Horse-chestnut (*Aesculus hippocastanum*) seed extract for venous leg ulceration: a comparative multiple case study of healers and non-healers

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Abstract

**Background** Venous leg ulceration (VLU) is a chronic and recurrent condition that affects around 0.12–1.1% of the Western population. One intervention that is showing promise as a treatment for VLU is horse-chestnut (*Aesculus hippocastanum*) seed extract (HCSE), with evidence suggesting that HCSE treatment may reduce wound slough, the frequency of dressing changes and the overall cost of VLU management. However, it remains unclear as to the types of patients that HCSE is likely to benefit.

**Objective** To illustrate the types of patients that may benefit from the use of HCSE for the treatment of VLU, and the typical response patterns that may be observed.

**Methods** Comparative multiple-case study of VLU healers and non-healers treated with HCSE.

**Results** When comparing the HCSE-healed cases with the HCSE non-healed cases, what emerges is that HCSE treatment may be most effective when the following elements are present: mild to moderate venous insufficiency, a small wound of short duration, a short history of ulceration, and no signs of wound infection.

**Conclusions** A number of variables were identified as having an influence on the trajectory of venous ulcer healing among patients treated with HCSE. Further investigation is needed to validate these findings.

**Keywords** Comparative case study • herbal medicine • horse-chestnut seed extract • venous leg ulceration • wound healing

**Background**

Venous leg ulceration (VLU) is a chronic and recurrent condition that affects around 0.12–1.1% of the Western population. Apart from the many physical manifestations, VLU is associated with significant psychosocial and financial implications, such as depression, anxiety, social isolation, immobility and unemployment. It is therefore desirable that venous ulceration be effectively managed with the aim not only of improving patient health and well-being, but of decreasing healthcare expenditure and the burden on community resources. While compression therapy remains the cornerstone of VLU treatment in most Western countries, and the best available evidence clearly supports its use, patient compliance with compression therapy is often poor. This suggests that the development of a more effective and well-tolerated treatment of venous ulceration would represent a significant contribution to wound care.

In the area of CAM, several therapies are demonstrating potential benefit in the treatment of chronic wounds, of which horse-chestnut (*Aesculus hippocastanum*) seed extract (HCSE) is one. This herbal extract exhibits a range of pharmacological effects that target the pathological processes that lead to venous insufficiency. Since chronic venous insufficiency (CVI) is a precursor of venous ulceration, it is crucial to consider the potential role of HCSE in the management of this condition.
and the clinical efficacy of HCSE in the treatment of CVI is already established,9 it has been argued that this extract may be beneficial to patients with VLU.

Findings in Australia from a prospective, double-blind, randomised, placebo-controlled trial10 and a subsequent cost-benefit analysis11 both indicate that HCSE may be useful for the management of venous ulceration. Even though improvements in the rate of wound healing and in most secondary outcomes were not statistically significant between groups in the horse-chestnut and venous leg ulcer trial (HAVLUT), HCSE had a significant effect (P=0.045) on the percentage of wound slough. This improvement in wound topography may have decreased the need for regular dressing changes, which could have led to the statistically significant decline in the number of nursing visits required in the HCSE group at week 12 (P=0.009), and the subsequent reduction in organisational costs (P=0.011). In fact, 12 weeks of horse-chestnut therapy was found to save the community nursing service up to 24% in VLU treatment costs. However, as with many wound-care trials, particularly those with small sample sizes, it is unclear exactly which types of patients the investigated treatment may benefit and how the benefit may be realised. To address this issue, the current study used a comparative multiple-case study design, as well as comparative baseline data from the HAVLUT, to identify the factors that may influence wound healing among patients receiving HCSE. The aim was to illustrate to clinicians, in a manner that preserves the treatment context, the types of patients who are most likely to benefit from HCSE treatment, and the typical response patterns that may be observed among these patients.

Methods

Study design

The study used a comparative multiple-case study design. Data for cases were derived from the HAVLUT, a prospective, double-blind, randomised, placebo-controlled trial examining the efficacy of HCSE for the treatment of VLU.10,11

Unlike experimental designs that focus on specific sets of variables, case studies examine a wide range of factors within the context of a given phenomenon to better understand why individuals progress in a particular manner.12-15 Such an approach is capable of capturing the complex and interactive elements of the human experience. A well-executed case study is characterised by the following elements: a prospective approach; repeated measures; a consistent clinical protocol; overt selection criteria; comparative cases; multiple data collection sources; and a comprehensive description of participants.12,15-17 The use of a comparative multiple-case study design, as well as the sourcing of data from the HAVLUT, meant that all of these criteria were achieved.

Study objectives

The objectives of this study were to:

1. Identify cases characterising a VLU healer and non-healer from the HCSE group within the HAVLUT.
2. Illustrate the typical response patterns observed among patients using HCSE for the management of venous ulceration.
3. Discuss the types of patients that may benefit from the use of HCSE in the management of venous ulceration.

Sample

Cases considered for selection were required to have had a venous leg ulcer that was previously treated with HCSE, and managed using one of three dressing protocols. The rationale and description of these protocols is discussed elsewhere.10 These conditions, in addition to the HAVLUT selection criteria,10 reduced the number of variables that could have influenced wound healing and, therefore, enabled the researcher to isolate factors that best predicted a patient’s response to treatment. Of the 27 HAVLUT participants who met these criteria, two archetypal cases were chosen. These cases were characteristic of a VLU healer and non-healer from the HCSE group within the HAVLUT. As asserted by Yin,12 the use of representative cases was necessary to minimise the risk of misinterpretation.

Logistic regression was initially used to guide the selection of cases by identifying the factors that predicted venous ulcer healing. The small sample and insufficient variability of data, however, did not support the use of logistic regression. Instead, the selection of cases was guided by the comparison of means and medians. In particular, the subjects who most closely matched the medians and means of the healed and non-healed groups of HCSE-treated participants, particularly those variables that were significantly related to wound healing, were selected as representative cases.

Data collection

Following the selection of the two cases, patient data were extracted from the HAVLUT documents and trial database. The most useful sources of information were the participant details form, the written wound assessment tool, and the Alfred–Medseed Wound Imaging System (AMWIS) software. A detailed description of these instruments, as well as the process of data collection, has been reported elsewhere.10
Statistical analysis
Data were analysed using SPSS (version 21.0; Chicago, IL) software. Baseline differences between the healers and non-healers were calculated using chi-squared analysis or Fisher’s exact test for categorical data, and the t-test for independent groups for continuous data. Frequency distributions and percentages were used to describe the categorical data. Measures of central tendency and variability were used for descriptive data where values were approximately normally distributed, while medians and the interquartile range were used to describe continuous data with skewed distributions.

Each of the cases was described and individually analysed using a narrative approach known as explanation building. The patterns of commonality and disparity across cases were also examined. The two cases selected for discussion are presented below, with pseudonyms used in place of real names to protect participant confidentiality. This study was reviewed and approved by the University of South Australia Human Research Ethics Committee.

Results
Twenty-seven participants of the HAVLUT received oral HCSE (375 mg twice daily, standardised to 75 mg aescin) for the treatment of VLU. The wounds under investigation had healed in 12 (44%) subjects within 12 weeks. In comparing the means and medians of the healed and non-healed groups of participants, there were few statistically significant differences between groups; however, there were several marginally significant differences that are worth noting. An archetypal healer typically reported a duration of venous ulceration of 20.5 weeks (P=0.09), an ulcer history of 42 months (P=0.09), wound surface area of 153 mm² (P=0.12), the use of psychotropic medication (P=0.03) and no history of skin grafting (P=0.08) (Table 1). Features characteristic of a non-healer were venous ulcer duration of 51 weeks (P=0.09), ulcer history of 96 months (P=0.09), wound surface area of 430 mm² (P=0.12), non-use of psychotropic medication (P=0.03), and a history of skin grafting (P=0.08) (Table 1). There were no marked differences between groups in terms of age, gender, tobacco use, alcohol use, ankle-brachial pressure index, ulcer location, number of ulcer episodes, blood pressure, body mass index, ankle and calf girth, number of current leg ulcers, wound depth, wound pain, dressing protocol used, frequency of dressing changes, nutritional supplement use, and compliance with HCSE treatment. Cases closely approximating these characteristics (i.e. representing an archetypal healer and non-healer under HCSE treatment), are presented below.

Case study one: healed ulcer
History
Colin was a 53-year-old man who over the past 18 months had reported two episodes of leg ulceration, of which the most recent (i.e. the ulcer under investigation) had been active for 25 weeks. The participant also reported a history of asbestosis, obesity (BMI=37), deep-vein thromboses, epilepsy, hypertension, bilateral patellectomy and appendicectomy. Prescribed medications included morphine, celecoxib, aspirin, sodium valproate, trandolapril, verapamil and mirtazapine. Colin was a non-smoker and consumed on average two standard alcoholic drinks daily.

Baseline assessment
The participant initially presented with a venous ulcer to the right, antero-lateral gaiter. This wound was deep (5 mm), sloughy (55%) and painful (6/10), and was surrounded by dry, macerated and erythematous skin. The wound was dressed in accordance with the primary dressing protocol.

Week-4 assessment
After 4 weeks of HCSE treatment, the ulcer surface area had increased to 156 mm², wound pain rose to 7/10, and the exudate became haemopurulent. Whilst these signs were suggestive of wound infection, in this particular case, they appeared to be indicative of increased autolytic activity. In support of the latter, wound slough had decreased by 71% (to 12%), while the percentage of granulation tissue had increased 2.6-fold (to 88%). Other indicators of improvement included a 47% reduction in wound volume (to 312 mm³), a 46% decrease in surrounding erythema (to 531 mm²), a decline in the amount of exudate and the resolution of periwound maceration (to 0 mm²).

Week-8 assessment
By this point in the trial, both the ulcer under investigation and another leg ulcer had healed, wound pain had fallen to 2/10, and surrounding erythema had dropped a further 27%. Yet, complete wound closure had occurred 1-week prior and, because of this, compression therapy was ceased at week 7. This may explain why ankle diameter increased from 23 cm at week 4 to 27.5 cm at week 8, and why calf circumference rose from 32 cm to 33 cm over the same period. Even so, it is uncertain whether the increase in leg oedema, and the development of a new ulcer 4 weeks after trial discharge, had occurred by chance or had been a direct result of ceasing HCSE and compression therapy. Given that the participant was compliant with HCSE treatment, and that HCSE demonstrates a carry-over effect lasting between 4
and 6 weeks, it is unlikely that inadequate serum aescin levels (the active constituent of HCSE) were a factor.

Case study two: non-healed ulcer

History
Samuel was a 76-year-old man who neither smoked nor consumed alcohol, but was overweight (BMI = 33). The participant had a history of atrial fibrillation, benign prostatic hypertrophy, eczema, lymphoedema, a bilateral angioplasty, and a right shoulder repair. Prescribed medications included aspirin and sotalol. Samuel also self-administered a daily multivitamin.

Baseline assessment
On first examination, the participant was found to have a shallow (1 mm) venous ulcer to the right medio-posterior gaiter. This ulcer was predominantly sloughy (89%), caused little pain (3/10), and was surrounded by dry and macerated tissue. This wound was one of three presenting ulcers that had been active for the past 12 months, and one of eight ulcer episodes that had developed over the last 5 years. The wound was dressed in accordance with the secondary dressing protocol. In addition, the wound was treated with silver sulfadiazine (SSD) cream due to the presence of heavy wound colonisation with Pseudomonas aeruginosa, a gram-negative bacteria often associated with chronic wound infection.18

| Table 1 | Differences in baseline characteristics between healed and non-healed wounds in patients treated with horse-chestnut (Aesculus hippocastanum) seed extract (n=27) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| | Healed group (n=12) | Non-healed group (n=15) | Difference (95% CI) | P-value* |
| Median age, years (IQR) | 76.0 (10.0) | 79.0 (8.0) | -5.1–10.2 | 0.504 |
| Gender, n (%) | | | | |
| Male | 8 (66.7) | 11 (73.3) | - | 1.000 |
| Female | 4 (33.3) | 4 (26.7) | - | |
| Tobacco smoker, n (%) | 0 (0.0) | 3 (20.0) | - | 0.231 |
| Median alcohol consumption, n per day (IQR) | 0.5 (12.3) | 0.0 ± (7.0) | -6.1–2.2 | 0.337 |
| ABPI ± SD | 1.1 ± 0.1 | 1.1 ± 0.1 | -0.1–0.1 | 0.850 |
| Ulcer location, n (%) | | | | |
| Gaiter | 12 (100.0) | 15 (100.0) | - | 1.000 |
| Medial | 8 (66.7) | 10 (66.7) | - | 1.000 |
| Left | 8 (66.7) | 6 (40.0) | - | 0.252 |
| Posterior | 7 (58.3) | 9 (60.0) | - | 1.000 |
| Median duration of presenting ulcer, weeks (IQR) | 20.5 (36.3) | 51.0 (132.0) | -15.8–197.1 | 0.092 |
| Median total of all ulcer episodes, n (IQR) | 3.0 (3.5) | 3.0 (3.0) | 1.0–2.5 | 0.401 |
| Median ulcer history from first to present ulcer, months (IQR) | 42.0 (126.0) | 96.0 (180.0) | -160–195.2 | 0.092 |
| Mean blood pressure ± SD (mmHg) | | | | |
| Systolic | 138.3 ± 16.0 | 136.3 ± 19.6 | -16.4–12.4 | 0.778 |
| Diastolic | 70.8 ± 10.6 | 69.3 ± 11.6 | -10.4–7.4 | 0.732 |
| Mean BMI ± SD (kg/m²) | 29.9 ± 6.8 | 29.7 ± 5.4 | -0.5–4.7 | 0.951 |
| Median ankle diameter, cm (IQR) | 23.0 (2.4) | 23.5 (5.5) | -0.7–4.5 | 0.150 |
| Median calf diameter, cm (IQR) | 28.5 (4.8) | 31.0 (6.0) | -2.0–4.7 | 0.424 |
| Median number of existing leg ulcers, n (IQR) | 2.0 (1.8) | 2.0 (3.0) | -0.9–2.0 | 0.466 |
| Median wound depth, mm (IQR) | 0.5 (2.0) | 1.0 (2.0) | -0.5–1.8 | 0.280 |
| Pain score of ulcer ± SD (0–10 scale) | 5.1 ± 2.8 | 4.1 ± 3.3 | -3.4–1.5 | 0.431 |
| Dressing protocol, n (%) | | | | |
| Primary | 7 (58.3) | 5 (33.3) | | 0.398 |
| Secondary | 4 (33.3) | 7 (46.7) | | |
| Tertiary | 1 (8.3) | 3 (20.0) | | |
| Median frequency of dressing changes, n per week (IQR) | 2.0 (1.8) | 2.0 (1.8) | -0.8–1.3 | 0.746 |
| Median wound surface area, mm² (IQR) | 153.0 (254.8) | 430.0 (1035.0) | -217–1723.2 | 0.120 |
| Uses psychotropic medication, n (%) | 4 (33.3) | 0 | - | 0.028 |
| Uses nutritional supplements, n (%) | 6 (50.0) | 7 (46.7) | - | 1.000 |
| Has a history of skin grafting, n (%) | 0 | 4 (26.7) | - | 0.078 |
| Compliant with HCSE treatment, n (%) | 5 (41.7) | 10 (66.7) | - | 0.258 |

*Based on the mean difference between healed and non-healed cases.
ABPI, ankle brachial pressure index; IQR, interquartile range; (−), not applicable.
fallen to 1/10, and the surface area of granulation tissue had increased by 13% (to 11%). On the other hand, wound surface area had risen by 9%, slough had increased by 8% and ankle (28 cm) and calf girth (31 cm) had remained unchanged. There was also no change in the type or amount of wound exudate, or in the dressings applied.

Week-8 assessment
At week 8, the dressing regime and degree of wound pain (1/10) had remained unchanged, although signs of ulcer deterioration were present. Surface area, for instance, had increased a further 15% (to 538 mm²), wound slough had risen by another 7% (to 82%), and ulcer depth had returned to 1 mm. Although the type and degree of exudate remained the same, the surrounding maceration returned (to 212 mm²). Ankle and calf diameter had also increased to 28.5 cm and 34.5 cm, respectively. The only notable sign of improvement at this time-point was an 83% rise in wound granulation (to 18%) since week 4.

Week-12 assessment
By week 12, the ulcer surface area had reduced by 31%, wound slough had fallen by 25%, and calf diameter had dropped by 1 cm (to 33.5 cm). Other signs, however, were less promising, including a 60% reduction in granulation tissue, a 1 mm increase in wound depth (to 2 mm) and the emergence of another leg ulcer, bringing the total number of ulcers to four. The presence of heavy, green purulent exudate, surrounding excoriation, increased ulcer pain (to 6/10), a rise in ankle diameter (to 30 cm), and an 18-fold increase in periwound maceration were suggestive of heavy wound colonisation with *P. aeruginosa*. Since Samuel was compliant with HCSE treatment, and compression therapy was utilised, it is likely that the presence of wound infection hindered ulcer healing. Throughout the follow-up period, the main ulcer demonstrated signs of improvement, and at 12 weeks’ follow-up, two of the four ulcers had healed; although, given the remote nature of the follow-up, it was not possible to ascertain whether the chronic wound infection had resolved.

Discussion
The current study, through the process of explanation building, has highlighted a number of factors that may influence the trajectory of venous ulcer healing in patients receiving HCSE treatment. It has also illustrated the typical response patterns that may be observed among patients treated with this extract. These elements, if controllable, may be used to improve treatment decisions and patient outcomes by providing a more tailored approach to wound care, and by determining if HCSE treatment is warranted. If uncontrollable, these elements may be used to plan for appropriate ongoing care. The following section examines these factors further by discussing the patterns of commonality and disparity between the healed and non-healed groups.

From the comparison of group means and medians, the factors that predicted wound healing, both statistically significantly and marginally significantly, were wound surface area, ulcer duration, use of psychotropic medication and history of skin grafting. There is no evidence, however, that skin grafting and psychotropic agents influence wound closure directly. Even so, it is possible that the anxiolytic and antidepressant effects of some psychotropic medications may address the adverse effects that anxiety, stress and depression might otherwise have on wound healing.5,19,20

In comparing the two groups, it was observed that smaller wounds healed more rapidly than larger wounds, with the baseline wound surface area in the non-healed cases almost three times that reported in the healed cases. However, studies testing this assumption have generated conflicting results.18,21–25 Hence, the impact that wound surface area has on the rate of ulcer closure warrants further investigation.

A factor differentiating the healed case from the non-healed case was the degree of change in CVI-related outcomes. To illustrate, the amount of wound exudate observed in the healed case consistently decreased over time and whilst compression therapy was *in-situ*, ankle and calf girth remained stable, yet there were no signs of improvement in these parameters in the non-healed case. What this suggests is that patients treated with HCSE who demonstrate improvements in CVI-related outcomes may also demonstrate positive changes in venous ulceration.

One reason why CVI-related outcomes may have improved in the healed case might relate to the cumulative history of ulceration, with the healed case demonstrating a shorter ulcer history than the non-healed case. A possible explanation for this relationship is that the history of ulceration may be correlated with the severity of CVI. To support this claim, two separate studies have found that the effectiveness of HCSE in CVI26 and the rate of venous ulcer healing27 both reduce as the severity of venous insufficiency increases. Thus, HCSE may be most effective in patients with mild to moderate CVI. Venotonic therapy may therefore need to be recommended to patients in the early stages of venous insufficiency to not only reduce the need for compression therapy, but also minimise the associated impact on QoL.26

The most prominent feature to emerge from case two (non-healed case) was the presence of heavy wound colonisation at around 8–12 weeks. Some authorities suggest that this inverse relationship between microbial load and ulcer healing may be the result of increased inflammation and local tissue
Aside from systemic factors, the microbial load of an ulcer is likely to be influenced by the presence of wound slough.29 Thus, treatments that decrease ulcer slough, such as HCSE,10 may reduce the probability of wound infection and, in turn, foster ulcer healing.29 The current study observed that wound slough decreased consistently over time in the HCSE-healed case but not in the non-healed case, which suggests that a significant reduction in wound slough and a corresponding rise in the percentage of granulation tissue within the first 4 weeks of therapy may be a desirable pattern of response to HCSE treatment. It should be noted at this point, however, that a corresponding increase in wound pain and surface area within the first 4 weeks of HCSE treatment should not be mistaken for signs of wound deterioration. Instead, any decision to cease HCSE therapy should be reserved until at least 8 weeks after the commencement of treatment when noticeable signs of improvement are likely to occur.

Conclusions

By utilising a comparative case design, the current study has identified a number of variables that may influence venous ulcer healing while undergoing HCSE treatment, such as wound surface area and ulcer duration. The study has also highlighted that HCSE treatment may be most effective in those with mild to moderate CVI, smaller, less chronic wounds, a shorter history of ulceration and in those without signs of wound infection. Yet, given the limitations of the case study design and the lack of statistically significant predictors in the case selection process, such claims cannot be generalised to the wider population. The current study has instead used patterns of commonality and disparity to add to existing theories and highlighted areas for further research in order to improve future study design, treatment success, patient care and QoL.

Conflict of interest The Author is the Technical Editor for FACT.

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References


22 Warriner RA, Snyder RJ, Cardinal MH. Differentiating diabetic foot ulcers that are unlikely to heal by 12 weeks following achieving 50% percent area reduction at 4 weeks. *Intern Wound J* 2011; **8**: 632–7.


27 Trostrup H, Bjarnsholt T, Kirketerp-Moller K et al. What is new in the understanding of non healing wounds. *Ulcers* 2013; **2013**: Article ID 625934.


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