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ORIGINAL ARTICLE

A randomized controlled trial evaluating the effectiveness of autologous fibroblast culture in the healing of chronic venous leg ulcers at a tertiary care hospital in Sri Lanka

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Abstract

Background: Chronic venous leg ulcers are a common cause of morbidity and reduced quality of life, with many ulcers demonstrating delayed healing despite standard compression therapy. Fibroblasts play a central role in wound healing, and autologous fibroblast culture has emerged as a potential adjunctive therapy for chronic wounds. This study evaluated the effectiveness of autologous fibroblast culture combined with compression therapy in the healing of chronic venous leg ulcers.

Methods: A randomized controlled trial was conducted at the National Hospital of Sri Lanka from August 2019 to March 2020. Adults with chronic venous leg ulcers were randomized to either an experimental group receiving autologous fibroblast culture suspended in collagen mesh with four-layer compression therapy or an active control group receiving collagen mesh with compression therapy alone. Ulcer area was assessed weekly for 12 weeks using digital planimetry. Percentage reduction in ulcer area from baseline was analysed using a linear mixed-effects model to compare healing trajectories between groups.

Results: Nineteen participants were enrolled, and 17 completed the study (8 experimental, 9 active control). Complete ulcer healing was not observed in either group within the 12-week follow-up period. However, the experimental group demonstrated a significantly faster rate of ulcer healing over time compared with the active control group. Linear mixed-effects analysis showed a significant interaction between treatment group and time ($\beta = 0.271$, SE = 0.082, $P = 0.001$), indicating a greater reduction in ulcer area in the experimental group. No clinically significant adverse events were observed during follow-up.

Conclusion: Autologous fibroblast culture combined with compression therapy showed a favourable trend in healing chronic venous leg ulcers compared with compression therapy alone. The intervention appeared safe and may have potential as an adjunctive therapy. Larger studies with longer follow-up and stronger statistical power are required to establish efficacy, practicality, and cost-effectiveness.

Keywords: autologous fibroblast culture; chronic venous leg ulcer; compression therapy; wound healing; randomised controlled trial

Conflicts of Interest: None declared

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Introduction

A chronic leg ulcer is defined as an ulcer that shows no tendency to heal after 3 months of appropriate treatment, or that has not healed within 12 months.[1] The global prevalence of chronic leg ulcer ranges from 1.9-13.1%.[2] Venous disease is the commonest cause of chronic leg ulceration worldwide.[3] Also, it is associated with considerable pain, disability, impaired mobility, sleep disturbance, social isolation, and reduced quality of life.[4] Chronic venous leg ulcers also create a substantial economic burden for health services and for patients. The annual cost for treating chronic leg ulcer patients globally is estimated at some 25 million US dollars.[5]

Compression therapy remains the cornerstone of treatment for chronic venous leg ulcers. However, a considerable proportion of ulcers heal slowly or recur, highlighting the need for adjunctive therapies that enhance tissue repair. Wound healing depends on haemostasis, inflammation, cellular proliferation, and remodelling.[6] Fibroblasts have a central role in these processes through extracellular matrix production, secretion of growth factors and cytokines, and wound contraction after transformation into myofibroblasts.

Advances in tissue engineering have led to renewed interest in cellular therapies for chronic wounds. Fibroblasts, keratinocytes, platelet-rich preparations, and stem-cell-based approaches have all been explored.[7] Studies of bioengineered skin substitutes and allogeneic fibroblast-based products suggest potential benefits in chronic wounds, including venous ulcers.[8] Although autologous fibroblast culture has shown promise in other chronic wounds, evidence in chronic venous leg ulcers remains limited. This study, therefore, assessed whether autologous fibroblast culture combined with compression therapy improves the healing of chronic venous leg ulcers compared with compression therapy alone. The objectives of this study were to compare both the complete ulcer healing and the linear rate of ulcer healing in patients treated with a combination of autologous fibroblast culture and compression therapy versus those treated with compression therapy alone.

Methods

Study Design and Setting: This was a randomised controlled trial conducted at the Professorial Vascular Unit and other general surgical clinics of the National Hospital of Sri Lanka. Recruitment took place from 1 August 2019 to 1 March 2020.

Eligibility Criteria: Adults older than 18 years with a confirmed single chronic venous leg ulcer measuring 3-25 cm in diameter and present for 12-104 weeks were eligible. Exclusion criteria were peripheral arterial disease, uncontrolled diabetes mellitus (glycated haemoglobin >8% or more than two fasting blood glucose values >250 mg/dL within

the previous 6 months), peripheral neuropathy, haemoglobin <10 g/dL, clinical evidence of infection, documented osteomyelitis at the ulcer site, surgical or non-surgical intervention to improve venous return within the previous month, hypersensitivity to collagen dressing, intolerance to compression therapy, pregnancy, lactation, and refusal to provide consent.

Sample Size and Sampling: The planned sample size was 15 participants per arm, based on proportions derived from a prior study of fibroblast-based therapy in venous leg ulcers. Patients attending the vascular clinic were selected by simple random sampling using a random number table and then randomised equally to the experimental or active control group with allocation concealment. Recruitment was limited by the onset of the COVID-19 pandemic. Nineteen eligible patients consented to participate.

Interventions: A 5mm punch biopsy was obtained from the inner aspect of the arm under local anaesthesia using 2% lidocaine under aseptic conditions. The sample was transported on ice to the Faculty of Science, University of Colombo, where the dermis was separated and cultured under sterile conditions within a biosafety cabinet. Fibroblasts were expanded, suspended in collagen mesh, and prepared at a concentration of 10 million cells/mL. Fibroblast culture required 10-14 days.

Before application, the ulcer was cleansed, and the ulcer base was gently abraded with a No. 15 scalpel blade until pinpoint bleeding occurred. The experimental group received autologous fibroblast culture suspended in collagen mesh at weeks 0, 2, and 4, together with four-layer compression bandaging. The active control group received collagen mesh with four-layer compression bandaging. Compression was applied by a trained medical officer.

Outcome Assessment: Ulcer area was assessed at each visit by digital planimetry using standardised digital photographs. Participants were followed until complete healing or for 12 weeks, whichever occurred first. Complete healing was defined as complete re-epithelialisation. The healing rate was calculated from the change in ulcer area over the observation period. Adverse events, including pain, itching, and clinical infection, were monitored.

Statistical Analysis: Ulcer measurements were recorded weekly for 12 weeks in both experimental and active control groups. To account for differences in baseline ulcer size between patients, the percentage reduction from baseline ulcer size was calculated for each weekly measurement using the formula:

Percentage reduction = [(baseline ulcer area − weekly ulcer area) / baseline ulcer area] × 100.

A linear mixed-effects model was used to evaluate changes in percentage ulcer reduction over time between groups. The model included week, treatment group, and the interaction between week and treatment group as fixed effects, with patient included as a random effect to account for repeated measurements within individuals. The interaction term (week × group) was used to determine whether the rate of healing differed significantly between the two groups.

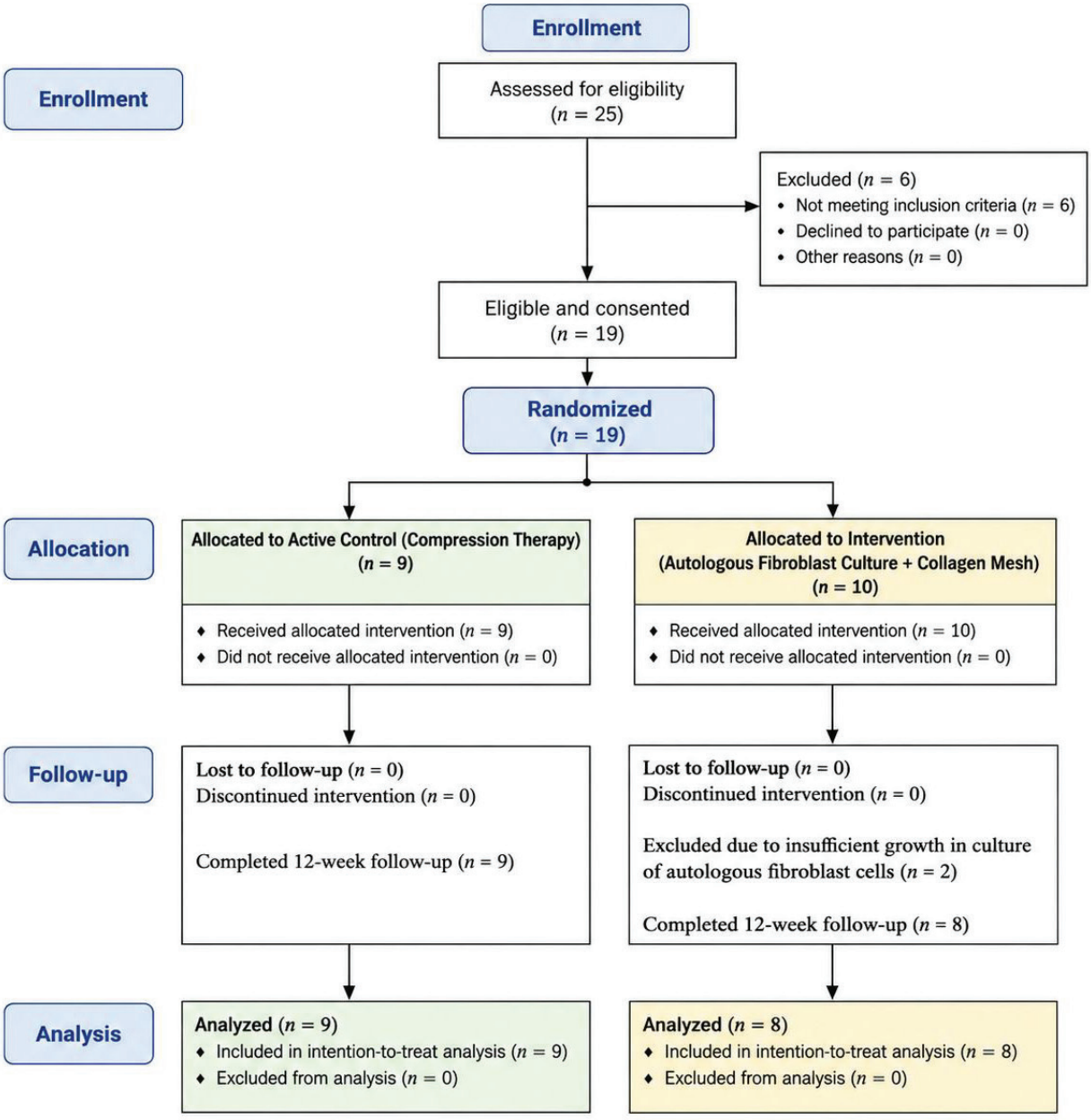
Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria) with the lme4 and lmerTest packages. A *P*-value < 0.05 was considered statistically significant.

Data were analyzed using a per-protocol approach. Two participants allocated to the intervention group initially were excluded before treatment initiation due to insufficient fibroblast culture growth, while all remaining participants completed the 12-week follow-up and were included in the final analysis.

Ethics: Written informed consent was obtained from all participants. Ethical approval was granted by the Ethics Review Committee of the National Hospital of Sri Lanka.

Results

A total of 25 patients were screened for eligibility, of whom 19 were eligible and consented to participate. Two participants allocated to the experimental arm were excluded prior to treatment initiation due to inadequate growth of autologous fibroblast cultures. None of the participants withdrew during the study period. Final analysis included 17 participants, comprising 8 in the experimental group and 9 in the active control group. Participant recruitment, allocation, follow-up, and analysis are summarized in the CONSORT flow diagram (Figure 1).



ITT, Intention-to-treat.
Two participants in the intervention group were excluded before treatment initiation due to insufficient growth in culture of autologous fibroblast cells. No participants withdrew from the study.

Figure 1. CONSORT flow diagram of participant recruitment, randomization, follow-up, and analysis.

The mean age of participants was 57.37 ± 10.03 years in the experimental group and 54.55 ± 14.88 years in the active control group, with no statistically significant difference between groups (P=0.700). Sex distribution, education level, financial status, smoking status, diabetes mellitus, hypertension, and dyslipidaemia were also comparable between groups (Table 1). Baseline clinical characteristics, including baseline ulcer area, ulcer duration, duration of varicose veins, and ulcer site, showed no statistically significant differences between groups (Table 2).

Table 1. Baseline demographic characteristics of participants

Demographic factors	Groups		*P* Value
	Experimental group (n=8)	Active control group (n=9)	
Age (Mean ± SD) (years)	57.37 ± 10.03	54.55 ± 14.88	0.700†
Gender			
Male	4(50.0)	5(55.6)	1.000*
Female	4(50.0)	4(44.4)	
Education levels			
Up to A/L	7(87.5)	8(88.9)	1.000*
Diploma/Degree	1(12.5)	1(11.1)	
Financial Status			
Rs <25000	4(50.0)	5(55.6)	
Rs 25000-50000	3(37.5)	3(33.3)	1.000*
Rs >50000	1(12.5)	1(11.1)	
Smoking			
Yes	2(25.0)	2(22.2)	1.000*
No	6(75.0)	7(77.8)	

† Independent samples t-test
* Fisher's exact test

Table 2. Baseline clinical characteristics of participants

Clinical characteristics	Groups		*P* Value
	Experimental group (n=8)	Active control group (n=9)	
Baseline ulcer area (cm²), Mean ± SD	39.23 ± 24.30	27.94 ± 19.84	0.316†
Ulcer duration (months), Mean ± SD	46.63 ± 27.41	40.89 ± 26.16	0.666†
Duration of varicose veins (years), Mean ± SD	11.00 ± 4.00	9.78 ± 3.77	0.528†
Ulcer site			
Right leg	5 (62.5)	5 (55.6)	1.000*
Left leg	3 (37.5)	4 (44.4)	
Diabetes mellitus	2 (25.0)	3 (33.3)	1.000*
Hypertension	3 (37.5)	4 (44.4)	1.000*
Dyslipidaemia	3 (37.5)	2 (22.2)	0.620*

Continuous variables were compared using the independent samples t-test (†).
Categorical variables were compared using Fisher's exact test (*)

Ulcer healing trajectories differed between the two groups over 12 weeks. In the experimental group, 7 of 8 participants (87.5%) showed a reduction in ulcer size by week 12, while 1 participant (12.5%) showed an increase. In the control group, 4 of 9 participants (44.4%) showed a reduction in ulcer size, 2 (22.2%) showed an increase, and the remainder showed little or no change. The experimental group demonstrated a more consistent healing trend across follow-up, whereas the control group showed greater fluctuation, particularly around weeks 3 and 4 (Figures 2 and 3).

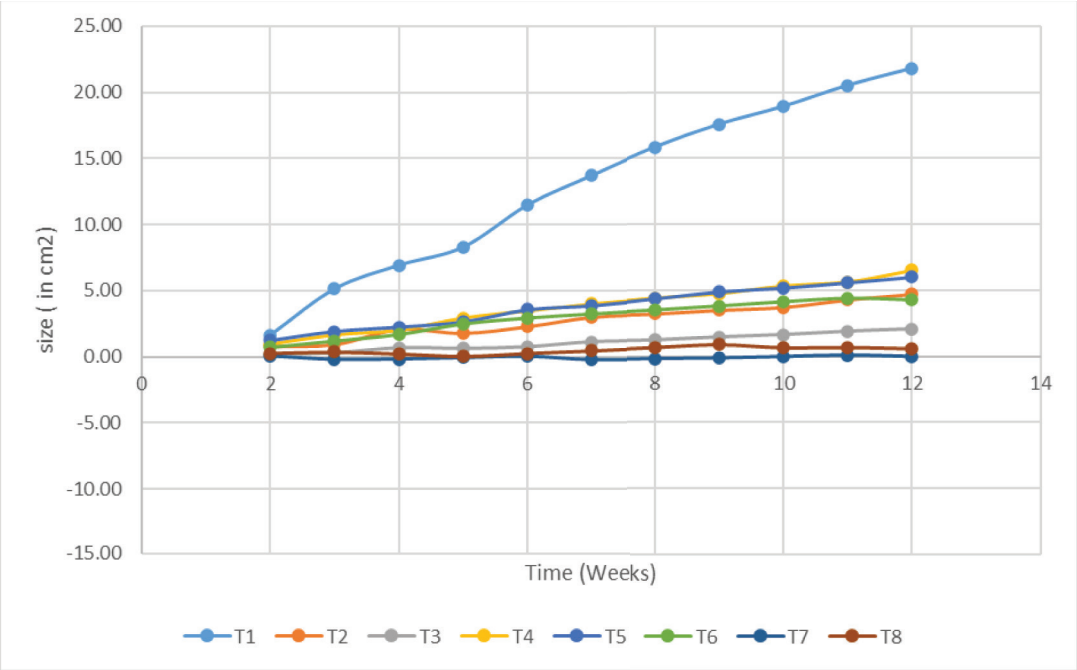


Figure 2. Change in ulcer area over 12 weeks in participants receiving autologous fibroblast therapy.

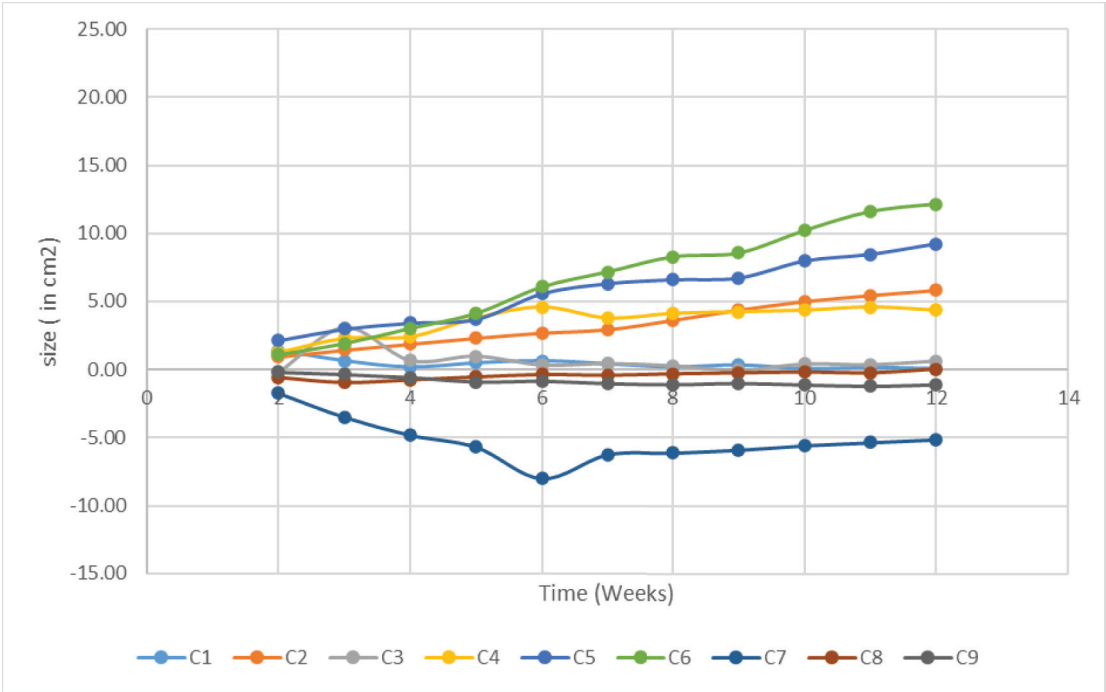


Figure 3. Change in ulcer area over 12 weeks in the active control group.

Mean ulcer area in the experimental group decreased from 39.22 ± 24.29 cm^2 at baseline to 35.81 ± 18.14 cm^2 at week 12. In the active control group, the mean ulcer area decreased from 27.94 ± 19.84 cm^2 to 27.24 ± 19.15 cm^2 over the same period. Although the experimental group had a numerically larger mean baseline ulcer area compared with the control group (39.23 ± 24.30 cm^2 vs 27.94 ± 19.84 cm^2), the difference was not statistically significant (P=0.316).

Both groups demonstrated progressive reduction in ulcer size over the 12-week follow-up period. However, the experimental group showed a significantly faster rate of healing compared with the control group. Complete ulcer healing was not observed in either treatment arm within 12 weeks, although one participant in the experimental group reportedly achieved complete wound closure by 24 weeks outside the primary study period.

Linear mixed-effects analysis of percentage reduction in ulcer size demonstrated a significant interaction between treatment group and time (β = 0.271, SE = 0.082, P = 0.001), indicating that the rate of ulcer healing over time was significantly greater in the experimental group than in the control group (Figure 4).

These findings suggest that the intervention used in the test group significantly accelerated ulcer healing compared with standard treatment.

No clinically significant adverse events, including worsening pain, itching, or signs of infection, were observed during the 12-week study period.

Control line = average % healing each week across control patients

Test line = average % healing each week across test patients

$$\text{“Percent Reduction”}_{ij} = \beta_0 + \beta_1 (\text{Week}_i) + \beta_2(\text{Group}_i) + \beta 3 (\text{Week}_{ij} \times \text{Group}_i) + u_i + \epsilon_{ij}$$

Where:

β_0 = intercept β_1 = effect of time (week)

β_2 = effect of treatment group

β_3 = interaction between week and group

$u_{\_i}$ = random effect for patients

ϵ_{ij} = residual error

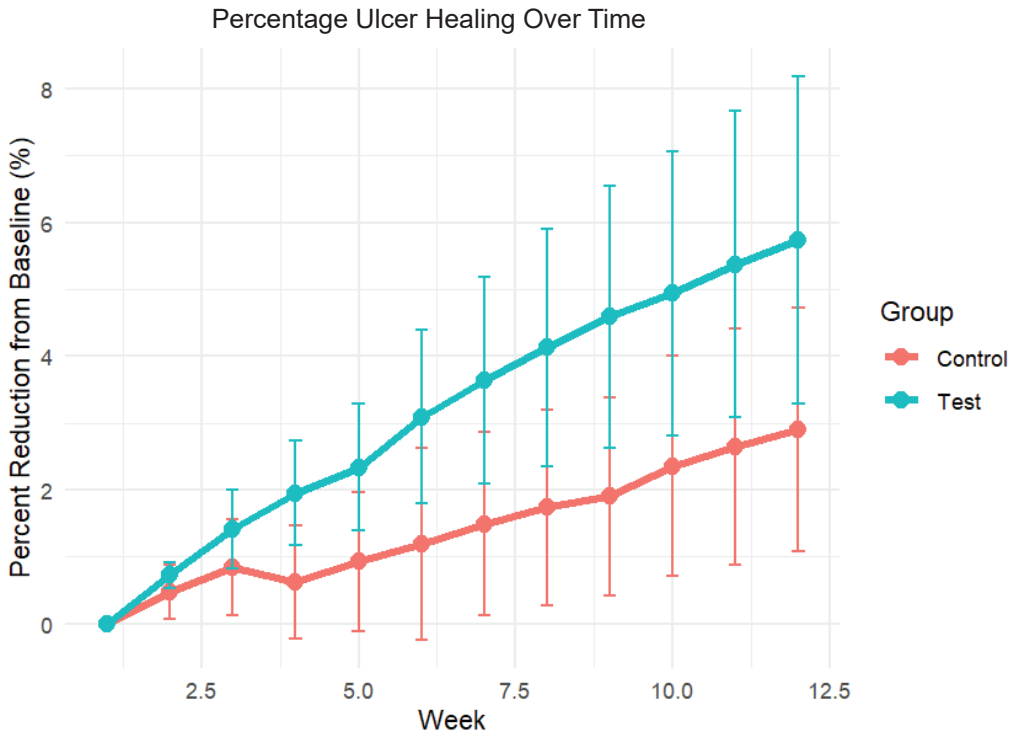


Figure 4. The average ulcer healing rate over 12 weeks between the experimental and active control groups.

Discussion

This randomised controlled trial explored the use of autologous fibroblast culture as an adjunct to compression therapy for chronic venous leg ulcers. Although complete ulcer healing was not achieved within the 12-week follow-up period, the intervention group demonstrated a faster rate of ulcer healing over time compared with the active control group. These findings suggest that autologous fibroblast culture may accelerate wound healing in chronic venous leg ulcers.

The findings are biologically plausible. Fibroblasts are central to wound healing through collagen synthesis, extracellular matrix formation, cytokine production, and wound contraction. Chronic venous ulcers are associated with fibroblast dysfunction and cellular senescence, which may impair repair.[9] Introducing viable autologous fibroblasts could therefore help restore a more favourable healing microenvironment. The present findings are also directionally consistent with prior work on fibroblast-containing bioengineered dressings and other cell-based therapies in chronic wounds.

This study has several strengths. It addressed an important clinical problem in a Sri Lankan tertiary-care setting, used a randomised comparative design, and employed serial digital planimetry for ulcer measurement. Safety findings were reassuring, with no clinically significant adverse events reported.

Several limitations of this study should be acknowledged. Although the experimental group demonstrated a statistically significant faster rate of ulcer healing compared with the control group, the relatively small sample size and short follow-up duration limit the strength and generalizability of the findings. Larger studies with broader patient cohorts and longer follow-up are required to determine the long-term clinical effectiveness and sustainability of healing outcomes.

Furthermore, the study was underpowered. The intended sample size was 15 participants per arm, but recruitment was curtailed by the COVID-19 pandemic, and only 17 participants were analysed. In addition, two patients randomised to the intervention group could not receive treatment because adequate fibroblast culture could not be generated, illustrating an important practical limitation of this approach. The 12-week follow-up period may also have been too short to capture the full benefit of a regenerative intervention in chronic venous ulcers.

In addition, the cost associated with autologous fibroblast culture, approximately 10-fold higher than active control treatment, and technical demands may limit its feasibility in routine clinical practice. While the higher upfront cost cannot currently be justified based on the present findings alone, autologous fibroblast therapy may still offer potential long-term economic value.

Overall, the study suggests that autologous fibroblast culture may have therapeutic promise as an adjunctive treatment for chronic venous leg ulcers, but definitive conclusions cannot yet be drawn. Larger, methodologically robust trials with longer follow-up, predefined primary endpoints, and formal cost-effectiveness assessment are needed before routine adoption can be recommended.

Conclusion

Autologous fibroblast culture combined with compression therapy showed a favourable trend in healing chronic venous leg ulcers compared with compression therapy alone. The intervention appeared safe and may have potential as an adjunctive therapy. Larger studies with longer follow-up and stronger statistical power are required to establish efficacy, practicality, and cost-effectiveness.

Ethics statement

Written informed consent was obtained from all participants. The Ethics Review Committee of the National Hospital of Sri Lanka granted ethical approval.

Author contributions

MN conceived the study, developed the research proposal, acquired funding, recruited participants, performed the skin biopsies, led the clinical execution of the study, and drafted the manuscript. JA supervised the study, provided overall guidance and oversight, and critically revised the manuscript. JS contributed to the conceptual development of the study and provided intellectual input into the study design and methodology. RC supported patient recruitment and clinical management. PR was responsible for the laboratory and technical aspects

of the study, including transport of biopsy specimens, fibroblast culture and expansion, and preparation and return of cultured cells for clinical application. PU supported the laboratory aspects of the study. HR performed statistical analysis, including sample size calculation, data analysis, and interpretation of the statistical findings.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

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