A Prospective, Randomized, Controlled, Multi-Center Comparative Study of Two Application Regimens of Amniotic Membrane Wound Graft Versus Standard of Care in the Management of Non-Healing Venous Leg Ulcers

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ABSTRACT

Venous leg ulcerations (VLUs) frequently represent a significant clinical challenge. Dehydrated human amnion and chorion allografts have shown great promise in the treatment of recalcitrant VLUs when compared to standard wound care (SOC) alone which includes debridement followed by multilayer compression therapy with a primary absorptive dressing. Adding placental grafts into the treatment regimen is often successful as they are rich in extracellular matrix proteins, growth factors, and cytokines, and as such can induce angiogenesis and dermal fibroblast proliferation which can lead to accelerated healing. Aseptically processed grafts may have a benefit over those that are terminally sterilized. The goal of this study was to compare aseptically processed dehydrated human amnion and chorion allograft (dHACA) applied weekly or biweekly combined with standard of care versus standard of care alone in facilitating wound closure in non-healing VLUs. The research was reviewed and approved by the Western Institutional Review Board and registered on ClinicalTrials.gov.

Patients with non healing VLUs treated with SOC (appropriate debridement, primary absorptive dressing and multilayer compression) after a 2-week screening period were randomized to either receive SOC (20 patients) or wound-size-specific dHACA plus SOC applied weekly (20 patients) or wound-size-specific dHACA plus SOC applied biweekly (20 patients) for up to 12 weeks. Primary endpoint of this clinical trial was percent of patients healed (completely epithelialized)at 12 weeks.

At study conclusion, both weekly and biweekly application of dHACA was statistically significantly better at healing VLUs then standard wound therapy and at a faster overall rate. In conclusion, aseptically processed dHACA should be considered as a viable option for the refractory venous leg wounds.

BACKGROUND

Lower extremity ulcers pose significant clinical, humanistic and economic burdens on society. Millions of Americans are afflicted with painful, open, draining sores on their lower extremities. These sores are referred to as venous leg ulcerations and comprise approximately 70% of all lower extremity ulcers[1]. Under the best of circumstances, these ulcers require weeks or months to heal. Not uncommonly wound care specialists see patients who have suffered for years or faced amputation of the limb as their only option to alleviate the pain. The consequence of long term disability has been estimated at 4.6 million work days lost per year and a cost to the healthcare system up to $2.5 million annually in the United States[1]. VLU healing rates with standard compression therapy have been reported as low as 30% in 24 weeks, therefore the development and availability of advanced therapies to aid in resuming the normal wound healing process in these burdensome wounds are imperative[2].

Human amniotic membrane has a long history of clinical use[3]. Unique properties, matrix composition and endogenous growth factors that facilitate wound healing have been shown to be maintained through aseptic processing used in production of dHACA[4]. Recent clinical data has shown that dHACA is more effective than bioengineered skin substitutes in the treatment of recalcitrant diabetic wounds[5]. This is the first study evaluating dHACA effectiveness in VLUs, using weekly and biweekly application regimens, and in comparison to standard of care (SOC) multi-layer compression bandaging.

PURPOSE

The purpose of this prospective, randomized, controlled, parallel, multi-center clinical trial was to compare the proportion of ulcers completely healed by use of dHACA versus SOC patients with venous leg ulcers. The study was conducted in eight outpatient wound centers and pre-registered in ClinicalTrials.gov (NCT02609594).

RESULTS

Results are summarized in Table 1 below, and Figures 1 and 2.

Table 1. Results summary table

Metric	SOC only	dHACA weekly	dHACA biweekly
Percent wounds healed (%) - 12 weeks	30% (6/20)	75% (15/20)	75% (15/20)
Mean percent wound area reduction (%)	57.8	80.7**	

**p=0.012, dHACA weekly+biweekly combined mean, vs SOC only

Table 2. Proportion of wounds healed statistics, chi-squared test (α=0.05)

Group	Vs SOC only
dHACA weekly	p=0.02
dHACA biweekly	p=0.02
dHACA (weekly+biweekly combined)	p=0.001

Figure 1a. Percent wounds closed over 12 weeks.

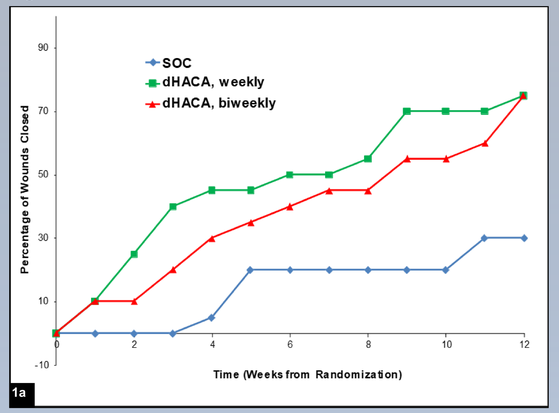


Figure 1b. Percent wound area reduction over time

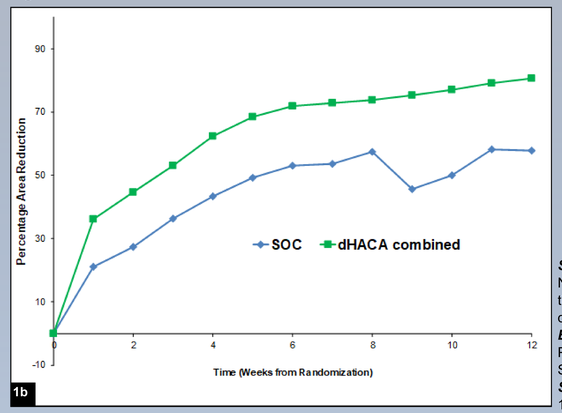
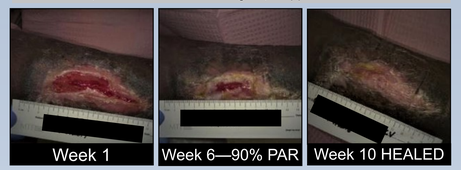
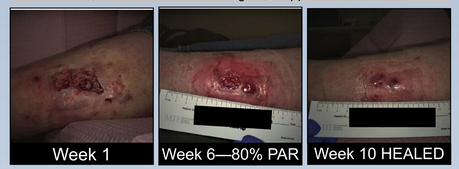


Figure 2. Representative case examples of patients healed with dHACA+SOC with either weekly or biweekly application

Case 1: Weekly application of dHACA, 73 year old patient
Starting wound size: 9.8 cm^2, VLU duration: 36 weeks
HbA1c 6.4%, Serum creatinine 1.0 mg/dL, 9 applications to close



Case 2: Biweekly application of dHACA, 67 year old patient
Starting wound size: 7.7 cm^2, VLU duration: 20 weeks
HbA1c 6.0%, Serum creatinine 0.7 mg/dL, 5 applications to close



CONCLUSIONS

Results from this multicenter randomized controlled study in VLUs demonstrate that dHACA results in greater percentage of patients healed within 12 weeks when compared to standard multi-layer compression therapy, and significantly improves patients' healing trajectory over time. These data suggest that dHACA serves to benefit patients previously failing to heal with the standard of care in venous leg ulcers.

METHODS

Table 1: Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
● At least 18 years old. ● Ankle Brachial Pressure Index (ABI) > 0.75 OR SPP > 30 mmHg OR TCOM > 30 mmHg.* ● Presence of a venous leg ulcer extending through the full thickness of the skin but not down to muscle, tendon or bone. ● The largest ulcer will be designated the index ulcer and the only one included in the study. If other ulcerations are present on the same leg they have to be more than 2 cm apart from the index ulcer. ● Study ulcer (i.e. current episode of ulceration) has been present for greater than one month prior to the initial screening visit, and has failed to respond to documented conservative measures for greater than (1) one month duration and is excluded if it has undergone 12 months of continuous high strength compression therapy over its duration. ● Study ulcer is a minimum of 2 cm2 and a maximum of 20 cm2 at the randomization visit. ● The target ulcer has been treated with compression therapy for at least 14 days prior to randomization. ● Ulcer has a clean, granulating base with minimal adherent slough at the randomization visit. ● Females of childbearing potential must be willing to use acceptable methods of contraception (birth control pills, barriers, or abstinence). ● Subject understands and is willing to participate in the clinical study and can comply with weekly visits and the follow-up regimen. ● Subject has read and signed the IRB/IEC approved Informed Consent Form before screening procedures are undertaken.	● Study ulcer(s) deemed by the investigator to be caused by a medical condition other than venous insufficiency. ● Study ulcer exhibits clinical signs and symptoms of infection. ● Known allergy to the components of the multi-layer compression bandaging, or who cannot tolerate multi-layer compression therapy. ● Study ulcer, in the opinion of the investigator, is suspicious for cancer should undergo an ulcer biopsy to rule out a carcinoma of the ulcer. ● Subjects with a history of more than two weeks treatment with immunosuppressants (including systemic corticosteroids), cytotoxic chemotherapy, or application of topical steroids to the ulcer surface within one month prior to initial screening, or who receive such medications during the screening period, or who are anticipated to require such medications during the course of the study. ● Subjects on any investigational drug(s) or therapeutic device(s) within 30 days preceding Screening. ● Study ulcer improving greater than 30% during the screening phase if the subject was not in adequate compression 14 days prior to screening. ● History of drug or alcohol abuse. ● History of radiation at the ulcer site. ● Presence of one or more medical conditions, as determined by medical history, hematologic, active auto-immune or immune diseases that, in the opinion of the investigator, would make the subject an inappropriate candidate for this ulcer healing study. ● History of having Acquired Immunodeficiency Syndrome (AIDS) or HIV. ● Study ulcer has been previously treated with tissue engineered materials (e.g. Apligraf® or Dermagraft®) or other scaffold materials (e.g. Oasis, Matristem) within the last 30 days ● Study ulcer requiring negative pressure wound therapy or hyperbaric oxygen during the course of the trial. ● Presence of any condition(s) which seriously compromises the subject's ability to complete this study, or has a known history of poor adherence with medical treatment. ● Ulcers on the dorsum of the foot or with more than 50% of the ulcer below the malleolus are excluded. ● Pregnant or breast feeding. ● Presence of diabetes with poor metabolic control as documented with a HgA1c > 12.0 within last 90 days ● Patients with renal dysfunction whose serum creatinine levels are 3.0mg/dl or greater within the last 90 days ● History of usage of tobacco products within the last 30 days ● History of Liver disease with active Cirrhosis of the liver

Study groups:
N=20 each for SOC only, dHACA+SOC weekly application, dHACA+SOC biweekly application. SOC only = absorptive wound dressings + multilayer compression bandages. dHACA+SOC = ADAPTIC TOUCH™dressing + SOC only dressings.

Endpoints:
Primary: Proportion of patients healed by 12 weeks
Secondary: Percent wound area reduction at 12 weeks

Study design:
1. Patients demonstrating < 30% wound area healing within 2 weeks of initial screening were randomized for treatment
2. Weekly patient visits included sharp debridement, saline lavage, graft application, dressing change, photography with Silhouette® camera (Aranz Medical) and measurement system.
3. Validation visit two weeks after 100% epithelialization of wound was required to confirm closure.

Data analysis:
1. Parametric or non-parametric tests used as appropriate
2. Adjusted two-sided p values < 0.05 were considered significant
3. PASW 26 (IBM, Chicago, IL) was used to perform the statistical testing

***dHACA = AmnioBand® Membrane is a registered trademark of Musculoskeletal Transplant Foundation, Edison, NJ. Silhouette® is a registered trademark of Aranz Medical, Christchurch, New Zealand. ADAPTIC TOUCH™ is a trademark of KCI USA, INC. San Antonio, TX. Study sponsored by: MTF Biologics, Edison, NJ**

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