Title: Treatment of Full-Thickness Wounds: NPWT Combined with Type-I Collagen Based Advanced Skin Substitute Versus NPWT Alone

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INTRODUCTION

Full-thickness wounds, which extend through the dermis into the underlying subcutaneous tissue or deeper structures, remain a formidable challenge in reconstructive and wound care practice. These wounds may arise from trauma, surgical dehiscence, pressure injuries, or chronic ulceration, and are often complicated by infection, vascular insufficiency, and comorbidities such as diabetes and peripheral vascular disease. They affect millions of patients worldwide and impose substantial economic burden on healthcare systems [1, 2]. They are a growing concern in healthcare due to their prolonged healing time, high recurrence, and associated morbidity [3, 4]. These wounds often demonstrate delayed healing and increased risk of complications including infection, chronic inflammation, and impaired tissue regeneration [5, 6]. Without optimal management, these wounds fail to heal through the conventional stages of wound repair, functional impairment, increased risk of limb loss, poor cosmetic results and high healthcare costs. The complex pathophysiology of wound healing involves intricate interactions between cellular components, growth factors, extracellular matrix proteins, and vascular elements, necessitating comprehensive therapeutic approaches to optimize clinical outcomes [7].

Negative Pressure Wound Therapy (NPWT) has emerged as an effective modality to accelerate wound healing by removing excess exudate, enhancing perfusion, promoting granulation tissue formation and maintains an optimal wound environment, and thus is a cornerstone in treatment of complex wounds [8, 9, 10]. By applying controlled sub-atmospheric pressure, NPWT reduces interstitial edema, increases local blood flow, removes exudate, and stimulates granulation tissue formation. The application of controlled negative pressure creates a conducive environment for cellular proliferation and angiogenesis, facilitating the wound healing cascade [11, 12]. Despite its advantages, NPWT alone may not suffice for extensive tissue regeneration and achieve rapid epithelialization, especially in large or complex wounds where the extracellular matrix (ECM) and vascular supply has been significantly compromised [13].

The integration of biological skin substitutes in wound healing has emerged as a promising adjunctive therapy to enhance wound healing outcomes [14, 15]. High Purity Type-I Collagen (HPTC) skin substitutes, such as Helicoll®, provide a bioactive scaffold that mimics native ECM, facilitating cellular migration, angiogenesis, keratinocyte proliferation and growth factor delivery. Helicoll® is an acellular dermal replacement product made of high purity (>97%) Type-I Collagen that provides a framework promoting blood vessel regeneration and biologic cell migration [16]. It is derived from bovine sources but processed to remove

antigenic components. Helicoll® undergoes a patented treatment process for purification, making it least immunogenic and highly biocompatible [17].

These bioengineered constructs offer several advantages including biocompatibility, biodegradability, and offer optimal bio-integration with host tissue while promoting natural healing processes [18, 19]. Recent RCTs have established its efficacy in chronic wound healing, including diabetic foot ulcers and venous leg ulcers [16, 20, 21]. Narayan et al. demonstrated that HPTC achieved significantly greater wound closure compared to dehydrated human amnion/chorion membrane (dHACM) in diabetic foot ulcers [16]. Similarly, an RCT in venous leg ulcers showed faster healing and better granulation quality with HPTC than dHACM [20]. Another dual-country RCT involving 55 patients reported consistent superiority of HPTC across different patient populations and healthcare settings [22]. These studies have shown superior healing rates, reduced healing time, and improved tissue quality compared to standard care approaches.

While these studies establish the role of HPTC in chronic ulcer management, the potential synergistic effect of combining HPTC with NPWT in full-thickness wounds has not been extensively studied. The rationale for combining NPWT with high-purity type-I collagen-based skin substitutes lies in their complementary mechanisms of action. Theoretically, NPWT could optimize the wound bed and vascular environment (mechanical environment), while HPTC provides the structural and biochemical support (biological framework) for accelerated tissue regeneration. This combination may result in faster and more complete healing than NPWT alone, addressing both the macroscopic and microscopic aspects of wound healing, potentially leading to superior clinical outcomes [12, 13, 20, 21, 23].

The present study aims to compare the clinical outcomes of NPWT combined with HPTC skin substitute versus NPWT alone in patients with full-thickness wounds, using a randomized controlled design, to provide robust evidence for clinical decision-making in advanced wound care. Our hypothesis is that the combination therapy will result in significantly greater wound area reduction, faster closure, improved scar quality, and better patient-reported pain outcomes, without increasing adverse events.

MATERIALS AND METHODS

This was a prospective, randomized, open-label, parallel-group clinical trial conducted at the Department of Plastic, Reconstructive, and Aesthetic Surgery, Adichunchanagiri Institute of Medical Sciences (AIMS), Karnataka, India. The study compared the efficacy of Negative Pressure Wound Therapy (NPWT) combined with High Purity Type-I Collagen (HPTC) skin substitute versus NPWT alone in the management of full-thickness wounds. Patient recruitment occurred between March 2025, and July 2025. The anticipated follow-up continued until August 2025, with each participant observed for a total of seven weeks (six weeks of intervention plus one-week follow-up). The trial was registered prospectively with **ClinicalTrials.gov (ID: NCT06873867)** and approved by the Institutional Ethics Committee **(Approval No: AIMS/IEC/013/2025)**. The study adhered to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent prior to enrollment after comprehensive explanation of study procedures, risks, and benefits. Patient confidentiality was maintained throughout the study period.

Patients aged 18-80 years with full-thickness wounds (wound depth extending through dermis into subcutaneous tissue), including traumatic, post-surgical dehiscence, burns ulcers, pressure ulcers, DFUs, or VLUs, wound size >20 cm^2 and <75 cm^2, with adequate vascular supply to the wound site, ability to comply with treatment protocol and follow-up visits, and provided written informed consent were eligible.

Exclusion criteria included active infection or osteomyelitis requiring systemic antibiotics, active malignancy at wound site, immunosuppression, uncontrolled diabetes (HbA1c > 9%), on systemic corticosteroids, patients on anticoagulation therapy with INR >3.0 used advanced wound care products within the last 30 days, autoimmune or connective tissue disorders or allergy to bovine collagen.

Sample Size - Sample size calculation was based on the primary outcome of wound area reduction. Assuming a mean difference of 30% in wound area reduction between groups, with a standard deviation of 20%, power of 80%, and alpha of 0.05, a minimum of 47 patients per group was required. Accounting for 10% dropout rate, at 52 patients per group, with a total of 104 patients were recruited. This calculation was informed by effect sizes reported in previous HPTC RCTs in diabetic foot, venous leg and pressure ulcers, which demonstrated mean differences of 10–15% in wound healing outcomes. [6,7].

Randomization and Blinding - Participants were randomized 1:1 into two treatment groups using a computer-generated randomization sequence with block sizes of 4, 6, and 8. Patients were assigned to either: - Group A: NPWT + HPTC or Group B: NPWT alone. Randomization was stratified by wound etiology. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes prepared by a research assistant not involved in patient care or outcome assessment. Due to the nature of the intervention, complete blinding was not feasible; however, outcome assessors, pathologists, and data analysts were blinded to treatment allocation.

Intervention Protocol

Group A (NPWT + HPTC) - The wound was first debrided to remove necrotic tissue and ensure a viable wound bed. A sheet of High Purity Type-I Collagen skin substitute (Helicoll®) was applied to completely cover the wound surface. This was followed by a non-adherent porous dressing layer. NPWT was then applied using polyurethane foam at ~125 mmHg intermittent pressure (10 minutes on, 2 minutes off) for 5–7 days. The dressing was changed as per SOC thereafter, with repeat application of HPTC and NPWT as needed.

Group B (NPWT alone) - Following debridement, a non-adherent porous dressing was applied directly over the wound. NPWT was then initiated with the same parameters (polyurethane foam, ~125 mmHg, intermittent mode) and followed by SOC dressing. NPWT was reapplied if required.

All patients received standardized wound care including sharp debridement as needed to remove non-viable tissue, infection control with topical antimicrobials when indicated, pressure redistribution and offloading as appropriate, nutritional assessment and optimization, glycemic control for diabetic patients, compression therapy for venous ulcers and pressure offloading for wounds when appropriate. Patient education on wound care was given.

Outcome Measures

The primary outcome of the study was percentage wound area reduction from week 1 through week 6 plus 1 week follow up, measured via digital photography. Measurements were performed by trained personnel blinded to treatment allocation.

Secondary outcomes included time to complete wound closure (in days) within 7 weeks, proportion of patients achieving complete closure by week 7, histological vascularity infiltration, between baseline (Day 0) and Day 5 biopsies, mean number of applications of the skin substitute required, incidence of adverse events (infection, allergic reaction, bleeding,

maceration), pain score change using a 0–10 Visual Analog Scale (VAS) from baseline to week 6, and scar quality assessed at week 7 using the Manchester Scar Scale (MSS). Complete wound closure is defined as 100% epithelialization. Histopathological assessment included taking punch biopsies (2 mm) from the wound edge at baseline and day 5 post-intervention under local anesthesia (2% lidocaine without epinephrine). Fixation in 10% neutral buffered formalin for 24 hours, processing through graded alcohol and paraffin embedding, and serial sectioning at 4 μm thickness was done. Samples were processed using standard histological techniques and stained with hematoxylin and eosin (H&E), Masson's trichrome, CD31 immunohistochemistry, and α-SMA immunohistochemistry. Assessment parameters included vascular infiltration (0-3 scale), neo-epithelialization (0-3 scale), fibroblast activity (0-3 scale), capillary density (vessels per mm^2), inflammatory response (0-3 scale) and collagen deposition (0-3 scale) (Table 1).

Quality of Life Assessment using EQ-5D-5L (EuroQol 5-Dimension 5-Level) [25] questionnaire, a standardized and widely used instrument for assessing health-related quality of life (HRQoL). Developed by the EuroQol Group [25], it provides a simple, generic measure applicable to a wide range of diseases and health conditions. The tool evaluates five key dimensions of health - mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is rated on five levels of severity - no problems, slight problems, moderate problems, severe problems and extreme problems or inability. These combinations describe a respondent’s health state, which can be converted into a single summary index score (ranging from less than 0, indicating health states worse than death, to 1.0, representing full health) using country-specific value sets derived from general population preferences. In addition, the EQ-5D-5L [25] includes a Visual Analogue Scale (EQ-VAS) [25], a 0-100 scale on which patients rate their overall health (0 = worst imaginable health, 100 = best imaginable health). The EQ-5D-5L questionnaire was used in its validated Kannada Version 1.1 format, obtained directly from the EuroQol Group under non-commercial registration (ID: 78665). The tool was administered in interviewer-assisted digital format to ensure accurate comprehension by all participants.

Scar quality was assessed using Vancouver Scar Scale evaluating vascularity, pigmentation, pliability and height/thickness with total score ranging from 0 to 13 (lesser the score better the scar) (Table 2).

Table 1: Histological parameters evaluated in the ulcer bed at baseline and on day five of application

Parameter	Measurement tool	Criteria	Score
Vascular infiltration	Assessed by counting new blood vessels (0–3 scale)	Minimal vascular ingrowth (<5 vessels/HPF)	0
		Mild infiltration (5–10 vessels/HPF)	1
		Moderate infiltration (11–20 vessels/HPF)	2
		Abundant infiltration (>20 vessels/HPF)	3
Neo-epithelialization	Measured as epithelial migration distance from wound edge (0–3 scale)	No epithelial migration	0
		Minimal migration (<25% wound coverage)	1
		Moderate migration (25–75% coverage)	2
		Extensive migration (>75% coverage)	3
Fibroblast activity	Quantified by counting α-SMA positive fibroblasts per HPF and assessment of fibroblast morphology (0–3 scale)	Sparse, inactive fibroblasts	0
		Moderate cellularity, minimal matrix production	1
		High cellularity, active-matrix synthesis	2
		Very high activity with extensive matrix deposition	3
Capillary density	Evaluated using CD31 staining, counted as vessels per mm² of tissue		
Inflammatory response	Graded semi-quantitatively (0–3 scale)	Minimal inflammatory infiltrate	0
		Mild chronic inflammation	1
		Moderate mixed inflammation	2
		Severe acute inflammation	3
Collagen deposition	Assessed using Masson's trichrome staining (0–3 scale)	Minimal collagen matrix	0
		Loose, immature collagen	1
		Moderate organized collagen	2
		Dense, mature collagen architecture	3

Table 2: Vancouver Scar Scale

Parameter	Score
Vascularity	**0–3**
Normal	0
Pink	1
Red	2
Purple	3
Pigmentation	**0–2**
Normal (matches surrounding skin)	0
Hypopigmentation	1
Hyperpigmentation	2
Pliability	**0–5**
Normal	0
Supple (flexible with minimal resistance)	1
Yielding (gives way to pressure)	2
Firm (resists movement)	3
Banding / rope-like tissue (may blanch on extension)	4
Contracture (permanent shortening producing deformity)	5
Height / Thickness	**0–3**
Flat / normal	0
< 2 mm	1
2–5 mm	2
> 5 mm	3

Parameter	Score
Total Scar Score (Higher scores indicate greater scar severity)	**0-13**

Data Collection and Measurement

Wound photographs were obtained using standardized digital photography with measurement grids. Standardized wound assessments were performed including digital photography, wound measurements using validated techniques, and clinical evaluations. Wound area was calculated by tracing the wound margin onto a sterile transparent film and photographing with a scale reference. Histological evaluation was performed on wound biopsies with stains as mentioned in Table 1. Pain assessments (Visual Analogue Scale) and quality of life score were completed at baseline, every week thereafter for 7 weeks.

Statistical Analysis

All data were analyzed using SPSS version 26.0 (IBM Corporation, Armonk, NY). Continuous variables were expressed as mean ± standard deviation and compared using independent t-tests or Mann–Whitney U tests where appropriate. Categorical variables were expressed as frequencies and percentages, compared using chi-square or Fisher's exact test. Repeated measures ANOVA was employed for longitudinal outcome analysis. Time-to-event outcomes were analyzed using Kaplan-Meier survival analysis with log-rank tests.