Title:

A Randomized, Controlled Clinical Trial Comparing the Use of High Purity Type-I Collagen-based Skin Substitute vs. Dehydrated Human Amnion/Chorion Membranein the Treatment of Diabetic Foot Ulcers

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Introduction

Chronic wounds, especially diabetic foot ulcers (DFUs), place a significant financial strain on healthcare systems. In the United States, the estimated annual cost for treating these wounds is about $30 billion. DFUs are the most prevalent form of lower extremity wounds, making up roughly 80% to 85% of such cases. Annually, between 6.5 and 7 million individuals in the U.S. are affected by chronic DFUs. With an aging population and increasing incidence of risk factors such as obesity and congestive heart failure, the prevalence of DFUs is expected to rise.

Chronic diabetic foot ulcers (DFUs) are linked to considerable suffering and a decline in quality of life, as the healing process is typically slow and painful. Even in optimal conditions, these ulcers can take weeks or months to recover, often experiencing a frustrating pattern of slow healing and repeated breakdown. Wound care specialists frequently encounter patients who have suffered from these ulcers for years, with some needing amputation as the only solution for pain relief.

Type-I collagen, when full, purified, and uncross-linked, offers 3,000 receptor sites per molecule for growth factors like fibroblasts to adhere to, making it an ideal matrix for wound healing. Type-I collagen shows 97% similarity across species, while Type-II and Type-III collagen only have 80% similarity within the same species. For instance, Type-I collagen in humans is quite similar to that in cows or birds. Furthermore, Type-I collagen is the least likely to provoke an immune response due to its lack of the sulfur-containing amino acid cysteine. In contrast, Type-II and Type-III collagen contain more cysteine, making them more immunogenic.

The objective of this study is to evaluate and compare the safety and effectiveness of High Purity Type-I Collagen-based Skin Substitute (HPTC) with Dehydrated Human Amnion/Chorion Membrane (dHACM) for treating diabetic foot ulcers (DFUs). This randomized, controlled clinical trial seeks to provide valuable insights into the best treatment strategy for enhancing healing outcomes and reducing the challenges posed by chronic DFUs.

Materials and Methods

Study will be carried out as a randomized, controlled open-label study to evaluate the safety and effectiveness of High Purity Type-I Collagen-based Skin Substitute (HPTC) compared to Dehydrated Human Amnion/Chorion Membrane (dHACM) for treating diabetic foot ulcers (DFUs). The trial will include patients with DFUs treated by wound care specialists at Adichunchanagiri Institute of Medical Sciences, B. G. Nagara, under the supervision of primary investigator Dr Naveen N. Informed consent will be obtained from all participants prior to any study-related procedures, and each patient will sign an Institutional Ethics Committee/Investigational Review Board (IEC/IRB)-approved consent form.

The investigator will comply with regulatory guidelines and Good Clinical Practice (GCP) in obtaining and documenting informed consent. All study products will be produced, handled,

and stored in accordance with Good Manufacturing Practices (GMP). Strict patient confidentiality protocols will be maintained throughout the study.

Patient Screening and Eligibility

The study population will consist of patients seeking treatment for DFUs. Eligible patients will be those willing to participate and comply with scheduled visits on days 7, 10, 14, 17, 21, and 28. The study will include two phases: screening and treatment. The screening phase aimed to determine patient eligibility for the treatment phase. The inclusion and exclusion criteria are detailed in Table 1. During screening, a series of assessments will be conducted, including demographics, medical history, concomitant medications, vital signs, physical examination, leg ulcer history, clinical infection signs at the ulcer site.

Study Treatment:

The treatment phase of the study will commence with a series of evaluations to ensure patients remained eligible. Participants who will continue to meet the inclusion criteria after the screening phase will be randomly assigned to one of two groups:

1. Standard of Care (SOC) with High Purity Type-I Collagen-based Skin Substitute (HPTC).
2. Standard of Care (SOC) with Dehydrated Human Amnion/Chorion Membrane (dHACM).

Neither the patients nor the clinicians will be blinded to group assignments. The randomization will follow a balanced schedule, using permuted blocks of 12. When a patient will be ready for randomization, the study site will contact a representative from the sponsor, who will open a sequentially numbered opaque envelope to disclose the group assignment, maintaining allocation concealment.

Throughout the 4-week treatment phase, patients will be reassessed on days 7, 10, 14, 17, 21, and 28. The SOC dressing applied in both groups consisted of a three-layer system:

- **First layer:** Non-adherent, porous paraffin gauze.
- **Second layer:** Absorbent gauze pads.
- **Third layer:** Soft roll and Crepe bandage.

Note:

a. 2 sizes of HPTC used:

i. 0.8 in x 1.6 in or 2 cm x 4 cm (8 sq cm)
ii. 1.6 in x 1.6 in or 4 cm x 4 cm (16 sq cm)

b. 2 sizes of dHACM used:

i. 5 cm x 5 cm (25 sq cm)
ii. 8 cm x 6 cm (48 sq cm)

If the study ulcer was found to be 100% re-epithelialized during the visit, no further study procedures will be conducted at that time. The patient will then be scheduled for a follow-up visit after one week to confirm the healing.

If full healing was not achieved, an evaluation will be carried out to check for any signs of clinical infection. If an infection is confirmed, treatment with topical antimicrobials or oral antibiotics will be permitted, though the use of topical antibiotics will be prohibited.
After this infection assessment, the ulcer would be cleaned, photographed, and debrided at the investigator's discretion to ensure a clean and granulating wound base with minimal adherent slough. The Standard of Care (SOC) will be then re-applied, and patients will be instructed to keep the bandage dry. Additionally, they will be advised to contact or return to the study site if the bandage became soiled or removed.

Study Completion:
Patients will complete the study 4 weeks after their initial treatment visit. However, if a patient's study ulcer healed before the 4-week period, they will be considered to have completed the study at the time of full healing.
Complete healing will be defined as 100% re-epithelialization of the ulcer with no drainage.
Throughout the study, patients will retain the right to decline participation or withdraw at any time without prejudice.
In the event of a patient's withdrawal, their last recorded wound measurement will be carried forward to determine the change in wound size and calculate their final outcome.

Study Outcomes:
Primary Endpoint:
- The primary outcome of the study will be the proportion of subjects who achieved improvement in wound healing, as observed on days 7, 10, 14, 17, 21, and 28. The wound closure of the target ulcer will be continuously monitored until the end of the 4-week period.

Secondary Endpoints:
- **Time to Achieve Complete Wound Closure:** Time taken for the target ulcer to achieve complete wound closure will be assessed on days 7, 10, 14, 17, 21, and 28.
- **Percentage Wound Area Reduction:** This will be measured weekly on days 7, 10, 14, 17, 21, and 28 using digital photography.
- **Mean Number of Repeated Applications of HPTC:** The average number of times the reapplication of High Purity Type-I Collagen-based Skin Substitute (HPTC) to achieve wound closure will be documented as part of the study process.

Exploratory Endpoint:
- The appearance, structural stability, and fragility of the newly formed skin will be documented at each visit. Any recurrence of the wound will also be monitored.

Subjects must be at least 18 years of age or older.	A subject known to have a life expectancy of less than 6 months.
Subjects must have a diagnosis of type 1 or 2 diabetes mellitus.	If the target ulcer is infected or if there is cellulitis in the surrounding skin.
At enrolment, subjects must have a target diabetic foot ulcer with a minimum surface area of 5.0 cm^2 and a maximum surface area of 10.0 cm^2, measured post-debridement using a ruler.	Presence of osteomyelitis or exposed bone, probes to bone or joint capsule on investigator's exam, or radiographic evidence.
The target ulcer must have been present for a minimum of 4 weeks and a maximum of 52 weeks of standard care prior to the initial screening visit.	A subject that has an infection in the target ulcer that requires systemic antibiotic therapy.
The target ulcer must be located on the foot, with at least 50% of the ulcer below the malleolus.	A subject receiving immunosuppressants (including systemic corticosteroids at doses greater than 10 mg of prednisone per day or equivalent) or cytotoxic chemotherapy.
The target ulcer must be full thickness on the foot or ankle and must not probe to bone.	Topical application of steroids to the ulcer surface within one month of initial screening.
Adequate circulation to the affected foot as documented by any of the following methods performed within 3 months of the first screening visit: a. Transcutaneous Oxygen Measurement (TCOM) ≥ 30 mmHg b. Ankle-Brachial Index (ABI) between 0.7 and 1.3 c. Peripheral Vascular Resistance (PVR): Biphasic d. Toe-Brachial Index (TBI) > 0.6 e. Alternatively, arterial Doppler ultrasound can be performed to evaluate biphasic dorsalis pedis and posterior tibial vessels at the level of the ankle of the target extremity.	A subject with a previous partial amputation on the affected foot is excluded if the resulting deformity impedes proper offloading of the target ulcer.
If the subject has two or more ulcers, they must be separated by at least 2 cm. The largest ulcer satisfying the inclusion and exclusion criteria will be designated as the target ulcer.	A subject with a glycated hemoglobin (HbA1c) greater than or equal to 13%, taken at or within 3 months of the initial screening visit.

The subject must consent to using the prescribed off-loading method for the duration of the study.	A subject with a serum creatinine ≥ 3.0 mg/dL within 6 months of the initial screening visit.
The subject must agree to attend the twice-weekly/weekly study visits required by the protocol.	A subject with an acute Charcot foot, or an inactive Charcot foot, that impedes proper offloading of the target ulcer.
The subject must be willing and able to participate in the informed consent process.	Women who are pregnant or considering becoming pregnant within the next 6 months.
Patients must have read and signed the IEC/IRB-approved informed consent form (ICF) before screening procedures are undertaken.	A subject with end-stage renal disease requiring dialysis.
	A subject who participated in a clinical trial involving treatment with an investigational product within the previous 30 days.
	A subject who, in the opinion of the Investigator, has a medical or psychological condition that may interfere with study assessments.
	A subject treated with hyperbaric oxygen therapy or a Cellular and/or Tissue Product (CTP) in the 30 days prior to the initial screening visit.

Table 1: Inclusion and Exclusion Criteria

Statistical analysis :-

Descriptive statistics will be used to summarize the data. Quantitative data will be presented as means or medians, while qualitative data will be expressed as frequencies and percentages. The study aims to assess the proportion of study participants achieving wound healing by the end of the fourth week. To measure the proportion of participants showing improvement in wound healing, observations will be conducted on days 7, 10, 14, 17, 21, and 28. The proportion of participants achieving wound healing would be compared between both the groups using Chi-square/ Fisher's exact test. Additionally, the average reduction in ulcer size from baseline to the end of the fourth week will be compared between groups, and the significance of the reduction will be analysed using the independent t test/Mann-Whitney U test.