A Prospective, Randomized, Multi-Center Comparative Study of Amniotic Membrane Wound Graft Application Versus Tissue Engineered Skin Substitute in the Management of Non Healing Diabetic Foot Ulcers

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ABSTRACT

Allogeneic grafts derived from amnion/chorion are known to be efficacious in healing chronic diabetic foot ulcerations (DFUs). The goal of this study was to compare aseptically processed dehydrated human amnion and chorion allograft (dHACA*) versus a tissue engineered skin substitute (TESS*) in facilitating wound closure in nonhealing DFUs.

The research was reviewed and approved by the Western Institutional Review Board and registered on Clinical Tri-Index wound diabetic in origin and present anatomically on the foot as defined Patients with a history of radiation therapy at the index wound site als.gov. Patients with non healing DFUs treated with SOC (off-loading, appropriate debridement, and moist wound by beginning below the malleoli of the ankle • Index wound is \geq 1 cm2 and <25 cm2 care) after a 2-week screening period were randomized to either SOC with TESS or wound-size-specific Index wound present for a minimum of 4 weeks duration dHACA plus SOC applied weekly for up to 12 weeks. Endpoints for this 12 week clinical trial included percent of patient's healed, time to healing, number of graft used and graft wastage.

Patients likely to receive negative pressure wound therapy or hyperbar-• HbA1c <12% within past 90 days unless under the care of a diabetologis At study conclusion of 12 weeks 27/30(90%) of the dHACA-treated DFUs plus SOC healed compared with 12/30 ic oxygen therapy Adequate circulation to the affected extremity, as evidenced by one of the fol-(40%) treated with TESS combined with SOC ($p=4.9 \times 10^{-5}$). A corresponding mean time to healing of 32 days(95%) lowing within the past 90 days: Dorsum transcutaneous oxygen test (TCOM) or SPP (skin perfusion pressure) \geq 30mmHg; or ABI with results of \geq 0.7 and \leq 1.2 in • Patients taking immunosuppressants in the past 2 weeks or likely to CI: 22.3-41.0) for dHACA treated wounds versus 63 days(95%CI: 54.1-72.6) for the TESS treated wounds was take such medications conjunction with Doppler arterial waveforms, which are triphasic or biphasic at appreciated (p=3.2 x 10⁻⁵). At 12 weeks, the mean number of grafts used per healed wound for the dHACA group Patients who have had cytotoxic therapy within 14 days or are likely to ankle of affected leg have such treatment was 4.4 (SD=3.71); median: 2.5 and for the TESS was 7.5 (SD=3.52); median: 6. The mean graft wastage for the Patient is of legal consenting age Osteomyelitis or bone infection of the affected foot as assessed by XdHACA treated wounds was 36.3% (SD: 15.03; median: 38.2) and was 94.6% for the TESS treated wound (SD: • Patient is willing to provide informed consent and is willing to participate in all ocedures and follow up evaluations necessary to complete the study. 6.26; median: 97.6). In conclusion, aseptically processed dHACA heals diabetic foot wounds significantly faster than Subjects with a known history of poor adherence to medical treatment TESS at 12 weeks with a significantly less graft usage and wastage. Patients who are pregnant or breast feeding.

BACKGROUND

Inadequate offloading during screening period Diabetes has become an epidemic in the United States of America with public health estimates showing 26 million Study groups: people or roughly 8.3% of the population having diabetes^{1,2}. Current data has shown that one in three Americans N=30 each for dHACA+SOC and TESS+SOC 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 amputa-Endpoints: tions^{3,4}. The ultimate goal of advanced wound therapies is to facilitate resumption of the normal healing process in Primary: Time to heal by 6 weeks Secondary: Proportion of patients healed at 6 and 12 weeks, Percent Area Reduction, Cost to Closure, Wastorder to prevent complications of limb and life threatening infections and amputations⁵.

Human amniotic membrane has a long history of clinical use⁶. 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'. It has previously been shown in a cohort of 80 patients that dHACA is effective in diabetic foot ulcer (DFU) management⁸. This study evaluates dHACA effectiveness as compared to TESS, one of the most commonly accepted tissues for the treatment of $DFUs^9$.

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 TESS 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 (NCT02870816).

References:

1Narayan KMV. The Diabetes Pandemic: Looking for the Silver Lining. Clinical Diabetes 2005;23(2):51-52.

METHODS

Table 1: Inclusion/Exclusion Criteria

- **Inclusion Criteria** Male or female age 18 or older
- Type 1 or type 2 diabetes mellitus (ADA diagnostic criteria)
- Signed informed consent
- Serum creatinine <3.0 mg/dL</p>

Study design:

- . 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 ruler measurement. Offloading was also employed.
- 3. Validation visit one week after 100% epithelialization of wound was required to confirm closure.

Data analysis:

- . 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

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

Metric	dHACA+SOC	TESS+SOC	p-value
Mean time to heal (days) - 6 weeks	24 days	39 days	0.00008
Mean time to heal (days) - 12 weeks	32 days	63 days	0.000032
Percent wounds healed (%) - 6 weeks	77% (23/30)	23% (7/30)	0.000036
Percent wounds healed (%) - 12 weeks	90% (27/30)	40% (12/30)	0.000049
Mean percent wound area reduction (%)	98%	44%	0.000031
Mean number of grafts to closure	3.7	6.1	n/a
Mean graft cost to closure (\$)	\$2200	\$7900	n/a
Mean graft wastage (%)	36.3%	94.6%	n/a

Exclusion Criteria

• Wounds of greater severity than Wagner I

• Other wounds within 2 cm of the index wound

• Patients participating in another clinical trial.

Patients with known or suspected local skin malignancy to the index

• Active infection at index wound site (at randomization)

 Patients who have received investigational drug(s), therapeutic device (s), or any kind of tissue-engineered product within the previous 30 days

Patients with wounds healing greater than 20% during the screening



Figure 2. Representative case example of patients healed with dHACA+SOC Case 1:

Starting wound size: L: 3.30 cm, W: 1.80 cm, D: 0.10 cm HbA1C 9.5%, Serum creatinine 1 mg/dL



Case 2:

Starting wound size: L: 1.00 cm, W: 1.10 cm, D: 0.10 cm HbA1C 5.9%, Serum creatinine 0.64 mg/dL



The completion of this randomized controlled multicenter clinical trial confirms positive outcomes previously reported for dHACA in published RCT data⁸. The study also establishes that dHACA in conjunction with standard of care is superior to TESS with SOC with regard to healing efficacy and cost effectiveness.

*dHACA = AmnioBand[®] Membrane is a registered trademark of Musculoskeletal Transplant Foundation, Edison, NJ. *TESS = Apligraf is a registered trademark of Novartis, Basel, Switzerland.

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CONCLUSIONS

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² CDC 2011 National Estimates – 2011 National Diabetes Fact Sheet – Publications – Diabetes DDT. URL http://www.cdc.gov/diabetes/pubs/estimates11.htm [accessed] on 16 December 2013]

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