An Evaluation of Healing with the use of Dehydrated Human Amniotic/Chorionic Membrane Allografts following Failure of Standard of Care in Patients with Chronic Diabetic Foot Ulcers

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Abstract

Introduction: Human amniotic membrane allografts have been used for a variety of reconstructive surgical procedures since the early 1900s.[1-4] Interest in utilization of amniotic membrane waned in the early 1980's due to concern regarding infectious disease transmission. To ameliorate this concern a method has been developed allowing the amniotic/chorionic membrane to be dehydrated and sterilized.[5] The method permits improved ease of use and storage while maintaining biological effectiveness. Our purpose is to evaluate healing of chronic diabetic foot ulcers with use of dehydrated human amniotic/chorionic membrane (dHACM) in patients failing standard treatment (SOC).
Methods: An IRB approved randomized clinical trial was conducted comparing SOC (n=12) to SOC+dHACM (n=13).[6] Included in the present study (n=11) were SOC patients failing to heal in the RCT. One week after withdrawal from the RCT these patients were offered and accepted treatment with dHACM. Subsequent evaluation of clinical records was made with IRB approval and patient consent. Each patient was used as their own control to compare reduction of wound size during the treatment periods and rate of complete healing achieved with dHACM.
Results: In the initial RCT, 92% vs. 8% of patients in the dHACM vs. SOC healed completely (p<0.001).[6] At time of dHACM application for those failing to heal with SOC in the RCT, mean wound chronicity was 21.0±12.4 weeks and mean wound size was 4.7±5.0cm^2. Complete healing was achieved in 6/55% by 4 weeks, 7/64% by 6 weeks, and 10/91% by 12 weeks with bi-weekly dHACM application. Mean healing time was 3.0±4.2 weeks for the 10 patients healed. Wounds decreased in size an average of 26.8±45.3% after 4 weeks of SOC treatment compared to 87.6±16.0% after 4 weeks of dHACM treatment (2 applications).
Conclusion: Use of dHACM provides superior rates of healing compared to SOC in patients with chronic DFU.

Introduction

Diabetes affects at least 6% of the population, or approximately 16 million people in the United States. Lower extremity ulcers are a serious complication for people with diabetes, developing in some 25% of individuals with the disease.[7] These ulcers are often difficult and expensive to treat, and lead to severe morbidities. Conservative treatments are based on clinical evaluation and judgment and may include sharp debridement, wet-to-moist dressings, application of enzymatic agent, and the application of standard dressings. Advanced therapies and biologic dressings are often initiated after conservative treatments have failed.

Amniotic Membrane[8]

- Encapsulates the fetal compartments: composed of amnion and chorion layers
- Non-vascular tissue consisting of epithelium cells, basement membrane, a thick compact layer and fibroblast layer
- Fibrous layer contains cell anchoring collagen types: IV, V, and VII
- Biochemical properties help to reduce inflammation and enhance soft tissue healing
- Has antibacterial and pain reduction properties, are self-signaling and mediate tissue repair via the contained growth factors*

EpiFix® - A Dehydrated Human Amniotic /Chorionic Membrane Allograft

- A biologically active implant or graft for tissue regeneration application
- Amniotic membrane obtained from screened and tested donors to ensure safety
- Cleaned, dehydrated, and sterilized by the proprietary PURION® process which produces a safe tissue with a 5 year, ambient temperature, shelf life

Study Design and Purpose

A retrospective crossover study of patients with Type 1 or Type 2 diabetes, having a diabetic foot ulcer (DFU) of at least 6 weeks duration that failed to heal with standard of care (SOC) was conducted. All patients had previously been enrolled in a prospective randomized trial comparing healing characteristics with SOC treatment alone vs. SOC with the addition of dHACM (EpiFix®, MiMedx, Marietta, GA) and had completed that study without healing of their DFU.

* These properties are present in native amniotic membrane and may not reflect the properties of processed amniotic allografts.

Methods

This retrospective study was conducted under an IRB approved protocol in Southwest Virginia. Patients read and signed an approved informed consent prior to any study involvement.

Included

Patients with DFU previously randomized to SOC (n=11) who failed to heal upon completion of the clinical trial (dHACM vs. SOC).

Study Outcomes

- Ulcer size reduction at 4 and 6 weeks
- Proportion of ulcers healed during the study period
- Mean time to healing

Treatment

- Following surgical debridement of all necrotic tissue, dHACM was applied to the wound.
- A non-adherent dressing was used to cover the dHACM, followed by a moisture-retentive dressing (hydrogel) and a compression dressing.
- All wounds were offloaded using a removable cast walker
- Dressing changes took place weekly during the office visit.
- If the ulcer had not completely epithelialized, an additional piece of dHACM was applied at week 2, week 4, week 6, week 8, and week 10.

Data Analysis

- Each patient was used as their own control to compare wound size reduction between treatment periods (SOC only vs. SOC with dHACM).
- Paired t-test or Mann Whitney rank sum test were used to compare continuous variables between study intervals.
- The level of statistical significance was set at p<0.05.

Results

Table 1. Patient characteristics.

Variable	N=11
Male Gender	7 (63.6%)
Age (yr)	61.5 ± 10.5
BMI (kg/m^2)	35.6 ± 6.9
Obese (>29.9 kg/m^2)	8 (72.7%)
Smoker	2 (18.2%)
Caucasian race	10 (90.9%)
Wound size (cm^2)	4.7 ± 5.0
Wound duration (weeks)	21.1 ± 12.4

Data presented as mean ± SD or percent as indicated. BMI = body mass index.

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Results

Table 2. Mean percent reduction in wound size vs. baseline during each treatment period.

Treatment week	SOC Period (RCT) (n=11)	After dHACM (n=11)	p-value
Week 1 (%)	21.4 ± 36.8	62.5 ± 29.9	0.013
Week 2 (%)	15.5 ± 52.3	76.2 ± 25.3	0.003
Week 3 (%)	13.3 ± 45.3	87.0 ± 15.9	<0.001
Week 4 (%)	26.8 ± 45.3	87.6 ± 16.0	<0.001
Week 5 (%)	6.7 ± 63.8	92.6 ± 12.6	<0.001
Week 6 (%)	-10.6 ± 65.8	93.9 ± 11.1	<0.001

Data presented as mean ± SD.

- In the initial study period while receiving SOC only, measurements of wound size were inconsistent week to week and by week 6 the overall mean wound size had increased over baseline. During the dHACM treatment period consistent reduction in wound size was noted week to week. (Figure 1)
- Wounds were reduced by > 50% in 81.8% patients (9/11) by week 2 (1 dHACM application).
- By week 4 (2 dHACM applications) all patients had achieved >50% reduction in wound size.
- Complete healing was achieved by 10/11 (91%) of patients once they received dHACM. (Figure 2)
- Long-term follow-up occurred in 18 of 22 patients at 9-13 months post-healing. 17 of 18 (94.4%) remained healed without DFU recurrence.

Figure 2. Percent of patients completely healed with dHACM after failing SOC.

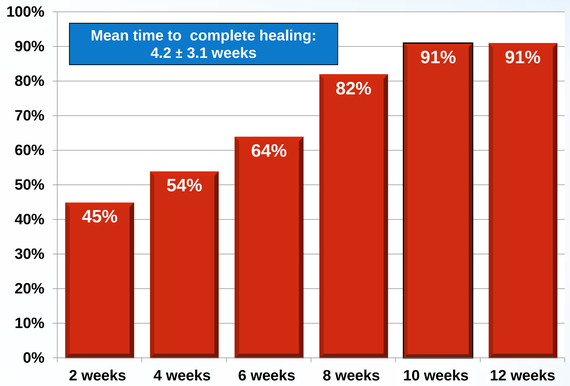
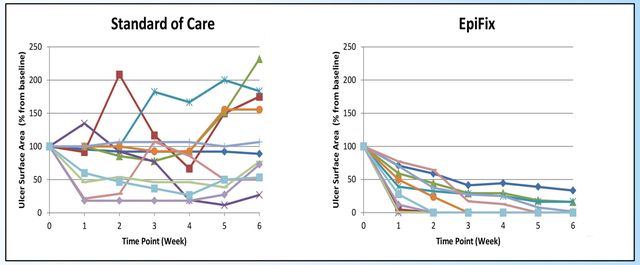
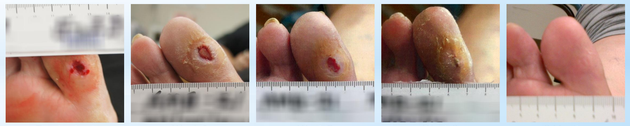


Figure 1. Rates of wound healing with SOC vs. dHACM (EpiFix®).



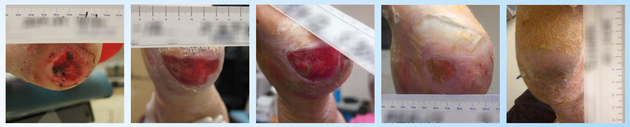
Examples of Subjects Healed with dHACM

Case 1. Patient healed in 2 weeks (1 EpiFix® application)



Randomized in RCT (SOC) | Week 6 RCT Exited | Week 7 1st EpiFix® Applied | Week 9 100% Epithelialized | 9 Months Remain Healed

Case 2. Healed in 9 weeks (5 EpiFix® applications)



Randomized in RCT (SOC) | Week 6 RCT Exited | Week 7 1st EpiFix® Applied | Week 16 100% Epithelialized | 13 Months Remain Healed

Conclusion

- In the present study of 11 patients with chronic diabetic foot ulcers that failed to heal with SOC, 11 (100%) showed >50% reduction in wound size within 4 weeks of starting treatment with dHACM and 10 (91%) had complete healing of their wound within 9 weeks of dHACM initiation.
- From the original 25 patients enrolled in the randomized trial, 23 (92%) were ultimately healed with dHACM.
- Limitations of the current study are inherent to those of a retrospective study design and small sample size. These findings should be confirmed and expanded with subsequent clinical trials.
- These results illustrate that the addition of dHACM to routine wound management can enhance wound healing in patients with diabetic foot ulcers.

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