA- and CE-marked, small, wearable, internally powered neuromuscular electrostimulator. The device was applied externally to the leg at the head of the fibula, as per the manufacturer's instructions. The device was set so that a visible intermittent dorsiflexion was observed. In this mechanistic study, the device was applied to patients for 30 minutes to take measurements (following a 5-minute equilibration period). Because standard treatment of 6 hours' daily use was not provided, the researchers did not examine rates of healing.

Laser Speckle Contrast Imaging

Microcirculatory flow in the wound bed and periwound area was measured using LSCI (Moor FLPI-2; Moor Instruments Ltd), calibrated according to the manufacturer's recommendations. This noninvasive, noncontact instrument is used to measure changes in superficial microcirculatory flux: a unitless quantity proportional to the speed of particles within the blood vessels. Pulsatility (an indication of the strength of pulse in the signal) is calculated as the root mean square deviation (also unitless) from the mean flux value. The LSCI imager was positioned 30 cm from the target area to record images in the wound bed, the periwound area, and a reference marker. The device recorded a baseline of 5 minutes followed by 30 minutes with the NMES device active.

The study outline and participant accountability flowchart is shown in Figure 1. At the patient's regularly scheduled appointment, each participant was placed in a recumbent position at room temperature, with the leg outstretched resting on an evacuated beanbag cushion to immobilize the leg for measurements. Any excess slough or liquid was removed prior to making any measurements. A reference marker, consisting of an opaque foil strip, was affixed to the skin adjacent to the wound, to allow for correction of movement artifact.[16] All patients responded to NMES therapy, so there were no screen failures to report.

Statistical Analysis

Sample size was based on pilot data, which suggested that the geko increases speckle flux by 152% ± 61%. Thus, assuming P = 0.05 and power = 90%, four

Figure 1. STUDY OUTLINE AND PARTICIPANT ACCOUNTABILITY FLOWCHART

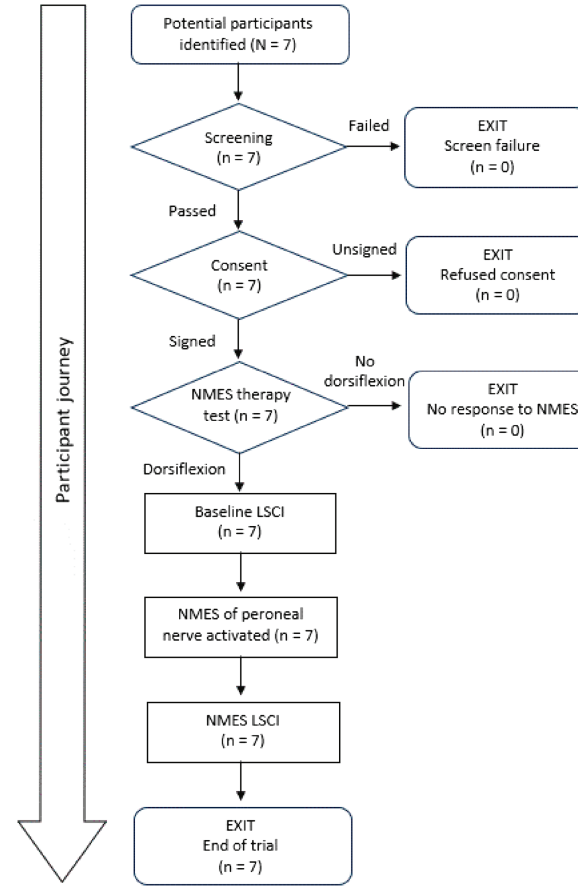


Table 1. PARTICIPANT DEMOGRAPHICS (N = 7)

Variable	Mean ± SD	Range
Age, y	70.88 ± 10.00	56.63–82.91
Height, m	1.67 ± 0.10	1.52–1.82
Weight, kg	88.09 ± 18.27	59.50–112.80
Body mass index, kg/m^2	29.51 ± 4.93	20.60–33.80
Wound area, cm^2	5.99 ± 4.46	1.77–14.19

participants would be required to demonstrate an effect based on the below formula:

$$N = f(\alpha/2, \beta) \times 2 \times \sigma^2/(\mu 1 - \mu 2)^2$$

where $\mu 1$ and $\mu 2$ are the mean outcome in the control and experimental group respectively, σ is the SD, α is the probability of a type 1 error, and β the probability of a type 2 error. The researchers initially increased the sample size to 10 participants to improve confidence. However, owing to recruitment constraints imposed by COVID, the sample was decreased to seven participants to reduce the overall timeline of the trial.

The trial was a within-participant controlled study design comparing differences between recordings at baseline versus during stimulation. Participants served as their own control. Results were calculated using a paired Student t test, and $P < 0.05$ was considered significant.

RESULTS

Demographics

Of the seven participants recruited into the trial, four were women and three were men. Given the low numbers of patients in each group, no statistical tests were undertaken by sex. The Table 1 provides demographic data for the participants. There was a high degree of heterogeneity between participants in demographic variables.

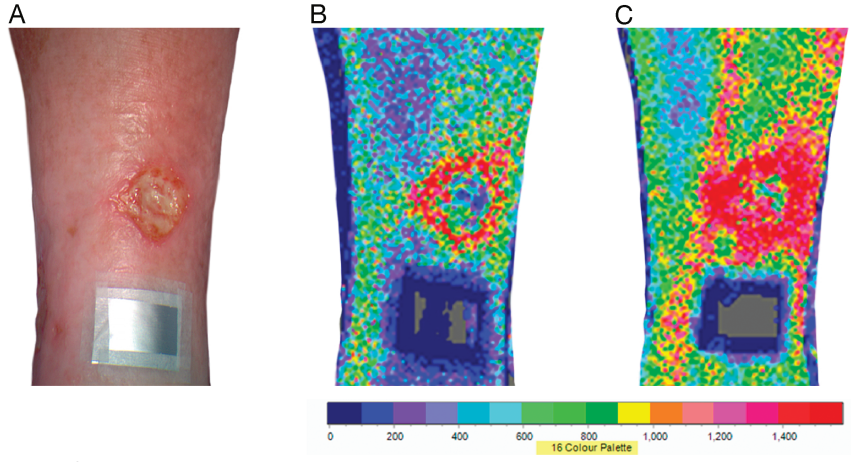
Figure 2A shows an example wound, with the foil reference marker just above (distal to) the wound. Researchers obtained LSCI measurements at baseline (Figure 2B) and during treatment (Figure 2C). In Figure 2, the color map indicates microvascular flux, with red indicating the highest level of flux and dark blue indicating the lowest level of flux. The flux pattern can be seen to change dramatically when the NMES device is activated. At baseline (Figure 2B), there is little perfusion in the wound bed, and perfusion in the periwound area is confined to a narrow annulus of erythematous skin. Activation of the NMES device results in a visible increase in flux throughout the foot (Figure 2C), especially in the bed and periphery of the wound. The opaque foil reference continues to show no flux, verifying that movement artifact is not contributing to the measured augmentation of flux. The portion of the marker covered in microporous tape is used as the zero reference, because this part exhibits no specular reflection from the surroundings.

Figure 3 shows a trace of microcirculatory flux in the wound bed and periwound over a 20-second sample time, for the same participant as shown in Figure 2. The blue trace shows the baseline flux in the wound bed (NMES device switched off), whereas the red trace shows the flux in the wound bed when the NMES device is switched on. In the baseline traces, a faint pulse is present, in both the wound bed and the periwound. When the device is switched on, the pulsatility increases greatly in both areas, and the 60 beats per minute coincides with the 1-Hz stimulation frequency of the device. The peak and mean values of flux increase substantially in both wound bed and periwound areas.

Figures 4 and 5 show the aggregated flux data for all seven mixed etiology ulcers. Wound bed flux increased by 38% (95% CI, 11%–73%; $P = .023$), and periwound flux

Figure 2. EXAMPLE MIXED ETIOLOGY LEG ULCER WITH BASELINE REFERENCE MARKER

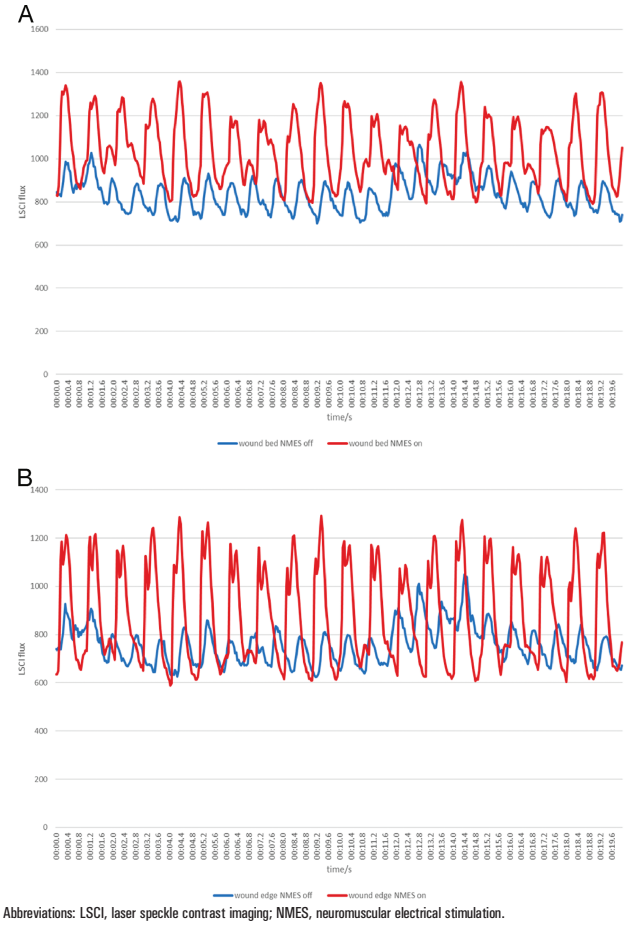
A, LSCI at baseline with NMES switched off. B, LSCI with NMES active.



Abbreviations: LSCI, laser speckle contrast imaging; NMES, neuromuscular electrical stimulation.

Figure 3. LSCI FLUX AT THE WOUND BED AND PERIWOUND WITH VERSUS WITHOUT NMES

A, Trace of LSCI flux in the wound bed of an example ulcer over a 20-second period, comparing NMES on with NMES off. B, Trace of LSCI flux at the periwound over a 20-second period, comparing NMES on versus NMES off.



Abbreviations: LSCI, laser speckle contrast imaging; NMES, neuromuscular electrical stimulation.

increased by 19% (95% CI, 9%–32%; $P = .009$). Pulsatility in the wound bed increased by 214% (95% CI, 51%–985%; $P = .017$), and pulsatility in the periwound increased by 122% (95% CI, 38%–299%; $P = .014$).

DISCUSSION

This study demonstrates that transdermal NMES of the common peroneal nerve at the fibular head activating the venous muscle pumps of the leg increases the microvascular flow in wounds of mixed venous and arterial etiology. Substantial increases are seen to both flow and pulsatility in the wound bed and periwound skin.

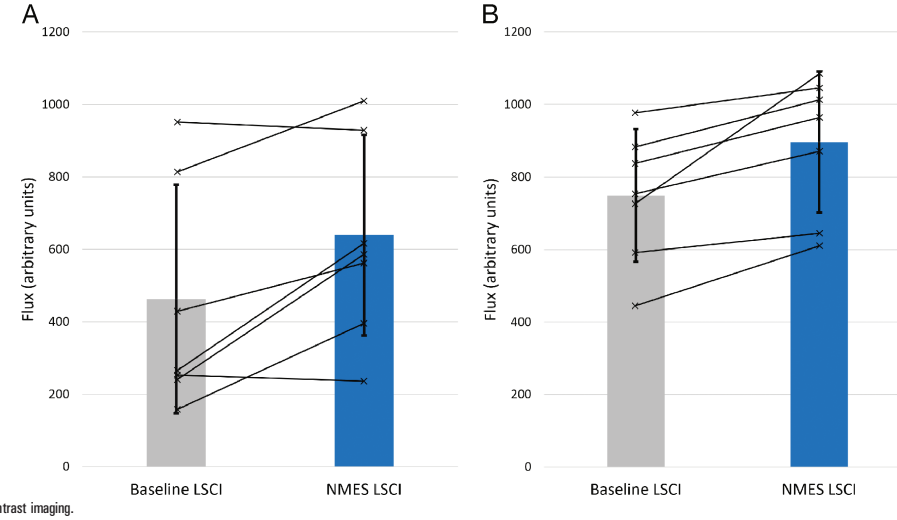
Between 17% and 25% of leg ulcers are now considered to have combined venous and arterial etiology.[17,18] This combined etiology has important ramifications for treatment, because the presence and extent of arterial disease are the main factors in determining a treatment regimen.[19] Whereas compression is routinely used for patients with venous leg ulcers to increase venous velocity,[20] reduce reflux,[21] and assist the action of the venous muscle pump,[22] its use in patients with arterial disease is more controversial.[23]

Compression has historically been contraindicated for patients with arterial occlusive disease, and guidelines consistently advise against the use of compression in patients whose ABPI is less than 0.5,[24] owing to the risk of arterial and microcirculatory occlusion. However, the balance between risk and benefit in the presence of more moderate arterial disease (eg, ABPI <0.8) is less clear,[25] and more complex decision algorithms have been proposed[26] involving toe-brachial pressure index[27] and transcutaneous oxygen assessments.[28]

An intervention that provides the hemodynamic benefits of compression without the attendant risks of

Figure 4. LSCI WOUND BED AND PERIWOUND FLUX (N = 7)

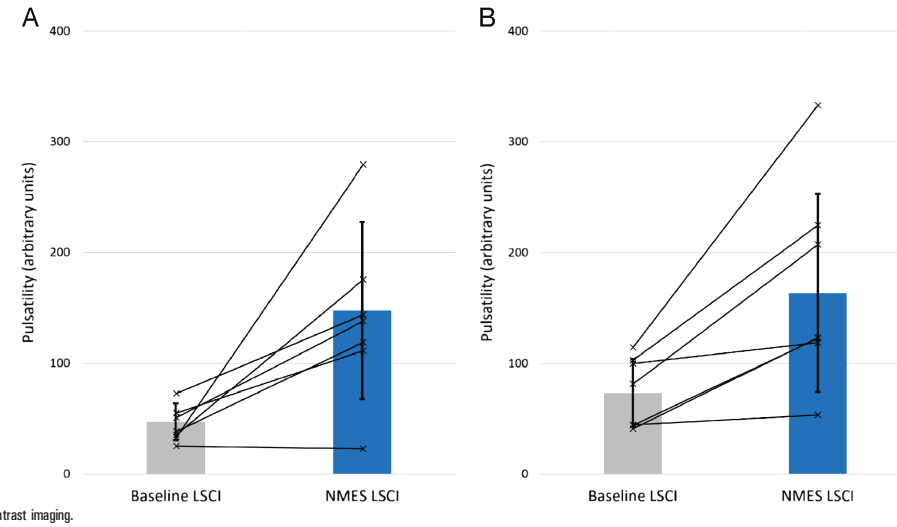
A, Wound bed. B, Periwound. Bars show the population means ± SD. Lines indicate the individual participant measures.



Abbreviation: LSCI, laser speckle contrast imaging.

Figure 5. LSCI WOUND BED AND PERIWOUND PULSATILITY (N = 7)

A, Wound bed. B, Periwound. Bars show population means ± SD. Lines indicate the individual participant measures.



Abbreviation: LSCI, laser speckle contrast imaging.

occlusion—which could exacerbate underlying peripheral arterial disease—has obvious attractions. The augmentative effect of NMES on the microcirculation, both in terms of flow and pulsatility, may provide a mechanistic insight into its value in wound healing. These possibilities are of particular interest when compression is contraindicated, or when there is no intervention available for improving macrovascular arterial supply. Although such patients may achieve wound healing, it is generally prolonged and requires adherence to a strict wound care protocol.[29] The NMES device may also have a role to play in treating patients with arterial rest pain, without wounds, who are unsuitable for revascularization. Some patients for whom compression is contraindicated may receive similar benefits from NMES.

The appropriate level and type of compression for use in mixed etiology leg ulcers are contingent upon certain hemodynamic factors. It may be that some patients receiving reduced levels of compression may enjoy augmented efficacy by using NMES as an adjunct to compression. There is evidence that NMES and compression (including inelastic compression) have a mutually supportive effect.[30]

Limitations

A limitation of the study is the relatively small and heterogeneous sample. Given the immense heterogeneity of patients with mixed etiology ulcers in general, it is unsurprising to see some degree of intragroup variation. This level of heterogeneity might be problematic in a classic intercohort randomized controlled trial design. However, in this self-controlled design, each participant's baseline LSCI was compared with his/her own NMES LSCI, accommodating these differences. The effect size is sufficient such that statistical significance was achieved despite the small sample size.

CONCLUSIONS

Research has previously found that intermittent NMES of the common peroneal nerve is effective in augmenting microvascular flow in healthy skin, as well as in the wound bed of patients with venous or arterial disease. This study verifies that NMES is also effective in augmenting microvascular flow in patients who have *both* venous and arterial disease. ●

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