

Healing trajectories as an indicator of clinical outcomes in patients with venous leg ulcers

KEY WORDS

- ▶ Externally Applied Electroceutical (EAE)
- ▶ Follow-up
- ▶ Healing
- ▶ Recurrence
- ▶ Venous leg ulcer
- ▶ Wound-healing trajectory

Background: Venous leg ulcers (VLUs) account for the majority of leg ulcers and are common among individuals with risk factors such as obesity or immobility. As a substudy of a large-scale, prospective, randomised double-blind, placebo-controlled trial, this substudy aimed to ascertain VLU healing rates and recurrence rates of patients excluded from the trial as they were deemed to be progressing along a normal healing trajectory. **Methods:** A wash-out entry-gate process was used to determine patients' wound-healing trajectories. At the end of the 28-day wash-out process, patients whose VLUs were deemed to be following a normal healing trajectory continued to receive a standard treatment regimen and the healing and recurrence of ulcers in this patient group was assessed after 12 months. The primary endpoint was the incidence of complete wound healing at 1 year. **Results:** Forty-one patients from a total cohort of 141 were deemed to be following a normal healing trajectory at 28 days. One year later, 37% ($n=15$) of the 41 patients' ulcers had healed; however, 53% ($n=8$) of the ulcers had recurred in that period. **Conclusion:** There is a low VLU healing rate in patients with a normal healing trajectory, which suggests that healing trajectory is not a good indicator of healing and/or that current wound management for VLU is unsatisfactory.

Venous leg ulceration is a common, chronic, and recurrent condition that imposes significant demands on healthcare resources. Venous leg ulcers (VLUs) account for 80–85% of all leg ulcers, and are particularly common among individuals with risk factors such as obesity or immobility, a personal or family history of varicose veins, and a personal history of deep vein thrombosis or leg trauma (Simon et al, 2004). It is estimated that there are up to 190,000 people with VLUs in the UK, incurring an estimated annual cost to the NHS of approximately £168–£198 million (Posnett and Franks, 2008). Community nursing services account for a great proportion of the healthcare costs associated with VLUs (Simon et al, 2004; Posnett and Franks, 2008).

Standard treatment for VLUs consists of sustained compression with bandages or stockings,

together with a simple, non-adherent dressing and specific measures directed towards the cause of the ulcer (Simon et al, 2004; Scottish Intercollegiate Guidelines Network [SIGN], 2010). Approximately 50% of ulcers will not have healed at 1 year, however, even with compression therapy, the cost of treating such ulcers has been estimated to be up to three times greater than that of treating healing ulcers (Rippon et al, 2007).

The processes involved in wound healing depend upon the interaction between many time-dependent components (Payne et al, 2011). Understanding healing duration is vital in wound management; increased time to healing correlates with greater rates of infection, scarring and non-healing. A wound-healing trajectory integrates the many time-dependent processes

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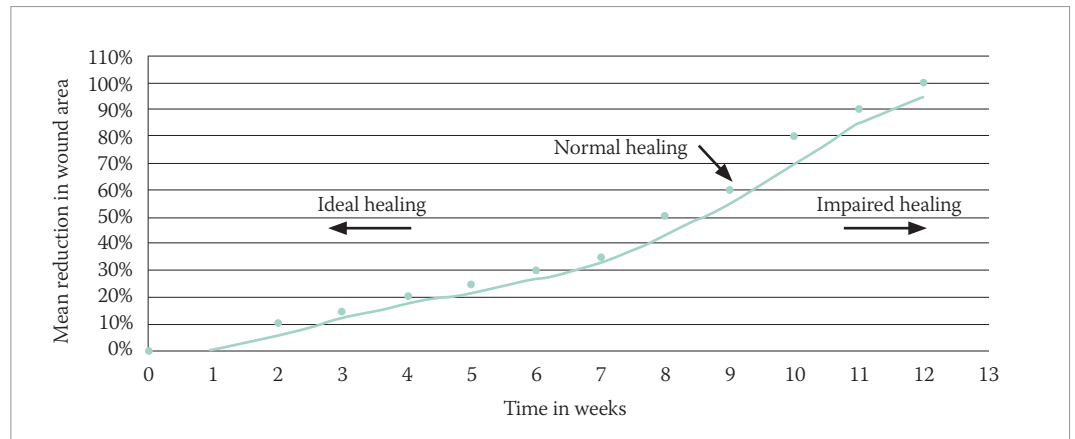


Figure 1. The normal wound healing curve showing reduction in wound area over time. Patients' wound healing trajectories can be plotted against this to determine whether the healing of their ulcers is delayed or impaired.

that are part of the healing process, and is affected by systemic and local deterrents to healing. It can clearly demonstrate improved healing (with a left shift) or delayed/impaired healing (with a right shift) when compared against the normal healing curve (*Figure 1*). *Figure 1* also shows that normal healing rates are different from what can be described as an ideal rate.

WOUND-HEALING TRAJECTORIES

As the healing of open wounds follows an exponential curve, wound-healing trajectories (percentage of wound closure versus time) have been used to describe chronic wound healing (Payne, et al 2011). Although wound healing trajectories were initially intended for acute wounds, they can also be used to evaluate the healing of chronic and complex wounds, such as diabetic foot ulcers, pressure ulcers, and venous stasis ulcers (European Wound Management Association, 2008). The trajectory curve, similar to the Gompertz growth curve for biological systems, is sigmoid-shaped, with time on the x-axis and percentage of wound closure on the y-axis (Windsor, 1932; Payne et al, 2011). This exponential healing process is based on the equation expressed by Du Noüy (Du Noüy, 1916; Hokanson et al, 1992), with the rate of change in wound area decreasing as the residual wound area approaches total closure.

This analytical strategy has been successfully applied to large groups in experimental wound-healing studies. In this method of analysis, a wound-healing trajectory is created

by plotting the percentage of wound closure against time since the start of wound treatment, which can then be used to predict healing and determine the efficacy of a given treatment. With a wound-healing trajectory plot, the time required to achieve a certain percentage of healing can be measured using survival analysis methods as described by Kaplan and Meier (1958).

OBJECTIVE

The usefulness of wound-healing trajectories as predictors of efficacy of treatment for diabetic foot ulcers and venous stasis ulcers has been demonstrated and validated (Steed et al, 2006). As an outcome measure for pressure ulcer treatment, these trajectories are a useful tool for predicting healing times and can be utilised to assess treatment regimens. This study aimed to assess the use of wound-healing trajectories in predicting recovery for patients deemed to be on a normal healing course. A VLU is deemed to be following a normal healing trajectory when it has reduced in cross-sectional area by 20% following 28 days of good standard treatment by a suitably qualified practitioner (Kimmel and Robin, 2013).

METHOD

This substudy was a part of a larger prospective, randomised, double-blind, placebo-controlled trial that aimed to assess the efficacy of an externally applied electroceutical, Accel-Heal®, on healing outcomes in patients with a VLU, conducted at four centres in the UK. Patients

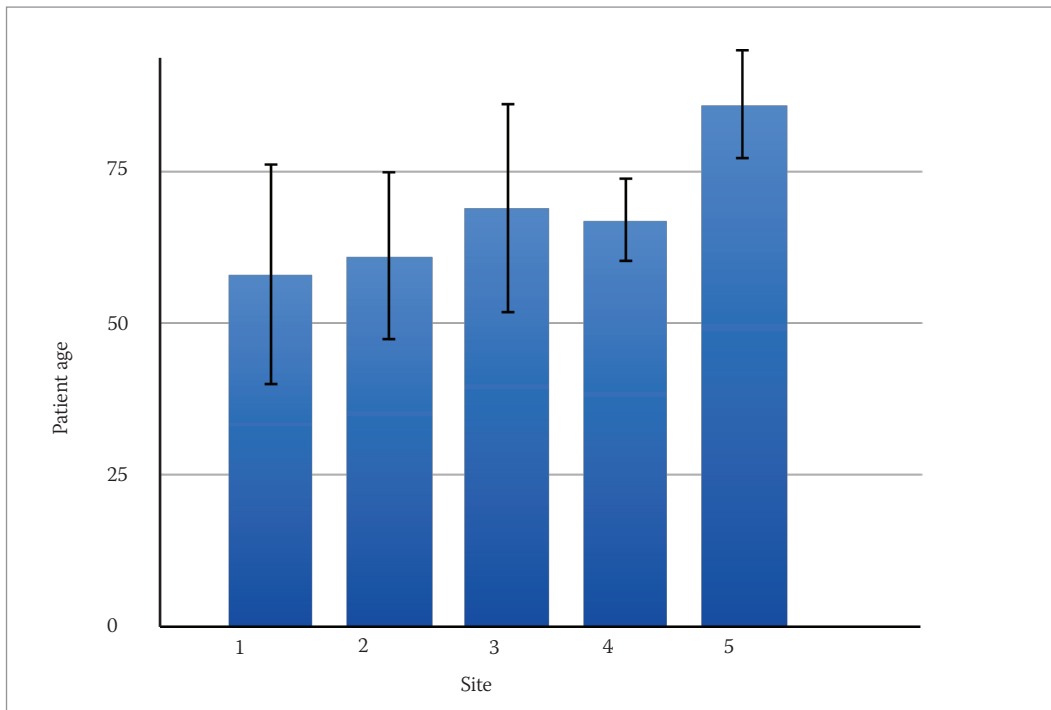


Figure 2. Age distribution between sites including standard deviation ($n = 141$).

included in the substudy were part of the group excluded from the randomised controlled trial (RCT) as they were deemed to be on a normal healing trajectory and were therefore not treated with Accel-Heal or placebo. The RCT and this substudy followed the principles of good clinical practice, the Declaration of Helsinki (2008 update) and the laws and regulations of the European Union.

The primary efficacy endpoint was the incidence of complete wound healing at 1-year follow-up.

Patients

Adult patients (aged ≥ 18 years) were eligible to participate in the RCT study if they had a VLU that had not decreased in size by at least 20% following a 28-day run-in period

during which they received good standard care, including compression bandaging and appropriate dressings (Young and Ballard, 2001). Patients who were deemed to be on a healing trajectory by demonstrating a 20% reduction in wound size over a 28-day period of receiving good standard care were excluded from the RCT but included in the substudy discussed here. The area of the ulcer was measured using the Eykona Wound Measurement System (Fuel 3D Technologies Ltd, Chinnor, UK), was required to be between 1 cm² and 100 cm² at baseline, and to fit within a single frame of the Eykona camera. If a patient had more than one VLU, then a single wound was chosen for the treatment study and the other ulcers received standard care. All patients were required to have an ankle-brachial pressure index of between 0.8 and 1.3 inclusive.

Table 1. Venous leg ulcer healing trajectory and healing rates at 1 year

Site	Number of patients recruited and assessed	Number of patients with normal healing trajectory after 28 days	Number of patients with healed ulcers at 1 year follow-up	Percentage healed (%)
1	35	13	4	31
2	43	6	5	83
3	36	15	5	33
4	17	7	1	14
Total	141	41	15	Mean: 37

Table 2. Recurrence of venous leg ulcers within 1 year

Site	Number of healed ulcers that recurred	Percentage recurrence (%)
1	2	50
2	3	60
3	2	40
4	1	100
	Total: 8	Mean: 53

Patients were excluded from the RCT and this substudy if they had any clinically significant medical condition that could impair wound healing, or if they had been diagnosed with suspected collagen disorders, such as vasculitis, rheumatoid arthritis or osteomyelitis. Other exclusion criteria included chronic renal insufficiency requiring haemodialysis, known alcohol or drug abuse, or psychiatric conditions that could have affected follow-up or treatment outcomes. Criteria also included the receipt of short courses of corticosteroids within 60 days, or oral or parenteral chronic immunosuppressants within 120 days, prior to screening. Women of childbearing potential were required to be using reliable contraception throughout the study. Written informed consent was obtained from all patients prior to entry to the study.

Patients were recruited from four centers, one of which had two clinical sites. The centers were a combination of specialist wound care and community settings. Information about patient age, sex, ulcer size at the start of the assessment, and duration of the ulcer was recorded. *Figure 2* shows the age distribution of patients at the different sites.

Treatments and assessments

At the end of the 28-day run-in period, patients with non-healing VLUs, as defined above, were randomised in a 1:1 ratio to receive treatment for 12 days with routine standard care, including compression and dressings plus either Accel-Heal® or a placebo device that was identical in appearance and were included in the RCT.

The 41 patients whose VLUs were deemed to be following a normal healing trajectory

continued to follow a good standard treatment regimen without the addition of Accel-Heal® or placebo and were included in this substudy. The patients' ulcers were assessed 1 calendar year after completion of the 28-day run-in period for both the RCT and the substudy.

At the follow-up assessment, the number of weeks it took for the ulcer to heal, if it did, following the 28-day assessment, was noted for both the RCT and the substudy. If the ulcer remained unhealed, the size of the ulcer was noted and compared with the ulcer size on presentation. The average size of wounds that did not heal was 7.09 cm² on presentation. Following standard care for a period of 12 months, these wounds reduced by an average of 53% across the board, but did not heal to closure.

RESULTS

A total of 141 patients were recruited across the sites. Of these, 41 had VLUs that were deemed to be following a normal healing trajectory at 28 days. The patients were excluded from the RCT and included in this substudy. One year later, 37% ($n=15$) of these patients had ulcers that had healed (*Table 1*). Despite healing, however, VLUs recurred in more than half of this group (53%, $n=8$) within the 1-year period (*Table 2*).

DISCUSSION

There is no simple definition of what constitutes a complex wound, but in practical terms it is a wound with one or more complicating factors, such as exudate, infection, comorbidity, polypharmacy, etc. Currently, there appears to be a knowledge deficit on how to adequately manage complex wounds, given the low healing rates reported; for example, 50% of VLUs remaining unhealed after 1 year of treatment (SIGN, 2010). Standard treatment for VLUs consists of sustained compression with bandages or stockings, together with a simple, non-adherent dressing and specific measures directed towards the cause of the ulcer (Simon et al, 2004; SIGN, 2010).

The literature varies greatly in predicted healing rates over time, with ranges from approximately 30% of ulcers not being healed

at 1 year, to 90% not healing or recurring, even with compression therapy (Margolis et al, 1999; SIGN, 2010). This investigation demonstrated that, across a number of different specialist wound care centres and community settings, even when an ulcer was deemed to be on a healing trajectory 63% of VLUs did not go on to complete wound closure. Of the 37% of ulcers that did heal, over half recurred. These results suggest that current wound management for VLUs is unsatisfactory and is fiscally burdensome. The cost of treating these complex ulcers has been estimated to be up to three times greater than that of treating healing ulcers (Rippon et al, 2007).

The poor recovery rate of patients in this substudy who had a normal healing trajectory — an ulcer that reduced in cross-sectional area by 20% following 28 days of good standard treatment by a suitably qualified practitioner (Robson et al, 2001) — raises the question as to whether this measure is a reliable indicator of healing. The current study results suggest that healing trajectories are not a reliable indicator and/or that current standard management is not achieving the primary objective of wound closure. It may be suggested that a change in management from one clinical setting to another is sufficient to produce a transient change in the wound, but this is not sustained to full wound closure.

One inconsistency that could occur when mapping a wound-healing trajectory is the actual measurement of the wound size. Even when using digital photography, non-invasive measurements of wound area are subject to errors in defining the wound edge, particularly when different operators are responsible for obtaining and analysing the images. This is even more apparent when clinicians use a paper ruler to take a measurement. Furthermore, such methods only measure the area of the wound, and provide no information about changes occurring in the wound bed or in the surrounding tissues. These limitations were addressed in this study by the use of the Eykona Wound Measurement System, which allows an accurate and reproducible

measurement of wound size, wound volume and tissue condition, provided that the image fits within a single frame.

CONCLUSIONS

It is expected that if a VLU is on a normal healing trajectory following 28 days of good standard treatment that it would proceed to healing. The results presented here have demonstrated that this is often not the case. As this paper demonstrates, further work is needed to evaluate the usefulness of wound-healing trajectories in predicting patient outcomes. WUK

REFERENCES

- Du Nöuy PL (1916) Cicatrization of wounds II: mathematical expression of the curve representing cicatrization. *J Exp Med* 24(5): 451–60
- European Wound Management Association (2008) *Hard-to-Heal Wounds: a Holistic Approach*. MEPLtd, London
- Hokanson JA, Hayward PG, Carney DH et al (1992) A mathematical model for the analysis of experimental wound healing data. *Wounds* 13:213–20
- Kimmel HM, Robin AL (2013) An evidence-based algorithm for treating venous leg ulcers utilizing the Cochrane Database for Systematic Reviews. *Wounds* 25(9):242–50
- Kaplan E, Meier P (1958) Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 53(282):457–81
- Margolis DJ, Berlin JA, Strom BL (1999) Risk factors associated with the failure of a venous leg ulcer to heal. *Arch Dermatol* 135(8): 920–6
- Payne WG, Bhalla R, Hill DP, et al (2011) Wound healing trajectories to determine pressure ulcer treatment efficacy. *Eplasty* 11:e1.
- Posnett J, Franks PJ (2008) The burden of chronic wounds in the UK. *Nurs Times* 104(3):44–5
- Rippon R, Davies P, White R, Bosanquet N (2007) The economic impact of hard-to-heal leg ulcers. *Wounds UK* 3(2): 58–69
- Robson MC, Steed DL, Franz MG (2001) Wound healing: biologic features and approaches to maximize healing trajectories. *Curr Prob Surg* 38(2):61–140
- Scottish Intercollegiate Guidelines Network (2010) SIGN Guideline 120: Management of Chronic Venous Leg Ulcers. Available at: <http://www.sign.ac.uk/pdf/sign120.pdf> (accessed 21.10.2015)
- Simon DA, Dix FP, McCollum CN (2004) Management of venous leg ulcers. *BMJ* 328(7452):1358–62
- Steed DL, Hill DP, Woodske ME et al (2006) Wound-healing trajectories as outcome measures of venous stasis ulcer treatment. *Int Wound J* 3(1):40–7
- Windsor CP (1932) The Gompertz curve as a growth curve. *Proc Natl Acad Sci USA* 18(1):1–8
- Young SR, Ballard K (2001) Wound assessment: diagnostic and assessment applications. Part 2. In: *Electrotherapy: Evidence-Based Practice*. Churchill-Livingstone, London