

## The impact of a new intervention for venous leg ulcers: A within-patient controlled trial

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### Introduction

One reason for the apparent lack of adoption of new wound-healing interventions is the insistence on complete healing as a primary outcome alongside a conventional randomised controlled trial (RCT). Chronic wounds frequently take many months to heal, and the heterogeneity of ulcers and their trajectories make it difficult to match control and intervention groups. There has been a call for alternate endpoints such as speed of wound closure (rate of healing) to be used for new product evaluations.



### Objective

The objective of this randomised self-controlled trial was to compare the rate of wound margin advance (WMA) for venous leg ulcers (VLUs) receiving intermittent neuromuscular electrostimulation (NMES) of the common peroneal nerve for 12 hours per day as an adjunct to compression compared with compression alone.



### Method

Sixty patients with VLUs were randomised to two groups: one received standard of care (SOC) consisting of commercially available multi-layer, multicomponent compression bandaging or hosiery kits indicated for treating VLUs, and the other group received NMES for 12 hours per day in addition to SOC. For inclusion and exclusion criteria please refer to the original paper.

In the case of both arms, each patient spent 4 weeks on a run-in control phase receiving SOC only. Thereafter, the SOC randomised cohort continued to receive SOC for a further 4 weeks, whereas the NMES randomised cohort received NMES in addition to SOC for a further 4 weeks. The study was not designed to compare healing rates between the two randomised cohorts, but rather for each cohort to compare the rate of healing between intervention phase and run-in phase of the same patient (the patient being their own control).

Nine patients were withdrawn post-randomisation due to randomisation criteria failures, non-compliance or withdrawn consent, leaving 22 patients in the SOC arm and 29 in the NMES arm.





## Results

Figure 1 shows the rate of WMA in millimetres per week for the run-in phase with compression therapy alone compared with the treatment phase with NMES in addition to compression therapy. It can be seen that the treatment phase with NMES as an adjunct to compression had a significantly faster healing rate ( $p=0.016$ , paired t-test) than compression alone. Meanwhile, no significant difference was found between run-in phase (compression only) and treatment phase (compression only) in the SOC randomised arm of the study.

In figure 2, the data collected from the same wounds was assessed using a different metric: percentage area reduction (PAR). The data showed that the healing rate during treatment phase when the NMES was added to SOC was significantly higher than the run-in phase ( $p=0.011$ , paired t-test). Again, the SOC cohort showed no significant difference between run-in and treatment phases.

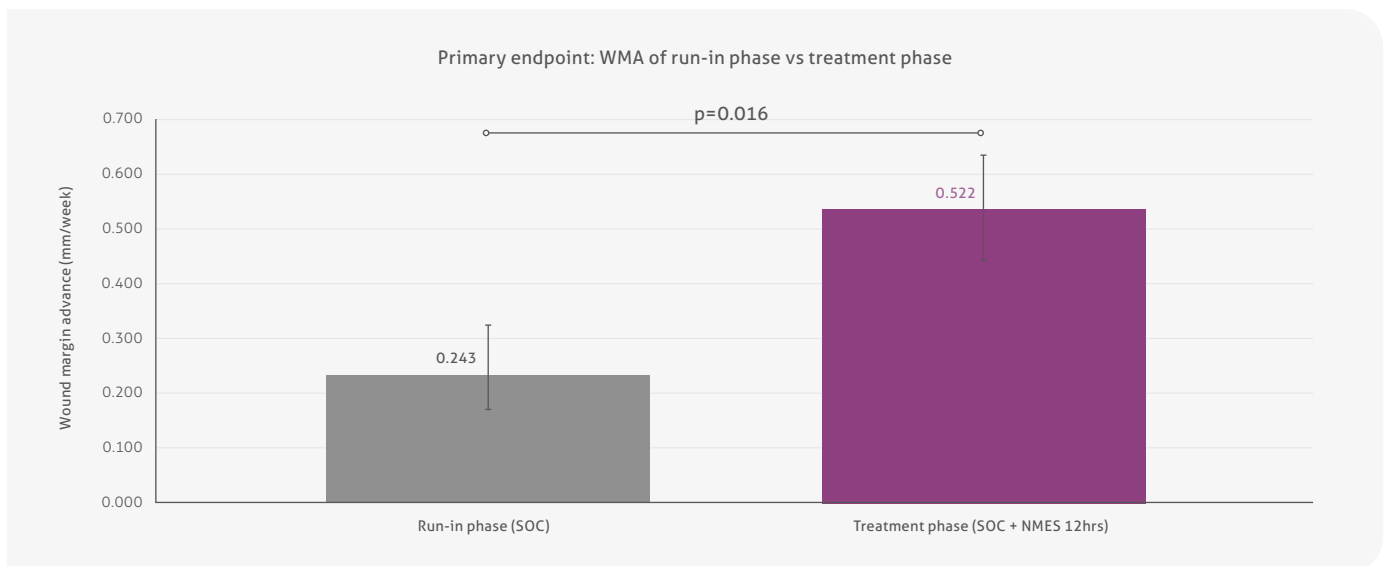


Figure 1. Rate of WMA of the run-in phase (SOC only for 4 weeks) compared with the treatment phase (SOC + NMES for 12 hours per day over 4 weeks),  $n=29$ .

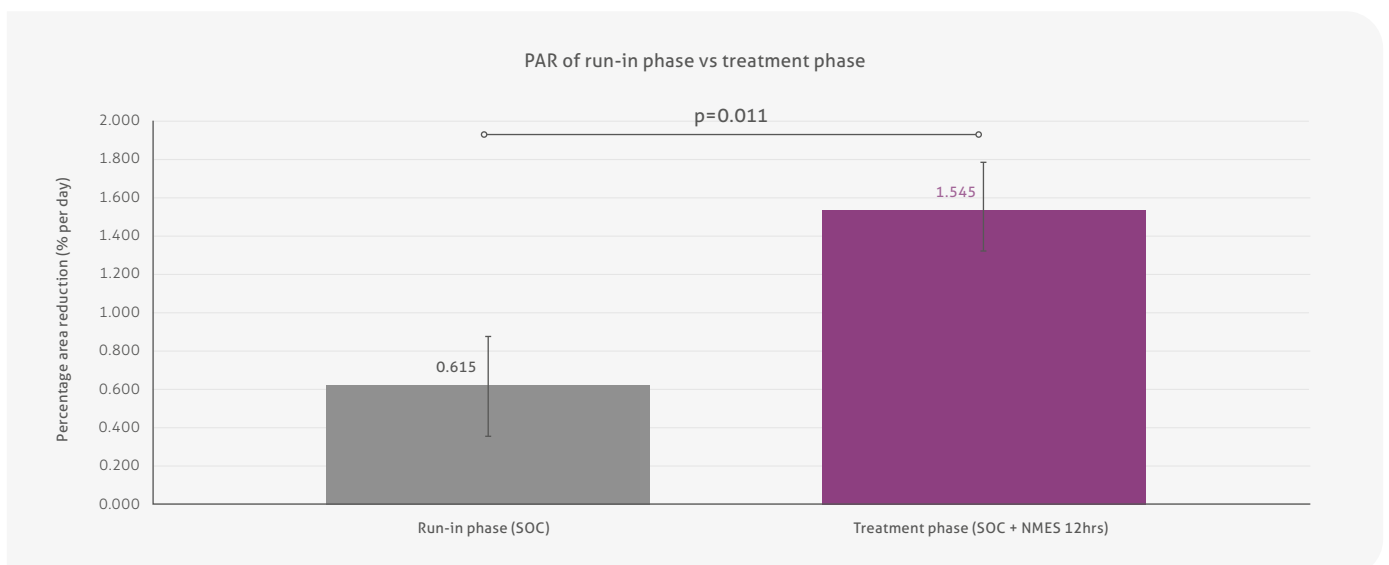


Figure 2. PAR of the run-in phase (SOC only for 4 weeks) compared with the treatment phase (SOC + NMES for 12 hours per day over 4 weeks),  $n=29$ .

A typical series of weekly assessments is shown for a single wound in figure 3. The wound was photographed weekly for the 4-week run-in phase followed by the 4-week treatment phase.

Note that the size and perimeter of the wound remain relatively static during the run-in phase but that the area progressively reduces, and wound margin progressively advances, during the treatment phase when the NMES device is added to SOC.

### Run-in phase (SOC only)



### Treatment phase (SOC + NMES)



**Figure 3.** A typical trajectory of a single wound over the 8-week study period for a patient in the NMES cohort that experienced a run-in phase of SOC for 4 weeks, then a treatment phase of SOC + NMES for 12 hours per day over 4 weeks.

Results for secondary endpoints are reported in table 1 below. A substantially greater proportion of patients in the NMES cohort had wounds that healed completely during the course of the study and the 3-month follow-up period.

Mean reduction in the visual analogue scale (VAS) pain score was greater for patients who received NMES compared with patients who received SOC only. Similarly, vascular clinical severity score (VCSS) shows a mean improvement for SOC plus NMES when compared with SOC alone.

	SOC	SOC plus NMES (12 hours per day)
Mean improvement in VCSS <sup>a</sup>	12.8%	15.1%
Mean reduction in VAS <sup>b</sup>	21.1%	30.1%
Wounds completely healed at 3-month follow-up <sup>c</sup>	27.0%	42.0%

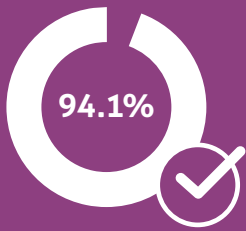
<sup>a</sup>Mean improvement in score from recruitment to end of treatment period.  
<sup>b</sup>Mean improvement in score from randomisation to end of treatment period.  
<sup>c</sup>Percentage of wounds healed between randomisation and end of long-term follow-up period.

**Table 1.** Secondary endpoints comparing percentage of wounds healed and pain reduction for SOC plus NMES vs SOC alone.



## Conclusion

In this self-controlled study, the addition of intermittent NMES of the common peroneal nerve over a 4-week period more than doubled the rate of WMA towards the centre of the wound relative to a 4-week run-in period with compression alone ( $p=0.016$ ). This rate of healing was also calculated using PAR and the same results were seen: the rate of healing more than doubled ( $p=0.011$ ). By contrast, the SOC cohort maintained the same healing rate throughout the run-in and treatment phases of the study.



The NMES device was well tolerated with 94.1% of patients adhering to therapy.

This study demonstrates that the use of the endpoint metrics WMA and PAR allows for a self-controlled study model, which provides a means to distinguish between the relative efficacies of interventions more rapidly, with greater sensitivity, and with fewer patients than a conventional RCT cohort model.

