Use of an Aseptically Processed Dehydrated Human Amnion and Chorion Membrane* Improves Likelihood and Rate of Healing in Chronic Diabetic Foot Ulcers: A Prospective, Randomised, Multi-Centre Clinical Trial in Eighty Patients

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ABSTRACT

Allogeneic grafts derived from amnion/chorion are known to be efficacious in healing chronic diabetic foot ulcerations (DFUs). Aseptically processed grafts may have a benefit over those that are terminally sterilized. The goal of this study and final cohort analysis of 80 patients was to compare aseptically processed dehydrated human amnion and chorion allograft (dHACA) versus standard of care (SOC) in facilitating wound closure in non-healing DFUs.

Patients with DFUs treated with SOC (off-loading, appropriate debridement, and moist wound care) after a 2-week screening period were randomized to either SOC or wound-size-specific dHACA applied weekly for up to 12 weeks plus SOC. Primary endpoint was the percentage of wounds healed at 6 weeks between groups.

At 6 weeks, 68% (27/40) of the dHACA-treated DFUs healed compared with 20% (8/40) treated with SOC alone($p=1.9x10^{-6}$). Furthermore, at 12 weeks, 85% (34/40) of the DFUs in the dHACA group healed compared with 33% (13/40) in the SOC group($p=6.0x10^{-6}$), with a corresponding mean time to heal of 37.0 and 67.3 days, respectively. At 12 weeks, the mean number of grafts used per healed wound for the dHACA group was 4 (median 3.5), and mean cost of the tissue to heal a DFU was $1771. The mean wastage at 12 weeks was 35.3%. Three adverse events and 1 serious adverse event occurred in the dHACA group; none were graft related. Eight adverse events and 3 serious adverse event occurred in the SOC group.

BACKGROUND

Diabetes has become an epidemic in the United States of America with public health estimates showing 26 million people or roughly 8.3% of the population having diabetes[1,2]. Current data has shown that one in three Americans born in 2000 is projected to develop diabetes. It is estimated that 25% of diabetics will develop an ulcer in their lower extremity over their lifetime. Studies show that these ulcerations precede nearly 85% of lower extremity amputations[3,4]. The ultimate goal of advanced wound therapies is to facilitate resumption of the normal healing process in order to prevent complications of limb and life threatening infections and amputations[5].

Human amniotic membrane has a long history of clinical use[6]. 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[7]. It has previously been shown in a cohort of 40 patients that dHACA is effective in diabetic foot ulcer (DFU) management[8]. This study continues the evaluation to a total of 80 patients for confirmation of results in a higher sample size.

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 the standard protocol of wound care (SOC) in diabetic patients with a DFU with adequate arterial perfusion. The study was conducted in five outpatient wound centers and pre-registered in ClinicalTrials.gov (NCT02399826).

References:

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METHODS

Table 1: Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Male or female age 18 or older	• Wound probing to bone (UT Grade III/A-D).
• Type 1 or type 2 diabetes mellitus (ADA diagnostic criteria).	• Index wound greater than 25cm^2
• Signed informed consent	• HbA1c greater than 12% within previous 90 days.
• Patient's wound diabetic in origin and larger than 1 cm^2	• Serum creatinine level 3.0mg/dL or greater.
• Wound present for a minimum of 4 weeks duration, with documented failure of prior treatment to heal the wound.	• Patients with a known history of poor compliance with medical treatments.
• Wound has no signs of infection.	• Patients previously randomized into this study, or presently participating in another clinical trial.
• Wound present anatomically on the foot as defined by beginning below the malleoli of the ankle.	• Patients currently receiving radiation therapy or chemotherapy.
• Additional wounds may be present but not within 3 cm of the study wound.	• Patients with known or suspected local skin malignancy to the index wound.
• Serum creatinine less than 3.0 mg/dL.	• Patients with uncontrolled autoimmune connective tissues diseases.
• HbA1c less than 12% taken prior to randomization	• Nonrevascularizable surgical sites.
• Patient has adequate circulation to the affected extremity, as demonstrated by one of the following within the past 60 days:	• Active infection at index wound site
• Dorsum transcutaneous oxygen test (TCOM) ≥30mmHg	• Any pathology that would limit the blood supply and compromise healing.
• ABI with results of ≥0.7 and ≤1.2	• Patients who have received a biomedical or topical growth factor for their wound within the previous 30 days.
• Doppler arterial waveforms, which are triphasic or biphasic at the ankle of affected leg	• Patients who are pregnant or breast feeding.
• Patient is of legal consenting age.	• Patients who are taking medications that are considered immune system modulators that could affect graft incorporation.
• Patient is willing to provide informed consent and is willing to participate in all procedures and follow up evaluations necessary to complete the study.	• Patients taking a Cox 2 inhibitor.
	• Patients with wounds healing greater than 20% during the screening period.

Study groups:
N=40 each for dHACA+SOC and SOC only

Endpoints:
Primary: Proportion of patients healed at 6 weeks
Secondary:
Proportion of patients healed at 12 weeks, Time to Heal, Wastage, Number of Applications, Cost to Closure

Study design:
1. Patients demonstrating < 20% wound area healing within 2 week of initial screening were randomized into either of the two treatment arms.
2. Weekly patient visits included sharp debridement, cleaning, graft application, dressing change, photography, and wound measurement via acetate tracing and length,width,depth ruler measurement. Offloading was also employed.
3. Validation visit one week 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 19 (IBM, Chicago, IL) was used to perform the statistical testing

RESULTS

1. At 6 weeks, 68% (27/40) of dHACA-treated wounds had healed compared to 20% (8/40) for the wounds treated with SOC only (p=0.000019). See Figure 1a.
2. At 12 weeks, 85% (34/40) of dHACA-treated wounds had healed compared to 33% (13/40) for the wounds treated with SOC only (p=0.000006). See Figure 1a.
3. Time to heal at 12 weeks was 37.0 days compared to 67.3 days for SOC only (p=0.000006). See Figure 1b.
4. Mean number of applications to closure was 4 (median 3.5).
5. Mean wastage was 35.3%
6. Mean Cost to Closure was $1771.00.

RESULTS

Figure 1a. Percent of wounds healed by week by group.
Figure 2a. Time to closure (days) at 6 weeks and 12 weeks by group.

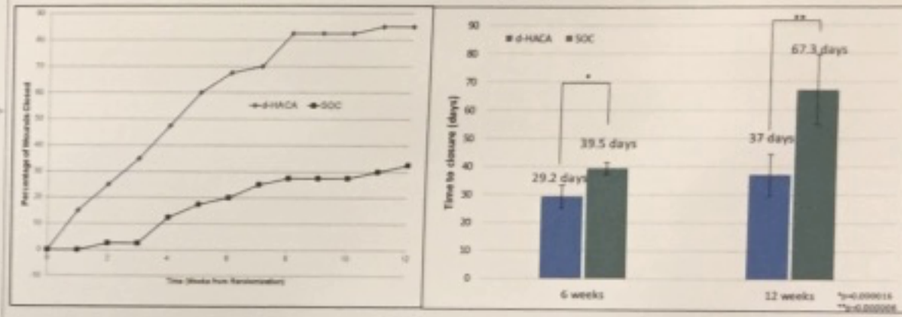
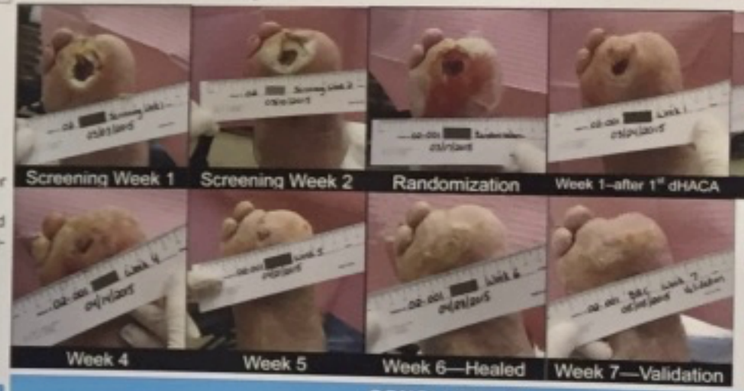


Figure 1. Representative case example of patient healed with dHACA

Patient history:
61 y/o morbidly obese male presenting with chronic right plantar forefoot ulceration, 36 week ulcer history.
HbA1C 10.5%, Serum creatinine 1 mg/dL



CONCLUSIONS

The completion of the randomized controlled multicenter clinical trial in 80 patients has confirmed positive outcomes previously reported for dHACA in published interim data[8]. In including additional patient data, the study establishes that dHACA in conjunction with standard of care results in improved likelihood of DFU healing at 12 weeks, while also maximizing economical benefits.

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