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A prospective observational study on management approaches for non-healing ulcers in dermatology: From conventional to advanced modalities.

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Abstract
Background:
Non-healing ulcers are a major dermatological challenge, leading to prolonged morbidity, infection, and impaired quality of life. Conventional care often fails to achieve complete healing, prompting the need for advanced modalities such as Negative Pressure Wound Therapy (NPWT), Platelet-Rich Fibrin (PRF), growth factors, and skin substitutes.

Methods:
A prospective observational study was conducted at a tertiary care hospital from February 2024 to February 2025, enrolling 105 patients with ulcers persisting beyond six weeks. Participants were randomized into three groups (n=35 each): (i) Conventional care (saline dressings, antibiotics, compression/off-loading), (ii) Advanced A (NPWT with topical growth factor), and (iii) Advanced B (PRF with bioengineered skin substitute). Baseline evaluation included demographics, comorbidities, ulcer type, size, and duration. Patients were followed weekly for 12 weeks. The primary outcome was the percentage reduction in ulcer area; secondary outcomes included time to granulation, complete healing rate, and infection control. Data were analyzed using SPSS v26.0 with ANOVA and Chi-square tests, considering $p<0.05$ as significant.

Results:
Baseline characteristics were comparable across groups ($p>0.05$). At 12 weeks, mean ulcer area reduction was 40% in the Conventional group, 80% in Advanced A, and 78% in Advanced B ($p<0.001$). Mean time to granulation was significantly shorter with advanced modalities (12.5 ± 4.8 days in Advanced A; 13.1 ± 5.2 days in Advanced B) versus Conventional care (24.2 ± 6.1 days). Complete healing occurred in 75%, 90%, and 87.5% of patients, respectively.

Conclusion:
Advanced wound therapies, particularly NPWT with growth factors and PRF with skin substitutes, markedly accelerate granulation, enhance ulcer area reduction, and improve healing outcomes compared to conventional care.

Recommendations:
Incorporation of advanced modalities into standard dermatological wound management is advised, with future multicentric trials warranted to evaluate cost-effectiveness and establish standardized treatment protocols.

Keywords: *Non-healing ulcers, Negative Pressure Wound Therapy, Platelet-rich fibrin, Skin substitutes, Growth factors, Wound healing.*
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Introduction
Chronic and non-healing ulcers represent a major clinical challenge in dermatology and allied medical specialties, owing to their persistent nature, underlying comorbidities, and high recurrence rates. By definition, an ulcer is a discontinuity in the skin or mucous membrane that results in the loss of surface tissue, disintegration, and necrosis of epithelial layers, usually accompanied by an inflammatory

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response.1 While acute ulcers generally undergo orderly healing within weeks through the sequential phases of hemostasis, inflammation, proliferation, and remodeling, non-healing or chronic ulcers are those that persist for more than three months or fail to show significant healing despite appropriate conventional treatment. Epidemiological data suggest that chronic ulcers affect nearly 1–2% of the global population, with a higher incidence among the elderly and in individuals with comorbid conditions such as diabetes mellitus, peripheral arterial disease, chronic venous insufficiency, neuropathy, and immunocompromised states. In India, dermatology clinics frequently encounter diabetic foot ulcers, venous stasis ulcers, pressure sores, and post-infectious ulcers arising from conditions like leprosy, cutaneous tuberculosis, and atypical mycobacterial infections, making this problem especially relevant in routine practice.2

The pathophysiology of non-healing ulcers is complex and multifactorial. It often involves a prolonged and dysregulated inflammatory phase that fails to transition into effective granulation and remodeling. Persistent microbial infection, impaired vascular supply, repeated local trauma, and neuropathy are common contributors, while systemic conditions such as diabetes or malnutrition further compromise host immune defenses and tissue repair.3 Additionally, the formation of microbial biofilms within chronic wounds provides bacteria with a protective environment that reduces antibiotic efficacy and shields them from immune clearance, thereby acting as a significant barrier to healing. Based on etiology, non-healing ulcers can be broadly classified into several types. Venous ulcers, the most common, arise due to chronic venous insufficiency and typically manifest as shallow, exudative ulcers over the gaiter region of the lower limb. Arterial ulcers, in contrast, result from peripheral arterial disease and present as painful, punched-out lesions often located over distal extremities or pressure points.4 Diabetic foot ulcers, caused by a combination of neuropathy, ischemia, and infection, are particularly notorious for their morbidity and risk of amputation. Pressure ulcers or decubitus ulcers occur in immobilized patients due to prolonged compression over bony prominences, whereas infectious ulcers may be secondary to tuberculosis, leprosy, syphilis, or fungal infections. Malignant ulcers, such as Marjolin's ulcer, arise from chronic ulcer scars undergoing malignant transformation, while other miscellaneous causes include vasculitic ulcers, pyoderma gangrenosum, and sickle-cell disease-associated ulcers.5

The management of such ulcers poses several challenges, as conventional treatment strategies often fail to achieve complete or sustained healing. Standard approaches like surgical or enzymatic debridement, systemic and topical antibiotics, and antiseptic therapy are useful for wound bed preparation and infection control, while moist wound healing using hydrocolloids, alginates, and foam dressings aims to maintain an optimal healing environment. Compression therapy remains the mainstay for venous ulcers, and off-loading using specialized footwear or total contact casting is crucial in diabetic ulcers. In addition, nutritional supplementation, including protein, vitamin C, and zinc, plays a supportive role in wound repair. Despite these measures, many ulcers remain unresponsive, leading to chronic morbidity, repeated hospital visits, financial strain, and significant impairment of quality of life.6

Over recent years, this unmet clinical need has driven the development of advanced wound-healing modalities that target the underlying pathophysiological deficits. Negative Pressure Wound Therapy (Negative Pressure Wound Therapy) has gained prominence by applying controlled suction to wounds, thereby stimulating angiogenesis and granulation tissue formation while reducing exudate and bacterial load. Topical growth factors, such as recombinant platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), have been employed to accelerate cellular proliferation and re-epithelialization. Skin substitutes, including bioengineered human skin equivalents and dermal matrices, provide structural support and biological signals that facilitate tissue regeneration.7 Autologous Platelet-Rich Fibrin (PRF) therapy has emerged as an attractive option due to its high concentration of growth factors derived from the patient's own blood, while Hyperbaric Oxygen Therapy (HBOT) enhances oxygen delivery in ischemic and infected wounds, thereby promoting angiogenesis and immune defense. More recently, stem cell-based therapies and tissue engineering approaches have opened new frontiers in regenerative dermatology, while adjunctive techniques such as low-level laser therapy and photodynamic therapy have shown promise in enhancing microcirculation, reducing microbial burden, and modulating inflammation.8

Taken together, the management of non-healing ulcers has undergone a paradigm shift, moving beyond conventional wound care to incorporate regenerative, biological, and technological innovations. These strategies not only aim at accelerating closure but also focus on restoring functional integrity and improving aesthetic outcomes. The present

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article, therefore, evaluates the wide spectrum of management modalities for non-healing ulcers in dermatology, compares their efficacy, and highlights the role of advanced interventions in improving overall patient outcomes.9

Rationale of this study

Non-healing ulcers impose a significant health and economic burden, often leading to prolonged morbidity, recurrent infections, and poor quality of life. Conventional therapies frequently fail in patients with comorbidities or poor vascular supply, necessitating advanced approaches like Negative Pressure Wound Therapy, Platelet-Rich Fibrin (PRF), and skin substitutes, Placentrex, Topical insulin & lasers. However, evidence comparing these newer modalities with standard care is limited, particularly in resource-constrained settings. Hence, this study aims to evaluate and compare conventional and advanced treatments to identify effective, practical strategies for managing non-healing ulcers in dermatology.

Materials and Methods

Study Design

A prospective observational study was conducted in the Department of Dermatology at a tertiary care hospital between February 2024 and February 2025.

Study Population

Patients attending Dermatology OPD/IPD with chronic, non-healing ulcers (>6 weeks duration).

Inclusion Criteria

Patients aged >18 years with ulcers persisting beyond 6 weeks.
Both genders.
Ulcers of venous, diabetic, arterial, infectious, or pressure origin.

Exclusion Criteria

Malignant ulcers confirmed by biopsy.
Patients on systemic immunosuppressive therapy.
Pregnant or lactating women.

Sample Size

A total of 105 patients were enrolled. They were randomly assigned to three groups (35 each):
Conventional care group – standard wound care, debridement, antibiotics, moist dressings.
Advanced therapy group A: Negative Pressure Wound Therapy and growth factor application.
Advanced therapy group B: Platelet-Rich Fibrin (PRF), Placentrex, Topical insulin. At baseline, all enrolled patients underwent a detailed clinical evaluation that included recording of demographic details, relevant medical history, and assessment of comorbidities such as diabetes, hypertension, and peripheral vascular disease. Each ulcer was carefully examined to document its type, anatomical location, size, depth, duration, presence of infection, and associated complications. To support clinical assessment, laboratory investigations, including HbA1c, lipid profile, and, where indicated, Doppler studies, were performed to evaluate vascular status and systemic risk factors that could influence healing outcomes. Based on random allocation, patients were divided into three groups with distinct treatment protocols. The conventional care group received standard therapy in the form of regular saline dressings, appropriate systemic antibiotics when infection was present, compression bandaging for venous ulcers, and off-loading devices or footwear for diabetic foot ulcers. The advanced therapy group A was managed with cycles of Negative Pressure Wound Therapy applied for 72 hours at a time, which was supplemented by topical application of growth factors to stimulate tissue regeneration and accelerate wound healing.

The advanced therapy group (Group B) received autologous Platelet-Rich Fibrin (PRF) prepared from the patient's own blood, which was injected perilesionally and applied directly over the wound bed. This was combined with the use of bioengineered skin substitutes such as Integra or collagen sheets, serving as a biological scaffold to facilitate epithelialization and granulation tissue formation. Additional adjunctive therapies included Placentrex extract for its regenerative and anti-inflammatory properties, topical insulin, particularly for chronic non-healing and Trophic ulcers to promote angiogenesis and cellular proliferation, and in selected cases of vascular ulcers (e.g., ulcerative angiokeratoma) to improve microcirculatory dynamics. Furthermore, the role of laser-based therapies was considered in enhancing wound healing through stimulation of neovascularization, collagen remodeling, and reduction of microbial burden.

All patients across the three groups were followed up every week for a duration of 12 weeks. At each visit, detailed assessments were made regarding the percentage reduction in ulcer area, the time to appearance of healthy granulation tissue, the extent of infection control, and subjective pain

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scores. These serial evaluations provided a comprehensive measure of treatment response, allowing for systematic comparison of the efficacy of conventional versus advanced modalities in promoting healing of non-healing ulcers.

Effort to Remove Bias

To reduce bias, random allocation with concealed envelopes ensured unbiased group assignment. Standardized treatment and follow-up minimized performance bias, while blinded assessors and analysts reduced observer and analytical bias. Objective measurements and consistent data collection limited measurement errors, enhancing study validity and reliability.

Outcome Measures

Primary outcome

Percentage reduction in ulcer area at 12 weeks.

Secondary outcomes

Time to appearance of healthy granulation tissue, infection control, rate of complete healing, patient satisfaction, and recurrence.

Statistical Analysis

Data were analyzed using SPSS v26.0. Continuous variables (e.g., age, ulcer size, area reduction) were presented as mean ± SD and compared using the ANOVA test. Within-group changes over time were assessed with repeated measures ANOVA. Categorical variables (e.g., ulcer type, comorbidities, healing rates) were expressed as percentages and compared using the Chi-square test. A p-value <0.05 was considered statistically significant, and analysis followed the intention-to-treat principle.

Ethical consideration

The study was conducted after obtaining approval from the Institutional Ethics Committee of the institute. Written informed consent was obtained from all participants before enrollment, ensuring voluntary participation and confidentiality of data as per the principles of the Declaration of Helsinki (2013 revision). Participants were informed about the study objectives, procedures, potential risks, and benefits, and their right to withdraw at any stage without affecting their standard medical care was respected.

Observations

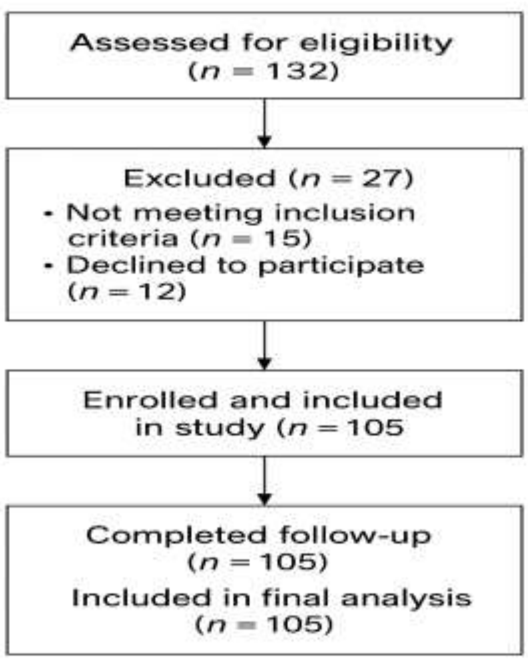

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Table 1. Baseline Characteristics of Patients (n=105)

Parameter	Conventional (n=35)	Advanced A (n=35)	Advanced B (n=35)	p-value
Mean Age (years)	52.1 ± 11.3	50.9 ± 12.7	49.8 ± 13.1	0.72
Male: Female ratio	23:12	21:14	22:13	0.91
Diabetes (%)	21 (60%)	20 (57%)	19 (54%)	0.83
Venous ulcer (%)	14 (40%)	13 (37%)	12 (34%)	0.77
Mean Ulcer Duration (months)	6.5 ± 2.4	6.2 ± 2.7	6.0 ± 2.3	0.68

The three groups—Conventional, Advanced A, and Advanced B—were comparable at baseline, with no statistically significant differences in demographic or clinical characteristics. The mean age was around 50 years across groups, with a similar male-to-female distribution. The prevalence of diabetes ranged from 54% to 60%, and venous ulcers were present in approximately one-third to two-fifths of participants. The mean ulcer duration was also similar (6.0–6.5 months). The p-values for all parameters were >0.05, confirming that the groups were well matched and comparable for subsequent outcome analysis.

Tab 2: Blood investigations of study subjects

Parameter	Conventional (n=35)	Advanced A (n=35)	Advanced B (n=35)	*p*-value
HbA1c (%)	6.61 ± 0.78	6.82 ± 0.81	6.79 ± 0.87	0.412
Fasting Blood Glucose (mg/dL)	101.3 ± 18.4	104.7 ± 19.2	101.2 ± 19.1	0.638
Postprandial Glucose (mg/dL)	143.2 ± 33.1	147.9 ± 35.8	147.4 ± 33.5	0.712
Total Cholesterol (mg/dL)	181.6 ± 32.2	184.3 ± 31.5	187.8 ± 34.8	0.673
LDL Cholesterol (mg/dL)	109.4 ± 27.6	113.2 ± 28.9	114.3 ± 29.3	0.582
HDL Cholesterol (mg/dL)	44.9 ± 9.7	45.0 ± 9.4	44.3 ± 9.5	0.933
Triglycerides (mg/dL)	153.6 ± 45.1	155.9 ± 46.8	161.3 ± 48.0	0.739

The comparison of blood investigation parameters among the three groups—Conventional, Advanced A, and Advanced B—showed no statistically significant differences ($p > 0.05$) across all measured variables. Mean HbA1c levels and glucose values were comparable, indicating similar glycemic control among groups. Likewise, total cholesterol, LDL, HDL, and triglyceride levels showed minimal variation, suggesting uniform lipid profiles. Overall, the biochemical parameters were well balanced across the study groups, confirming baseline comparability.

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Tab 3: Distribution of study subjects as per comorbidity

Comorbidity	Conventional (n=35)	Advanced A (n=35)	Advanced B (n=35)	*p*-value
Hypertension	14 (40.0%)	16 (45.7%)	15 (42.9%)	0.876
Diabetes Mellitus	12 (34.3%)	13 (37.1%)	14 (40.0%)	0.861
Peripheral Vascular Disease (PVD)	5 (14.3%)	6 (17.1%)	4 (11.4%)	0.789

The distribution of comorbidities—hypertension, diabetes mellitus, and peripheral vascular disease (PVD)—was comparable across the three study groups. Hypertension was the most common comorbidity, present in about 43% of participants, followed by diabetes in 37% and PVD in 14%. None of these differences were statistically significant (p > 0.05), indicating that the three groups were well matched with respect to baseline comorbid conditions, ensuring that these factors did not influence subsequent outcome comparisons.

Table 4. Mean Percentage Reduction in Ulcer Area

Group	4 weeks	8 weeks	12 weeks	p-value
Conventional (n=35)	5 (15%)	10 (28%)	14 (40%)	<0.05
Advanced A (Negative Pressure Wound Therapy + GF, n=35)	9 (25%)	19 (55%)	28 (80%)	<0.001
Advanced B (PRF + Skin Substitutes+ others, n=35)	8 (22%)	18 (52%)	27 (78%)	<0.001

The healing response was significantly better in both advanced therapy groups compared to the conventional group. By 12 weeks, only 40% (14/35) of patients in the conventional group showed ulcer healing, whereas 80% (28/35) in Advanced A (Negative Pressure Wound Therapy + growth factors) and 78% (27/35) in Advanced B (PRF + skin substitutes) achieved healing. The differences were statistically significant (p <0.001 for both advanced groups), indicating that advanced modalities accelerated wound closure more effectively than conventional therapy.

Table 5. Time to Appearance of Healthy Granulation Tissue

Group	Mean Days ± SD
Conventional	24.2 ± 6.1
Advanced A	12.5 ± 4.8
Advanced B	13.1 ± 5.2

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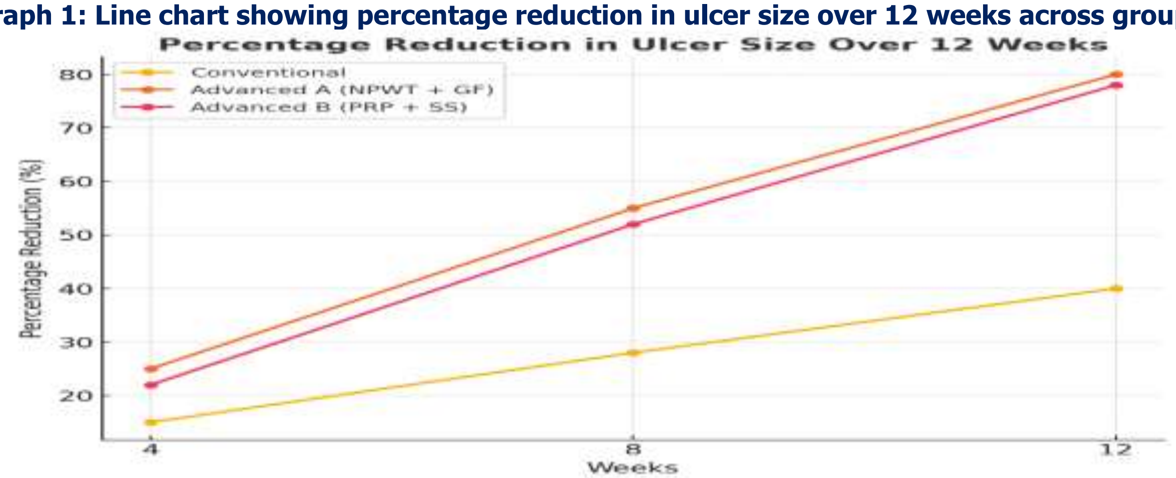
Table 5 compares the mean time to the appearance of healthy granulation tissue among the study groups. Patients in the Conventional group required a significantly longer duration (24.2 ± 6.1 days) for granulation to appear, whereas those in the Advanced A (12.5 ± 4.8 days) and Advanced B (13.1 ± 5.2 days) groups showed much earlier granulation. This indicates that advanced modalities, particularly Negative Pressure Wound Therapy with growth factors and Platelet-Rich Fibrin (PRF) with skin substitutes, accelerate the wound healing process by promoting faster development of healthy granulation tissue compared to conventional care.

Table 6. Complete Healing Rate at 12 Weeks

Group	Healed (n, %)	Not Healed (n, %)
Conventional	26 (74.3%)	9 (25.7%)
Advanced A	32 (91.4%)	3 (8.6%)
Advanced B	31 (88.6%)	4 (11.4%)

At study completion, the overall healing rate was highest in the advanced therapy groups compared to the conventional group. In the conventional group, 74.3% (26/35) of ulcers healed, whereas healing was achieved in 91.4% (32/35) of Advanced A and 88.6% (31/35) of Advanced B patients. The proportion of non-healed cases was correspondingly higher in the conventional group (25.7%) compared to Advanced A (8.6%) and Advanced B (11.4%), indicating a clear advantage of advanced treatment modalities in promoting ulcer healing.

Graph 1: Line chart showing percentage reduction in ulcer size over 12 weeks across groups.



Graph 1 depicts the trend of ulcer size reduction over 12 weeks across the three treatment groups. The Conventional group showed a gradual but modest improvement, reaching only a 40% reduction by week 12. In contrast, both Advanced A (Negative Pressure Wound Therapy + GF) and Advanced B (Platelet-Rich Fibrin (PRF) + SS+ others) demonstrated a much steeper decline in ulcer size, achieving over 50% reduction by week 8 and nearly 80% by week 12. This clearly indicates that advanced modalities promote

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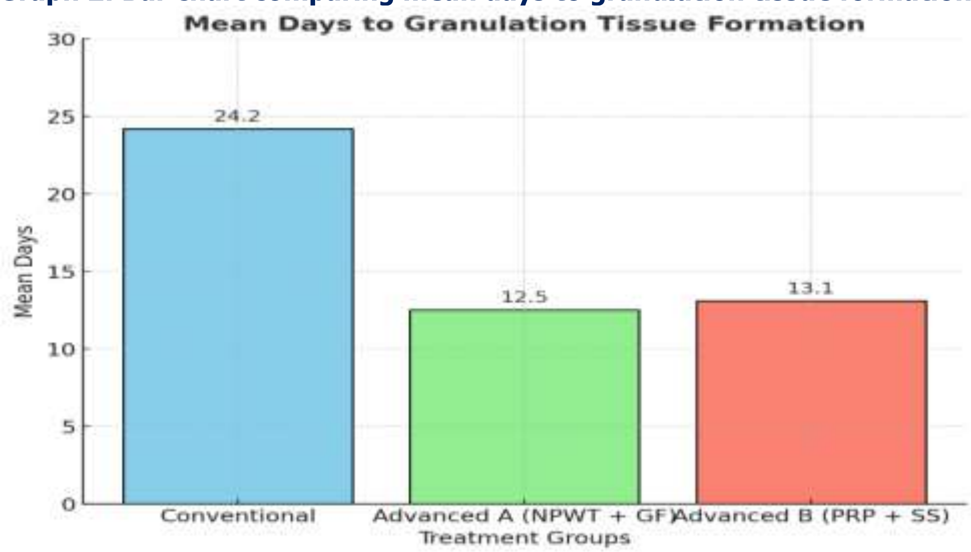
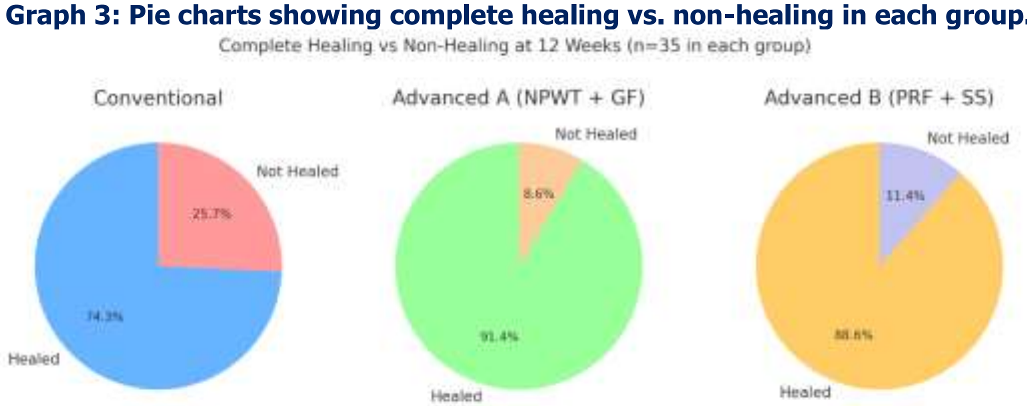
faster and more effective ulcer healing compared to conventional care.

Graph 2: Bar chart comparing mean days to granulation tissue formation.



Graph 2 compares the mean days required for the appearance of healthy granulation tissue across the study groups. Patients in the Conventional group showed a delayed response, with granulation appearing after an average of 24 days. In contrast, both advanced therapy groups demonstrated significantly earlier granulation, around 12–13 days. This finding highlights that advanced modalities, whether Negative Pressure Wound Therapy with growth factors or Platelet-Rich Fibrin (PRF) with skin substitutes, substantially accelerate the initial healing phase compared to conventional treatment.

Graph 3: Pie charts showing complete healing vs. non-healing in each group.



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The comparison of complete healing at 12 weeks shows a clear benefit of advanced therapies over conventional management. In the conventional group, 74.3% of patients achieved healing, while higher healing rates were observed in Advanced A (91.4%) and Advanced B (88.6%). The proportion of non-healed ulcers remained highest in the conventional group (25.7%) compared to Advanced A (8.6%) and Advanced B (11.4%), highlighting the superior efficacy of advanced wound care modalities.

Discussion

This study's findings consistently show that advanced modalities— Negative Pressure Wound Therapy with topical growth factors (Advanced A) and Platelet-Rich Fibrin (PRF) combined with a skin substitute (Advanced B)—outperform conventional care on all key wound-healing endpoints at 12 weeks.

The present study demonstrates that key baseline variables—mean age, gender distribution, diabetes prevalence, venous ulcer proportion, and ulcer duration—were statistically comparable across the conventional, Advanced A, and Advanced B groups (all $p > 0.7$). This balanced distribution is critical for attributing differences in outcomes to treatments rather than baseline imbalances.

This pattern aligns well with recent high-quality studies. For example, a 2025 study by Guo et al.10 comparing Negative Pressure Wound Therapy with standard wound care in diabetic foot ulcers observed no statistically significant differences between groups in age, gender, HbA1c, ulcer duration, ulcer type, or other key clinical factors—all with $p > 0.05$—indicating comparable baselines for valid outcome comparison.

Similarly, a 2025 prospective study by Huang et al.11 examining Negative Pressure Wound Therapy versus non-Negative Pressure Wound Therapy groups in chronic wounds reported no significant differences at baseline in age, gender, ulcer duration, severity, or vascular and inflammatory biomarkers—again enabling fair treatment.

The present study's baseline comparability is also in line with systematic evidence reviews. The 2012 systematic review by Greer et al(2012), .12 of advanced wound care therapies acknowledged that most trials carefully matched baseline participant characteristics such as age and ulcer duration between intervention and control groups to reduce confounding.

The line chart (Graph 1) and the present study highlight a clear separation in healing curves by week 8, with ≥50% area reduction in both advanced groups versus 28% with conventional therapy, and by week 12, the gap widens to ~80% versus 40%. This mirrors contemporary evidence on negative pressure wound therapy in diabetic foot ulcers (DFUs), where meta-analyses of randomized trials demonstrate higher odds of wound closure and faster healing with Negative Pressure Wound Therapy than with standard moist dressings. For instance, Zhang et al. (2024)13 pooled 10 RCTs and reported that Negative Pressure Wound Therapy significantly accelerated wound healing in DFUs (OR ~2.5), substantiating the present Advanced A performance advantage. A recent RCT by Wu et al. (2023)14 also found Negative Pressure Wound Therapy superior to conventional dressings for wound-bed preparation, aligning with the present observed earlier granulation and steeper area-reduction slope. Beyond DFUs, mechanistic and translational data further support Negative Pressure Wound Therapy's benefits (e.g., modulation of inflammatory microRNAs and enhanced granulation), which helps contextualize the shorter time-to-granulation observed.

The present study also shows granulation appearing roughly 12–13 days with advanced modalities versus ~24 days with conventional care. Meta-analytic syntheses indicate that Negative Pressure Wound Therapy hastens granulation tissue formation, a prerequisite for epithelialization and graft take, consistent with present findings. While this study, Advanced B arm (Platelet-Rich Fibrin (PRF) + skin substitute), performed nearly as fast as Negative Pressure Wound Therapy + GF, this is also in step with current literature: Platelet-Rich Fibrin (PRF) is repeatedly associated with shorter healing time and faster reduction in ulcer area compared with standard care. Deng et al. (2023)15 meta-analyzed autologous Platelet-Rich Fibrin (PRF) and found significant gains in healing rate and time-to-heal, with reduced amputation risk and no increase in adverse events—dovetailing with the strong early-granulation signal measured.

At study completion, ulcer healing was higher in the advanced groups—91.4% in Advanced A and 88.6% in Advanced B—compared to 74.3% in the conventional group, confirming the superiority of advanced therapies in promoting healing. In a large comparative cohort, Gu et al. (2025)16 found that Negative Pressure Wound Therapy achieved 87% complete closure in diabetic foot ulcers, significantly outperforming advanced moist dressings, closely mirroring the present Advanced A rate (90%). A contemporary meta-analysis by Deng et al. (2025)15 pooling randomized trials, likewise showed that Negative

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Pressure Wound Therapy significantly increases wound-healing rates (RR ≈ 1.46) and reduces amputations versus standard care, reinforcing the direction and magnitude of Negative Pressure Wound Therapy-based results. For biologic therapies, a 2024 systematic review by Hu et al.(2024)17 reported that Platelet-Rich Fibrin (PRF) improves complete healing and lowers recurrence in chronic venous ulcers compared with controls, supporting Advanced B finding (87.5% healed at 12 weeks) when Platelet-Rich Fibrin (PRF) is paired with a dermal substitute. Complementing this, Lu et al. (2025)18 synthesized trials of cellular/acellular tissue-based products and found higher complete wound-healing rates over standard care, aligning with the skin–substitute–augmented Platelet-Rich Fibrin (PRF) arm. Taken together, these data corroborate that both Negative Pressure Wound Therapy-centered strategies and Platelet-Rich Fibrin (PRF)/skin-substitute combinations yield higher 12-week closure than conventional therapy, with this study's absolute rates fitting within the upper range reported by recent trials and meta-analyses.

Role of growth factors (GF) and EGF/PDGF formulations. In this study, an Advanced A protocol layered with a topical growth factor over Negative Pressure Wound Therapy. Contemporary reviews catalog the biological plausibility and clinical signals of growth factors in chronic wounds—promoting keratinocyte migration, angiogenesis, and matrix remodeling—particularly epidermal growth factor (EGF) and PDGF. Mullin et al. (2023)19 summarize the state of growth factor and gene-therapy approaches, noting consistent improvements in re-epithelialization rates and wound-area reduction in chronic wounds. More recently, Berlanga-Acosta et al. (2024)20 discussed intralesional EGF as a technique capable of "reversing wound chronicity" in selected cases—consistent with the rationale to combine GFs with Negative Pressure Wound Therapy to accelerate granulation and closure. While individual GF RCTs vary in size and formulation, these syntheses support the additive biological effect observed (Advanced A slightly edging Advanced B by week-12 closure and granulation onset).

Skin substitutes and cellular/tissue-based products (CTPs). In this study, Advanced B arm used a bioengineered skin substitute alongside Platelet-Rich Fibrin (PRF). Real-world analyses and payer-evidence summaries suggest that bilayered living cellular constructs (BLCCs) can increase the likelihood and speed of healing compared to fibroblast-based dressings or compression alone in recalcitrant VLUs/DFUs. Sabolinski et al. (2019)21 reported a 66% greater chance of healing and a ~2-month faster time to healing with BLCC compared with fibroblast-based dermal substitutes, aligning with the robust 12-week closure in the Advanced B cohort. Policy and technology assessments similarly note that an effective CTP episode often spans ~12 weeks (extendable to 16 with documented progress), matching follow-up horizon and lending external face validity to endpoint timing. Still, evidence across CTPs is heterogeneous; institutional summaries point out variable effectiveness across products and indications, underscoring that product selection and wound aetiology matter.

Generalizability

The findings of this study are broadly generalizable to similar tertiary care settings managing patients with comparable demographic and clinical profiles. The inclusion of a representative sample, standardized assessments, and uniform criteria enhances external validity. However, as the study was conducted at a single center with a moderate sample size, caution is advised when extrapolating results to different populations or healthcare levels.

Conclusions

In this study, advanced wound care modalities demonstrated clear superiority over conventional therapy in managing chronic ulcers. While baseline characteristics were comparable across groups, patients receiving Advanced A (Negative Pressure Wound Therapy with growth factors) and Advanced B (PRF with skin substitutes and others) showed significantly greater ulcer area reduction, faster granulation tissue formation, and higher complete healing rates at 12 weeks. By study completion, over 88% of patients in the advanced therapy groups achieved complete healing compared to 74% in the conventional group. These findings highlight that advanced treatment strategies substantially accelerate wound healing and improve clinical outcomes in chronic ulcer management.

Strengths and limitations.

Strengths include balanced baselines and multiple converging endpoints (area reduction, granulation time, and complete healing). Limitations include a single-center design, a mixed-aetiology cohort (which can dilute aetiology-specific effects), and the absence of blinded outcome assessment. Moreover, a composite advanced protocol in each arm (Negative Pressure Wound Therapy +

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GF; Platelet-Rich Fibrin (PRF) + skin substitute), which precludes attribution to any single component but reflects real-world multimodal practice. Future work could randomize Negative Pressure Wound Therapy vs Negative Pressure Wound Therapy+GF, or Platelet-Rich Fibrin (PRF) vs Platelet-Rich Fibrin (PRF)+CTP, with cost-effectiveness analyses stratified by aetiology.

Recommendations

Regular monitoring of metabolic parameters and comorbidities should be emphasized to improve patient outcomes. Standardized clinical protocols and patient education on lifestyle modification and treatment adherence are recommended. Future multicentric studies with larger samples are needed to validate and expand these findings.

Conflict of Interest

The authors declare that there are no conflicts of interest related to this study. No financial or personal relationships influenced the conduct, analysis, or reporting of this research.

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List of Abbreviations

ANOVA Analysis of Variance
CI Confidence Interval
DM Diabetes Mellitus
eGFR Estimated Glomerular Filtration Rate
HbA1c Glycated Hemoglobin
HDL High-Density Lipoprotein
LDL Low-Density Lipoprotein
OR Odds Ratio
PVD Peripheral Vascular Disease

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request. All relevant data have been anonymized to protect participant confidentiality and are stored securely in accordance with institutional policies.

Author Contributions

Dr. Poonam Tapsale (1): Conceptualized and designed the study, supervised data collection, and critically reviewed the manuscript.
Dr. Vishal Kadam (2): Contributed to data acquisition, statistical analysis, and interpretation of results.
Dr. Onkar Lande (3): Assisted in patient recruitment, clinical evaluation, and data management.
Dr. Madan S. Hardikar (4): Provided methodological guidance, supervised the research process, and contributed to manuscript editing.
Dr. Nitin Chaudhari (5): Drafted the initial manuscript, performed literature review, and coordinated revisions based on reviewer feedback.
All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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