



Clinical Research

Microcirculatory Flux and Pulsatility in Arterial Leg Ulcers is Increased by Intermittent Neuromuscular Electrostimulation of the Common Peroneal Nerve

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Background: Neuromuscular electrical stimulator (NMES) devices increase blood flow to the lower limb by a process of intermittent muscular contraction initiated by a transdermal stimulus to the common peroneal nerve. However, its effects on localized microvascular blood supply to lower limb wounds are unknown. This study is a single-center open label study measuring the effect of neuromuscular stimulation of the common peroneal nerve on the microvascular blood flow within the wound bed of arterial leg ulcers.

Methods: Eight patients with ischemic lower limb wounds had an NMES (geko™) applied to the common peroneal nerve. Baseline and intervention analysis of blood flow to the wound bed and edge was performed using Laser Speckle Contrast Imaging. Mean flow (flux) and pulse amplitude (pulsatility) were measured.

Results: Stimulation of the common peroneal nerve with the NMES resulted in a significantly increased flux and pulsatility in both the wound bed and the wound edge in all 8 patients.

Conclusions: Neuromuscular electrical stimulation immediately increases microcirculatory blood flow to the wound bed and edge in patients with ischemic lower limb wounds. These data may provide mechanistic insight into the clinical efficacy of NMES in healing wounds.

www.clinicaltrials.gov [NCT03186560](https://www.clinicaltrials.gov/ct2/show/study?term=NCT03186560).

Funding: D.C.B. was funded by the Welsh Government through Health and Care Research Wales for part of this study.

Declaration of Interest: K.G.H. is supported by Welsh Wound Innovation Center (WICC) and receives funding from the manufacturer of the device to carry out product evaluation. The WICC is a company limited by guarantee and its members include Universities and Health Boards in Wales. It is a self-funded organization that receives income from academic grants, NHS organizations, and commercial concerns aimed at developing wound healing services and academic foundations for the subject. WICC and its previous forms of operating have received funding from over 80 companies. The members of staff in WICC have no direct financial interest in the companies or products that are evaluated. K.G.H. is the named inventor of a patent that identifies a gene signature in chronic wound tissue that predicts which chronic wound will heal and also has a patent that is based on an existing drug that is used for another clinical problem that could be repurposed to be used as a topical agent to assist healing. The remaining authors declare no conflict of interest.

Author's Contributions: K.G.H. helped in conception or design of the

work; N.I. and N.J. helped in data collection; D.C.B. and K.G.H. helped in data analysis and interpretation; and D.C.B., N.I., N.J., and K.G.H. helped in drafting the article, critical revision of the article, and final approval of the version to be published.

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Ann Vasc Surg 2020; ■: 1–7
<https://doi.org/10.1016/j.avsg.2020.07.030>

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Manuscript received: May 14, 2020; manuscript accepted: July 9, 2020; published online: ■ ■ ■

INTRODUCTION

Although the mainstay of treatment of venous leg ulcers is compression bandaging,¹ many patients have concomitant peripheral arterial disease,² and standard compression is contraindicated.³ Additionally, a proportion of patients with arterial leg ulcers are either too unfit for, or have a pattern of disease not amenable to, arterial revascularization.⁴ Consequently, there is a need for novel, alternative devices or strategies that can be used to complement or replace compression therapy.^{5,6}

An ideal treatment modality would optimize wound blood flow with minimal side effects.^{7,8} One such option is a neuromuscular electrical stimulator (NMES; geko™) device. Self-adherent integral electrodes are applied to the posterior-lateral aspect of the knee to apply a stimulus transdermally to the common peroneal nerve. This stimulation causes intermittent (1 Hz) isometric muscle contraction engaging anterior and lateral muscles in the leg, without affecting normal movement of the limb. This intermittent muscle contraction has been shown to augment venous, arterial, and microcirculatory flow in the lower limb^{9–11} and the device has been successfully used for the treatment of chronic wounds of various etiologies.^{12–14}

Previous measurements of NMES-augmented blood flow have used arterial and venous duplex ultrasound, and measurements of microcirculation using Laser Doppler Flowmetry (LDF).⁹ Although LDF is able to measure microcirculation in intact skin, it requires contact with the tissues to code the backscattered light and is therefore unable to assess microcirculation of the wound bed.¹⁵ Furthermore, measurements are only possible as single values at the specific location of the sensor. In contrast, Laser Speckle Contrast Imaging (LSCI) allows noncontact mapping of a region of interest in high resolution, allowing patterns of perfusion to be examined across the wound bed and edge. The imaging works by mapping the relative velocity of moving red blood cells within the microcirculation. LSCI has been shown to be accurate and reproducible in the measurement of microcirculatory perfusion¹⁶ and has been used to predict healing of venous ulcers.¹⁷ It rapidly responds to micro-circulatory changes in the limb and provides information on local wound microperfusion.¹⁸ LSCI has not been used previously to evaluate NMES effects on wound and peri-wound microcirculatory flow.

The objective of this study is to measure microcirculatory flow in the wound and peri-wound area of arterial ulcers and to determine if flow is augmented

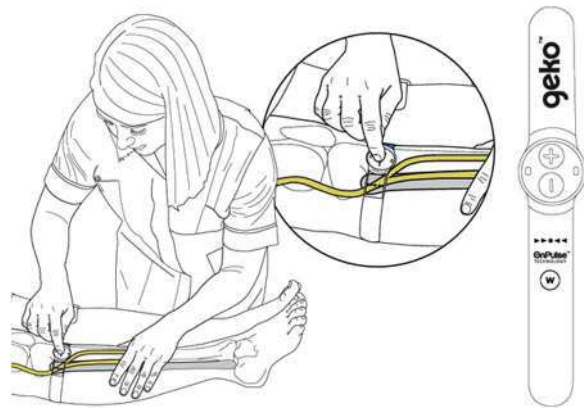


Fig. 1. The geko™ device, placed over the fibular head so that the negative electrode locates over the common peroneal nerve.

by intermittent NMES of the common peroneal nerve.

MATERIALS AND METHODS

The study is reported in line with STROBE reporting guidelines.¹⁹

Patient Population

The study was conducted in accordance 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. Patients attending outpatients 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 age ≥ 18 years; 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 an arterial leg ulcer. Arterial leg ulcers were diagnosed by a wound healing expert, using a combination of ankle brachial pressure index (ABPI) and the presence of peripheral vascular disease on an arterial duplex. The ulcers were classified as healing or nonhealing (healing was defined as reduction in wound area of greater than 20% over the preceding 2-week period).

Exclusion criteria were: significant wound infection (not colonization) either acute or chronic; history of significant hematological 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

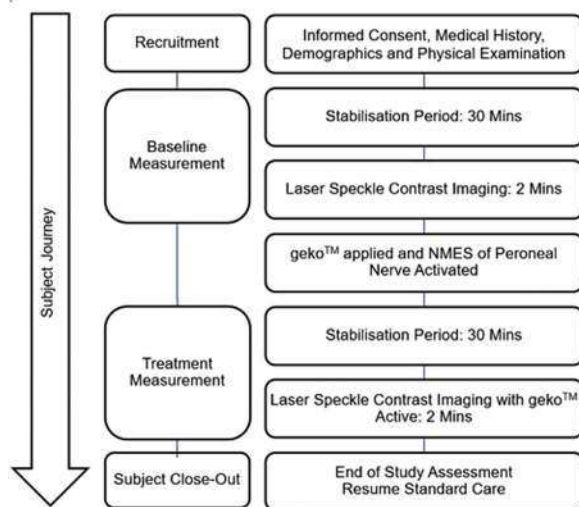


Fig. 2. Trial schematic.

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 (such as abdominopelvic or lower limb); and recent trauma to the lower limbs that would prevent stimulation of the leg with NMES; obesity (body mass index [BMI] > 35).

The geko Device

The geko device (Fig. 1) is a CE marked, small, disposable, internally powered NMES that is applied externally to the leg indicated "...to increase blood circulation and [for] the prevention of venous thrombosis; [for] the prevention and treatment of oedema, to promote wound healing and for the treatment of venous insufficiency and ischemia."

The negative electrode of the device is placed over the fibular head such that it lies directly above the common peroneal nerve (Fig. 1). The device setting is increased until a visible dorsiflexion (upwards and outward twitch of the foot) is observed. If no dorsiflexion is observed at the highest setting of the device, the patient is classified as a nonresponder, and deemed unsuitable for treatment with the device. Reasons may include severe edema, or the presence of emollients disrupting electrical contact to the skin. In this mechanistic study, the device was applied to patients for a few minutes to make measurements (following a short equilibration period). In contrast, standard treatment for promoting wound healing (not measured in this study) comprises 6 hr of geko use daily, until the ulcer heals.

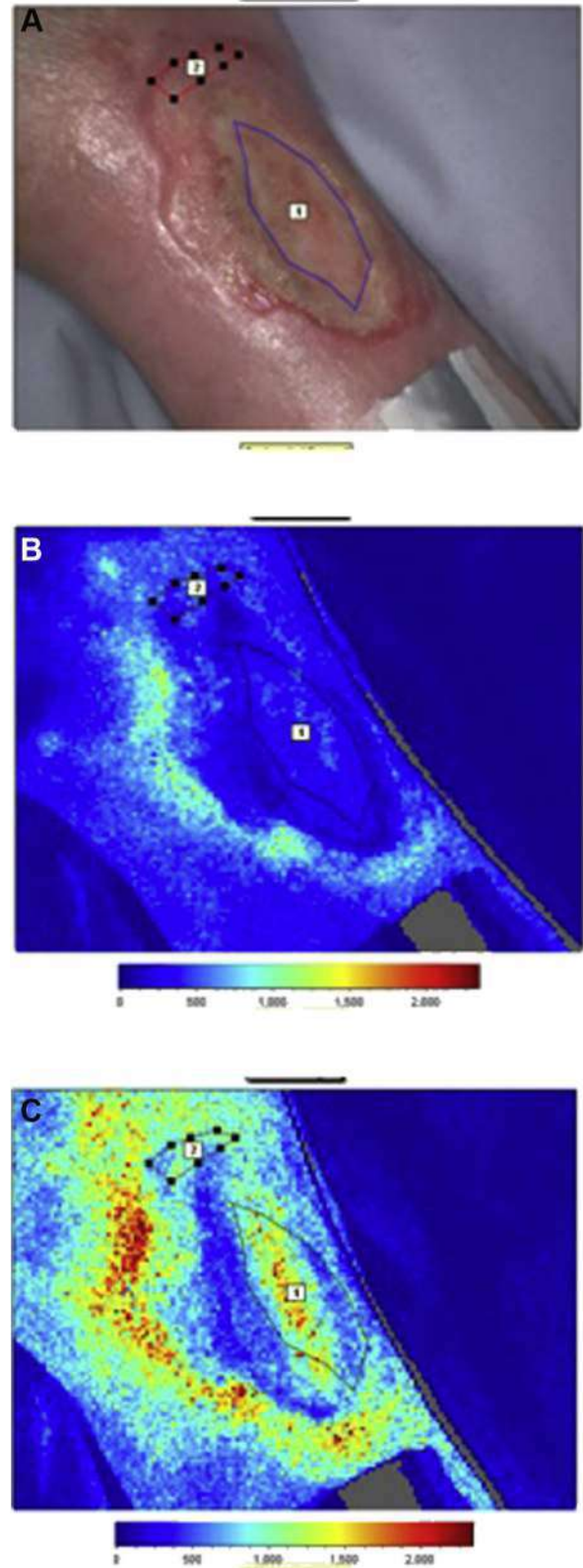


Fig. 3. (A) Example of subject color photograph demonstrating the wound bed (1) and wound edge (2). (B) Example of subject flux map at baseline measured using LSCI. (C) Flux map with geko™ device.

Table I. Baseline patient demographics

Patient	Healing status	Twitch elicited with geko™	Wound area (cm ²)	Type 2 diabetes	DVT
1	Nonhealing	Yes	14	No	No
2	Nonhealing	No	No data	No	No
3	Healing	Yes	15	Yes	No
4	Nonhealing	Yes	122.36	No	No
5	Nonhealing	Yes	45	Yes	No
6	Nonhealing	No	No data	No	No
7	Nonhealing	Yes	24	No	No
8	Nonhealing	Yes	50	No	No
9	Nonhealing	Yes	135	Yes	Yes
10	Nonhealing	Yes	3.36	Yes	No

DVT, deep venous thrombosis.

Laser Speckle Contrast Imaging

Microcirculatory flow in the wound bed and peri-wound area was measured using LSCI (moor FLPI-2™; Moor Instruments Ltd, Axminster, England), calibrated according to the manufacturer's recommendations. A 785 nm laser illuminates tissue to a maximum of 1 mm depth, giving a color coded tissue perfusion image. Perfusion measurement is based on a speckle pattern resulting from the interaction between photons and moving red cells. This noninvasive tool is therefore used to measure changes in microcirculatory flux where blood vessels are superficial.²⁰ The flux measurement obtained from the LSCI is 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 peri-wound area, and the reference marker. The device recorded a baseline of 5 min followed by 30 min with the geko active.

Study Overview

The overall study process and measurements are outlined in [Figure 2](#). Each subject was placed in a recumbent position at room temperature with the leg outstretched resting on an evacuated bean-bag cushion to immobilize the leg for measurements. Any excess slough or liquid was removed prior to making any measurements. The investigator selected 2 areas on each patient for data capture: the wound bed and wound edge (peri-wound). 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, according to a method previously described.²¹ The foil marker

can be seen proximal to the ulcer in [Figure 3A](#). Measurements were then obtained at baseline ([Fig. 3B](#)) and during treatment ([Fig. 3C](#)).

Statistical Analysis

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

$$n = f(\alpha/2, \beta) \times 2 \times \sigma^2 / (\mu_1 - \mu_2)^2$$

$n = 4$ subjects would be required to demonstrate an effect. This was increased to 10 subjects to improve confidence.

Individual patient data for flux and pulsatility are demonstrated in line graphs, with their standard error of difference. Differences between pre- and during stimulation recordings were calculated using a paired Student's t -test. $P < 0.05$ was considered significant.

RESULTS

Patient Cohort

Ten patients were recruited, of which 2 were excluded as the NEMS device did not elicit a muscular twitch. Of the 8 subjects (4 males, 4 females) participating in the study, the mean age was 72 ± 8 years, the mean BMI was 25.2 ± 3.1 kg/m² and mean ABPI was 0.5 ± 0.05 . Further demographic details are given in [Table I](#).

Microcirculation was assessed in both the wound bed and wound edge, using flux and pulsatility. [Figure 4](#) shows an example trace of microcirculatory flux in the wound bed and peri-wound area for an individual patient. The solid blue trace shows the baseline (device off) flux in the wound bed over a 12-sec period after equilibration. A faint pulse of

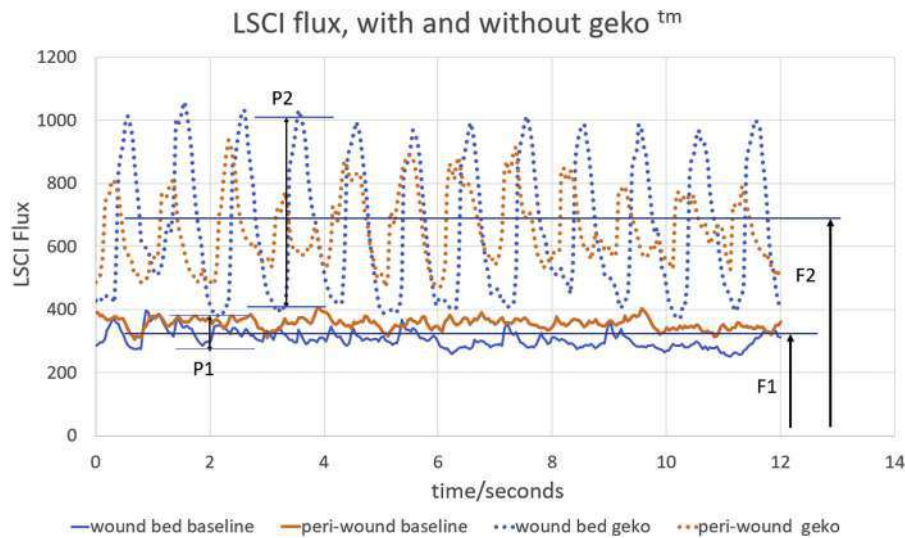


Fig. 4. (A) Example of color photograph showing the wound bed (1) and wound edge (2) for a single subject. **(B)** Example of subject flux map at baseline measured using

LSCI. **(C)** Example of flux map with the geko™ device turned on. Note that the perfusion increases dramatically with the device switched on, both in and around the wound.

approximately 72 beats per minute (BPM) is present, with a mean trendline giving a flux (F1) of 306 arbitrary units. The pulsatility is 27 units at baseline (P1). When the device is switched on (dotted blue trace), the mean flux increases from 306 to 652 units (F2), and the pulsatility increases from 27 to 219 units (P2). The “pulse” observed with device on is at 60 BPM, which is the frequency of muscle contractions elicited by the geko device. Similar phenomena are seen in the peri-wound area, shown in orange.

Results of Wound Base and Wound Edge Flux and Pulsatility

In both locations, and using both parameters, there was a statistically significant increase in all measurements, in all patients, with the use of the geko device. No patient had a decrease in any measured parameter.

NMES increased wound bed flux by a mean of 64% ($P = 0.0005$; Fig. 5), and pulsatility by a mean of 452% ($P = 0.004$; Fig. 6). Peri-wound area flux increased with use of the device by a mean of 37% ($P = 0.02$; Fig. 7), and pulsatility by a mean of 188% ($P = 0.002$; Fig. 8).

DISCUSSION

This study has demonstrated that the geko device causes an increase in perfusion, as measured by LSCI, to both the wound bed and to the peri-

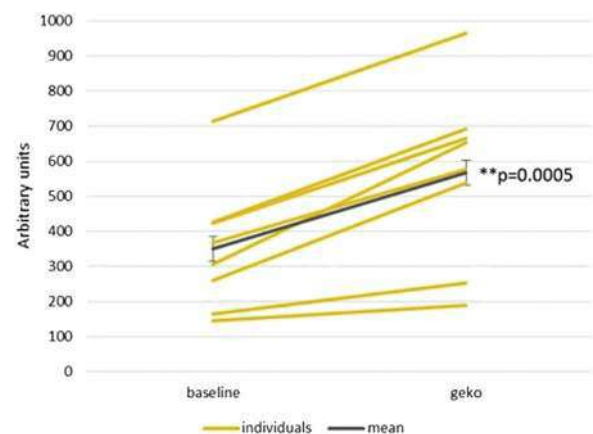


Fig. 5. Wound bed flux summary line graph. The black line shows the mean value for all subjects, and the error bars show standard error of difference.

wound area. The increase is noted for both flux and pulsatility. The latter is of pertinence, since pulsatile flow is considered vital for wound healing. Pulsatile blood flow results in shear forces at the endothelial surface and results in chemical signaling and transduction.²² This intermittent pressure and velocity in vessels result in forces at the cellular level, initiating biochemical changes including the production of growth factors, nitric oxide production, and the reduction of oxidative stress.²³ Indeed, the stated object of many wound treatment regimens including negative pressure therapy, alternating positive pressure therapy, ultrasound therapy, and other energy-based modalities is to

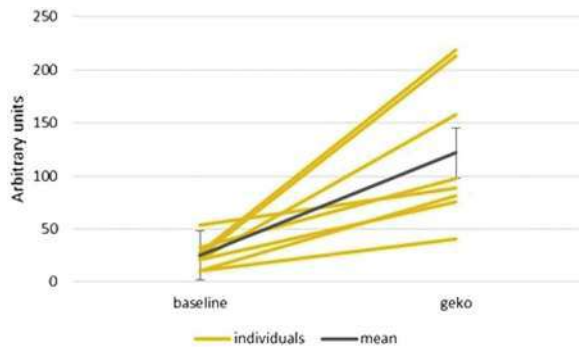


Fig. 6. Wound bed pulsatility summary line graph. The black line shows the mean value for all subjects, and the error bars show standard error of difference.

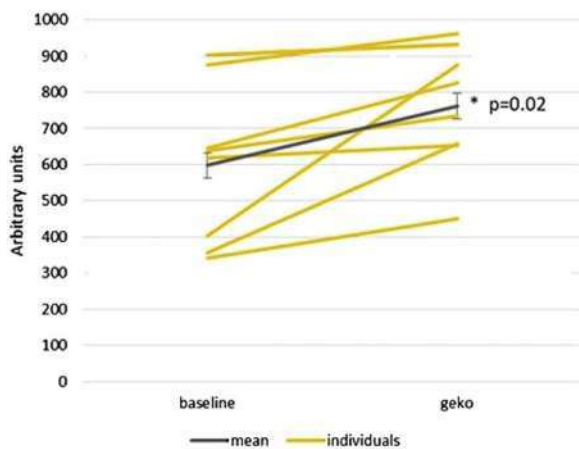


Fig. 7. Peri-wound flux summary line graph. The black line shows the mean value for all subjects, and the error bars show standard error of difference.

generate pulsatile flow.²⁴ Perfusion parameters as measured using LSCI have been shown previously to predict healing in venous ulcers with 92% sensitivity and specificity of 75%.¹⁷ Flux at the wound edge has proved especially predictive of healing.

It has been shown that pulsatile flow prolongs the period of capillary opening prior to occlusion,²⁵ whilst nonpulsatile flow causes a collapse of capillary structure, reduction in blood flow, and increase in capillary shunting, irrespective of the mean blood flow and arterial pressure.²⁶ Additional energy delivered to the tissues with pulsatile flow keeps the peripheral circulation open and promotes extracellular fluid exchange.²⁷ Cyclic motion of blood maintains the concentration gradients required for nutrient exchange, and pO₂ transients caused by flow motion oxygenate tissue domains which under steady state conditions would remain anoxic.²⁸

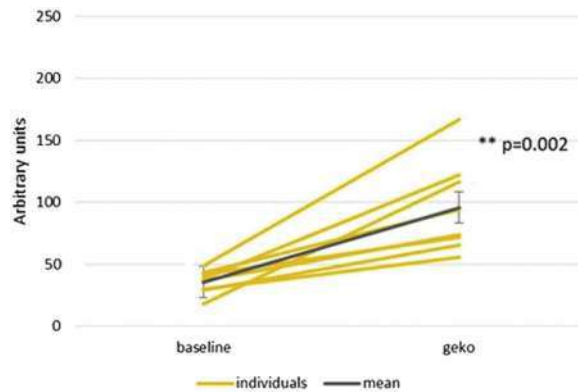


Fig. 8. Peri-wound pulsatility summary line graph. The black line shows the mean value for all subjects, and the error bars show standard error of difference.

The augmentative effect of the geko device on the microcirculation, both in terms of flow and pulsatility, may provide a mechanistic insight into its value in wound healing. These possibilities are especially of interest where compression is contraindicated, or when there is no intervention available for improving macrovascular arterial supply. Although these patients may achieve wound healing, it is generally prolonged and requires adherence to a strict wound care protocol.²⁹ The device may also have a role to play in treating patients with arterial rest pain, without wounds, who are unsuitable for revascularization.

The study has certain strengths. By using LSCI, the microvascular flow can be objectively assessed and quantified for comparative analysis. The response of all patients was similar, suggesting that its effect is relatively homogenous throughout the patient population. However, there are limitations to the study. Two patients did not respond to the device. LSCI measurements have been shown to be predictive of outcome in one study in patients with venous leg ulcers,¹⁷ although these data are based on a small patient cohort ($n = 17$), and robust data demonstrating that LSCI parameters can accurately predict outcomes are lacking. There are no data on long-term efficacy of geko or other NEMS on patients with arterial ulcers who are unsuitable for revascularization. Although it would be reasonable to hypothesize that geko may improve outcomes for patients with significant arterial disease, no long-term effects on flow parameters have been assessed. A randomized controlled trial to examine the clinical outcomes of patients treated with geko would therefore be of significant interest.

CONCLUSIONS

The geko device applied to the common peroneal nerve substantially and immediately augments microcirculatory flow and pulsatility in both the wound bed and the periphery of arterial leg ulcers. These data may provide mechanistic insight into the clinical efficacy of NMES in treating wounds.

The authors acknowledge the assistance of Firstkind Ltd, Hawk House, Peregrine Business Park, Gomm Road, High Wycombe, HP13 7DL for sponsoring the study.

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