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Healing Rate and Time to Closure of Venous Leg Ulcers: A Real-World Service Evaluation of Neuromuscular Electrostimulation as an Adjunct to Compression Therapy

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ABSTRACT
OBJECTIVE: To perform a service evaluation of neuromuscular electrostimulation (NMES) as an adjunct to compression therapy, comparing the rate of wound margin advance and time to closure with a matched retrospective control group.
METHODS: Fifteen patients with venous leg ulcers were prescribed NMES for 6 hours per day for 56 days or until wound closure (whichever occurred first), in addition to multilayer compression. Wounds were selected for size, with an inclusion criterion of a maximum of 12 cm^2. Wound progress was compared with 15 retrospective control patients who were matched for ulcer size and duration.
RESULTS: The retrospective group had a healing rate of 0.31 mm per week (95% CI, 29-37 mm/week), whereas the prospective compression plus NMES group had a healing rate of 0.56 mm per week (95% CI, 50-62 mm/week; $P = .004$). All wounds in both groups healed completely during the service evaluation. Mean time to closure for the retrospective group was 77 days (95% CI, 66-88 days), whereas the NMES group had a mean time to closure of 40 days (95% CI, 37-43 days; $P = .005$).
CONCLUSIONS: Adding NMES of the common peroneal nerve to a care bundle including multicomponent compression resulted in significantly faster wound margin advance and significantly less time to heal in comparison with retrospective matched controls. Future randomized controlled trials or self-controlled studies of this approach would be of great interest to inform clinical practice.

KEYWORDS: compression, geko, healing, neuromuscular electrostimulation, venous leg ulcer

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INTRODUCTION

Recent estimates place the prevalence of venous leg ulcers (VLUs) at 0.32% of the global population.[1] Many interventions have been posited to treat VLU. A systematic review[2] examined the effectiveness of numerous interventions currently indicated, including compression bandages and stockings, topical negative pressure, oral pentoxifylline, laser treatment, skin grafting, superficial vein surgery (perforator ligation, saphenous vein stripping), therapeutic ultrasound, leg ulcer clinics, leg elevation, and activity advice. Among these, only compression and pentoxifylline were found in that review to have statistically significant evidence to support their use.

A possible reason for the dearth of evidence to support interventions for VLUs is the traditional reliance on complete healing as an endpoint. The heterogeneous nature of wounds and the sporadic nature of healing give poor statistical power to this endpoint. Recently, experts have called for alternate endpoints to be deployed, such as rate of wound closure over a specified period.[3,4] In the US, the Food and Drug Administration has recently begun to consider new study endpoints for wound studies,[5] including percentage area reduction of the wound over a 4-week period as an endpoint.[6,7]

Current best practice in the treatment of VLUs is the early application of compression therapy.[8] The basis for compression therapy is found in the etiology and pathophysiology of VLUs, which (by definition) stem from compromised venous function.[9] The mode of action of compression is to mitigate the detrimental effects of venous insufficiency: edema, reduced venous flow, and reflux. Applying external pressure opposes hydrostatic pressures within the leg, thus reducing edema and assisting venous return.[10] Compression also reduces the diameter of veins, thus increasing venous velocity.[11,12]

Approximately 90% of venous return is driven by the muscle pumps, not by the heart.[13,14] The mechanisms by which chronic venous insufficiency causes leg ulcers can be exacerbated by calf muscle pump dysfunction, either due to immobility or abnormal gait.[15] Compression therapy has been shown to have further benefits for leg ulcer healing by improving calf muscle pump function and so reducing ambulatory venous hypertension.[16]

Mobility and exercise also improve VLU outcomes.[17] Patients who are encouraged and able to exercise during compression treatment see enhanced benefits of the compression,[18,19] and there is evidence that compression and leg movements are mutually supportive.[20,21] However, poor adherence has been reported to exercise regimens.[22]

A recent review[23] identified activation of the leg muscle pumps by neuromuscular electrostimulation (NMES) as a promising new technologic development for wound healing. Subsequently, Bull et al[24] conducted a within-patient controlled study to evaluate the effects of a new intervention on the healing rate of VLU.[24] The study found a significant improvement to the wound margin advance (WMA) over a 4-week period for VLUs receiving intermittent NMES of the common peroneal nerve as an adjuvant to compression, compared with compression alone.

Objective

In the present study, the authors investigated the use of NMES in a real-world setting over a longer period, following wounds to closure. The researchers compared WMA and time to complete closure of VLUs treated with NMES as an adjunct to compression therapy, with retrospective controls treated with compression only.

METHODS

This is a real-world service evaluation with 1:1 retrospective controls.

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FIGURE 1. APPLICATION OF NEUROMUSCULAR ELECTROSTIMULATION

Participants

Participants were 15 sequential patients with VLUs who were referred to Mississauga Halton Local Health Integration Network Home and community care program. Inclusion criteria were 19 years or older, on service for 30 days or less, VLU confirmed by ankle brachial pressure index assessment or the Venous Leg Ulcer Risk Assessment Tool, wound duration of 3 months or less, and use of optimal compression. Exclusion criteria were 18 years or younger, ankle brachial pressure index less than 0.5, active preexisting dermatitis, or active deep tissue infection.

Interventions

Patients in the study were prescribed NMES for 6 hours per day, 6 days per week for 56 days or until wound closure (whichever occurred first), in addition to multilayer compression. Compression consisted of multilayer, multicomponent compression with a presumed interface pressure of 40 mm Hg according to manufacturers' instructions.

For NMES, researchers applied the geko W-2 stimulator (Firstkind Ltd) to the lateral aspect of the leg at the fibular head, according to the manufacturer's instructions (Figure 1). The device is CE marked as a class II device and has regulatory approval from the Medical Devices Directorate for use in Canada to treat leg ulcers; the manufacturer has a vigilance system in place to collect data on any adverse incidents. The device was set to stimulate the common peroneal nerve at a frequency of 1 Hz, eliciting an intermittent twitch of the leg to activate the venous muscle pump.

The researchers selected the regimen of NMSE 6 hours per day 6 days per week because it was used in previous case series with promising results.[25,26] The duration of 56 days (8 weeks) was selected as the typical course of therapy for the retrospective group who received standard care. The small number of participants was chosen as a convenience sample and exceeded sample size calculations based on effect sizes seen in previous studies.[24] Wounds were assessed clinically as having venous etiology and were classified according to the Venous Leg Ulcer Risk Assessment Tool, which collected data on patient age, size and duration of ulcer, and history of previous ulcer or thromboembolism.[27]

Patients were compared with 15 retrospective control patients, matched for ulcer size and duration, who had received standard care comprising only multilayer compression.

Data Collection

Patients were selected based on wound size, with one of the inclusion criteria being a maximum area of 12 cm^2. Historic data in the standard care arm of the service evaluation were collected retrospectively; no informed consent was provided for these data in accordance with the ethical approval granted. As a service evaluation of a center-adopted device being used as per its indications for use, no ethics approval was required.

Wound area was measured at all clinic visits (mean, every 3.5 days). Wound length and width were measured to the nearest 1 mm using a tape measure. All measurements and all applications of interventions—NMES and compression (both prospective and retrospective)—were performed by the same two investigators for the duration of the study. Adherence to the regimen was patient-reported by query at each visit.

Researchers calculated the rate of WMA according to the Vidal method,[28] which calculates the ratio of wound area to perimeter and plots the change in this value over time. This method has been found to produce a near-linear trajectory over time, thus lending itself to evaluating the effects of treatments.[3] This value was treated as parametric, and an unpaired Student *t* test assuming equal variances was used to compare the prospective and retrospective groups.

Ethics

This study was conducted in accordance with the Declaration of Helsinki Guidelines for Good Clinical Practice. All interventions were on-label and compared with retrospective controls, and all data were anonymized. Ethical approval was granted by the Homewood Research Ethics Board. All prospective patients provided written informed consent for the collection of data. Data were stored securely on site and anonymized prior to processing, according to Canadian Institutes of Health Research best practices.

RESULTS

The wound size of VLUs among patients in the treatment group (median area, 82 mm^2; median perimeter, 54 mm) did not differ significantly from that of patients in the retrospective control group (median area, 190 mm^2; median perimeter, 58 mm; $P = .87$). The intervention and retrospective control groups also did not differ significantly in age ($P = .68$). Patient-reported adherence to NMES treatment was 100% (6 hours per day, 6 days per week), and no adverse incidents or comments were reported.

Referring to Figure 2, the two groups differed significantly in healing rate. Whereas the retrospective control group had a healing rate from the wound perimeter toward the center of the wound of

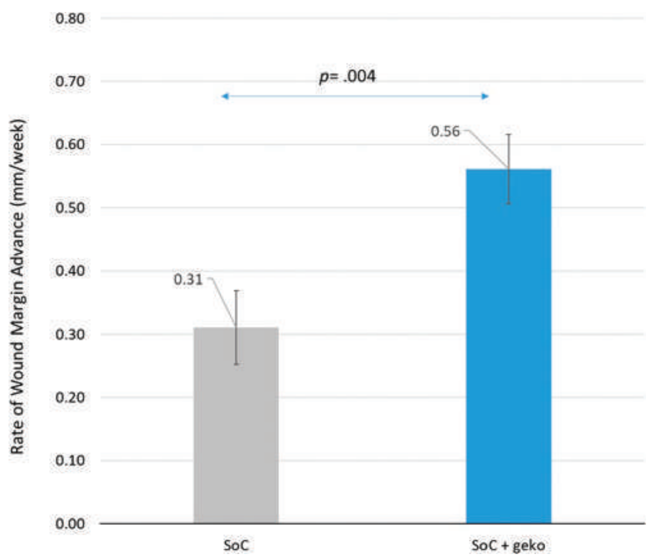

FIGURE 2. EFFECT OF NMES ON THE RATE OF WOUND MARGIN ADVANCE
Abbreviations: NMES, neuromuscular electrostimulation; SoC, standard of care.

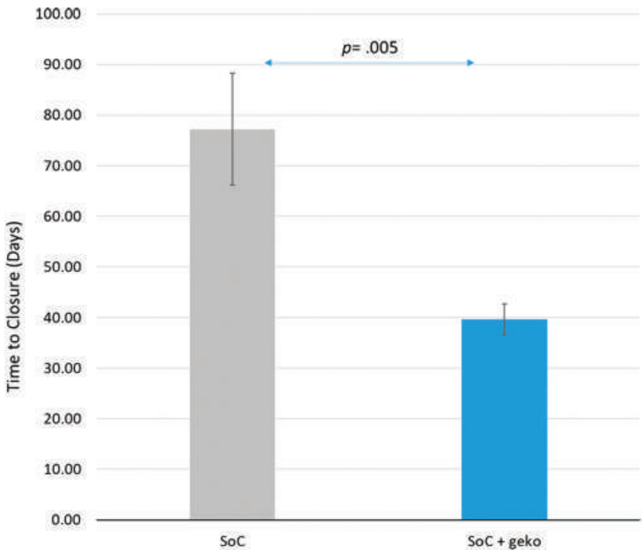

FIGURE 3. EFFECT OF NMES ON THE TIME TO WOUND CLOSURE
Abbreviations: NMES, neuromuscular electrostimulation; SoC, standard of care.

0.31 mm per week (95% CI, 29-37 mm/week), the prospective compression plus NMES group had a healing rate of 0.56 mm per week (95% CI, 50-62 mm/week; *P* = .004).

All wounds in both groups healed completely during the service evaluation. Wounds in the retrospective control group had a mean time to closure of 77 days (95% CI, 66-88 days), whereas wounds in the NMES group had a significantly shorter mean time to closure of 40 days (95% CI, 37-43 days; *P* = .005; Figure 3).

Figure 4 shows a Kaplan-Meier survival plot of the total healing of both groups. The trajectory of the NMES group diverges from the compression-only group within 23 days, with all patients in the NMES group exhibiting complete healing by day 64, as opposed to day 195 for the compression-only group. The difference between the two lots is highly significant according to a log-rank test (*P* = .0001).

DISCUSSION

Compression

Although compression is the therapy best accepted by clinicians for the treatment of VLUs,[29,30] patient acceptance of and adherence to compression therapy remain problematic,[31,32] and researchers have explored options to improve patient adherence.[33] Further, although it is difficult to measure interface pressures beneath compression systems,[34] researchers have noted that elastic compression stockings applied with constant tension do not apply uniform pressure to the leg.[35] Because the leg has a nonuniform radius in cross-section, less convex areas receive less pressure, and concave areas such as the retromalleolus receive no pressure.[36]

However, it appears that uniformly applied interface pressure is not necessary for VLU healing: research has suggested that achieving a high pressure over the calf muscles alone is hemodynamically more effective than uniformly applied or graduated pressure.[37] This finding suggests that improved venous pump function is the principal benefit of compression.[38]

Further, a high-stiffness compression system produces greater fluctuations in pressure in the leg during walking in comparison with a low stiffness system, therefore delivering the greatest improvements in venous blood flow. Low-stiffness systems produce the higher resting interface pressure and therefore less comfort.[39] The implication for clinical practice is that high-stiffness systems would allow for lower (more comfortable) resting pressures, as long as the calf muscle pump is regularly activated by some means.

NMES

Previous research has found that NMES is an effective means of activating the calf muscle pump when applied intermittently to the common peroneal nerve, replicating the effects of exercise.[40] In patients with VLUs, venous flow and arterial flow are increased,[41] as well as microcirculation in the wound bed and the wound periphery.[42] Similar effects are seen in arterial leg ulcers.[43] Research indicates that NMES may exceed intermittent pneumatic compression in terms of hemodynamic benefit.[44,45] Improved healing has been observed clinically when NMES has been applied to lower-limb wounds.[25,26,46] In a self-controlled study, Bull et al[47] demonstrated a twofold increase in VLU healing rate when NMES was added to compression.

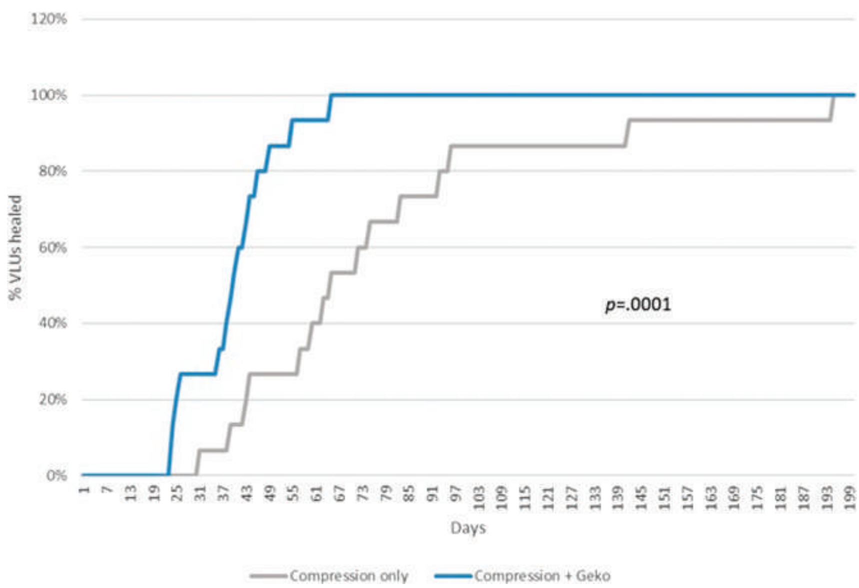

FIGURE 4. KAPLAN-MEIER PLOT OF CUMULATIVE WOUNDS HEALED OVER TIME WITH AND WITHOUT NEUROMUSCULAR ELECTROSTIMULATION

The findings of this service evaluation are consistent with the results of these earlier studies. Although the present service evaluation was not designed as a randomized controlled trial, and no run-in data were for self-control, VLUs healed at a significantly faster rate with NMES compared with historic controls matched for wound size and duration. Further, participants in the NMES group achieved complete VLU healing in a significantly shorter time than the retrospective control group.

Limitations

One limitation of this service evaluation is that no sociodemographic data were available for the retrospective controls, so it was not possible to check for confounding differences between the prospective and retrospective groups. In addition, with this study design, no randomization was possible. These limitations both lead to a risk of unmatched intervention and control groups.

It was also not possible to blind patients or assessors to the intervention because all prospective participants received the intervention, which was patently applied to the leg. It must likewise be acknowledged that the same personnel who applied the therapeutics also collected the data.

An additional limitation, common to many wound studies, is the difficulty of measuring wound size. In this case, calculating area as the product of measured height and width relies on modeling the wound as a rectangle, which is necessarily an approximation. The other endpoint of time to complete closure is less susceptible to this limitation.

CONCLUSIONS

Adding NMES of the common peroneal nerve to activate the venous pump of the leg for 6 hours per day, 6 days per week, to a care bundle including multicomponent compression resulted in significantly faster WMA and significantly less time to heal, in comparison with retrospective matched controls. Future randomized controlled trials or self-controlled studies of this approach would be of great interest to inform clinical practice.

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