A Multicenter Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Dehydrated Human Amniotic Membrane and Standard of Care vs Standard of Care Alone in the Treatment of 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. Adding placental grafts into the treatment regimen is often successful as they are rich in extra cellular matrix proteins, growth factors, and cytokines, and as such can induce angiogenesis and dermal fibroblast proliferation which can lead to accelerated healing.

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 and conducted at 8 wound care centers. Patients with non healing VLUs treated with SOC (appropriate debridement, primary absorptive dressing and multi-layer 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. Secondary endpoints included the proportion of ulcers achieving 40% closure at 4 weeks and the incidence of adverse events (AEs).

Among 101 patients screened for eligibility, 60 were eligible and enrolled. At 12 weeks, significantly more VLUs healed in the two dHACA-treated groups (30/40,75%)than in the SOC group (6/20, 30%), p=0.001. Treatment with dHACA remained significant after adjustment for wound area (p=0.002),with an odds ratio of 8.7 (95% confidence interval (2.2-33.6). Only six VLUs (30%) healed in the SOC group compared to 15 (75%) in the weekly dHACA group (p=0.02) and 15 (75%) in the biweekly dHACA group (p=0.02).There were no significant differences in the proportion of wounds with percent area reduction (PAR)≥40% at 4 weeks among all groups. The AE rate was 63.5%. Among the 38 AEs, none were graft- or procedure-related,

Aseptically processed dHACA should be considered as a viable option for the refractory venous leg wounds whether applied weekly or bi-weekly.

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.

REFERENCES

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*AmnioBand® Membrane (MTF Biologics, Edison, NJ)

METHODS

Study groups:

- N=20; SOC only (SOC dressings =absorptive wound dressings + multilayer compression bandages)
- N=20; dHACA+SOC weekly application
- N=20; dHACA+SOC biweekly application (dHACA+SOC = ADAPTIC TOUCH™dressing + SOC only dressings)

Endpoints:

Primary: Proportion of patients healed by 12 weeks

Secondary: Percent wound area reduction (PAR) at 12 weeks

Study design:

1. Patients <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 wound 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

Key Inclusion Criteria:

- Study ulcer is a minimum of 2cm^2 and a maximum of 20cm^2 at the randomization visit
- Target ulcer has been treated with compression therapy for at least 14 days prior to randomization
- Ankle Brachial Pressure Index (ABI) > 0.75 or SPP > 30mmHg or TCOM > 30mmHg
- Presence of VLU extending through the full thickness of the skin but not down to muscle, tendon or bone

Key Exclusion Criteria:

- Study ulcer improving greater than 30% during the screening phase if the subject was not in adequate compression 14 days prior to screening
- Study ulcer has been previously treated with tissue engineered materials (eg: Apligraft or Dermagraft) or other scaffold materials (eg: Oasis, Matristem) within the last 30 days
- Subjects on any investigational drug(s) or therapeutic device(s) within 30 days preceding screening

RESULTS

101 patients were screened, 60 were eligible and enrolled. At 12 weeks, there was significantly more VLUs healed in the two dHACA-treated groups (30/40, 75%) than in the SOC group (6/20, 30%), p = 0.001. Even after adjusting for the wound area (p=0.002), with an odds ration of 8.7 (95% confidence interval: 2.2-33.6), the dHACA treatment remained significant.

Only six VLUs (30%) healed in the SOC group compared to 15 (75%) in the weekly dHACA group (p=0.02) and 15 (75%) in the biweekly dHACA group (p=0.02). There were no significant differences in the proportion of wounds with percent area reduction (PAR) ≥40% at 4 weeks among all groups.

CONCLUSION

This multicenter randomized controlled VLU study demonstrated that the dHACA+SOC treatment, regardless of weekly or biweekly application, resulted in significantly greater healed VLUs within 12 weeks than SOC alone. The data suggests that aseptically processed dHACA serves to benefit patients previously failing to heal with the SOC and is an effective treatment option in healing chronic VLUs.

RESULTS

Table 1: Patient and Wound Characteristics

Variable	SOC	dHACA weekly	dHACA biweekly	P-values*
Mean Age (yrs)	70.0 (13)	70.0 (15.6)	69.1 (12.9)	0.77, 0.98, 0.88
Gender				
Male	13 (65%)	10 (50%)	9 (45%)	0.42
Female	7 (35%)	10 (50%)	11 (55%)	
Mean Wound Area (cm2)	6.0 (4.1)	6.0 (4.2)	4.7 (2.9)	1.0, 0.49, 0.54
Mean Wound Duration (weeks)	33.0 (41.2)	22.5 (29.8)	24.8 (37.0)	0.63, 0.76, 0.98

- Continuous variables reported as mean and standard deviation (SD);
- Categorical variables are a number (n) and percentage (%)

*P-values are SOC vs weekly; SOC vs biweekly; weekly vs biweekly

Figure 1a: Percentage wounds closed over 12 wks

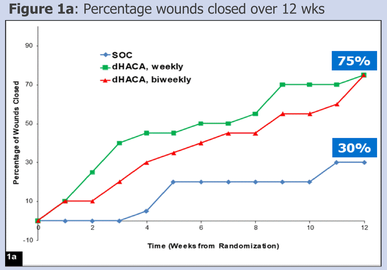
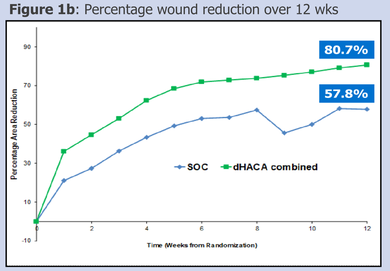


Figure 1b: Percentage wound reduction over 12 wks



Metric	SOC only	dHACA weekly	dHACA biweekly	P-values*
Percentage wounds closed at 12 weeks	30% (6/20)	75% (15/20)	75% (15/20)	0.02
Percentage wound area reduction	57.8%	80.7%		0.012

*p-values, dHACA weekly+biweekly combined mean, vs SOC only

Figure 2: Weekly case application of dHACA (73yr old patient)

T=0 (Wound open 36 weeks) | Week 6: >90% wound reduction (5 graft applications) | Week 10: Wound Healed (9 graft applications)

Weekly case: 73 year old
Starting wound size 9.8cm^2
VLU duration 36 weeks
HbA1c 6.4%
Serum creatinine 1.0mg/dL
9 applications to close

Figure 3: Biweekly case application of dHACA (67yr old patient)

T=0 (Wound open 20 weeks) | Week 6: >80% wound reduction (3 graft applications) | Week 10: Wound Healed (5 graft applications)

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