A Prospective, Randomized, Controlled, Multi-Center Comparative Effectiveness Study of Healing Using Dehydrated Human Amnion/Chorion Membrane Allograft, Bioengineered Skin Substitute, or Standard of Care for Treatment of Chronic Diabetic Lower Extremity Ulcers

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Desert Foot, November 18-20, 2015 in Phoenix, AZ

Background

- In 2012, more than 22.3 million people in the United States had a diagnosis of diabetes, with an attendant cost of approximately $245 billion, including $176 billion in direct medical cost and $69 billion in lost productivity.[1]
- Approximately 25% of people with diabetes will develop a lower extremity ulcer over their lifetime.[2] These wounds are often slow to heal and frequently reoccur.
- Diabetic ulcers precede 85% of lower-extremity amputations, and it is estimated that up to 85% of these amputations may be preventable.[3]
- The desired goal of diabetic ulcer treatment is to promote rapid and complete healing in order to reduce the risk for infection and its limb- or even life-threatening complications.
- The Wound Healing Society guidelines recommend consideration of advanced wound therapies if a diabetic ulcer does not reduce in size by 40% or more after 4 weeks of standard therapy.[4]
- Randomized, controlled clinical trials have demonstrated that bioengineered skin substitutes (BSS) and dehydrated human amnion/chorion membrane (dHACM) both promote wound closure, resulting in more frequent and rapid healing of chronic diabetic ulcers when compared to standard therapy, yet there is little data available with which to assess differences in clinical and cost effectiveness between commercially available products.[5-8]
- A retrospective analysis of data collected in separate randomized trials suggests that dHACM may be superior to several products in promoting rapid healing.[9]

Study Design and Statement of Purpose

The purpose of this prospective, randomized, controlled, parallel group, multi-center clinical trial was to compare healing effectiveness of chronic lower extremity diabetic ulcers treated with either weekly application of BSS, dHACM, or standard wound care (SOC) with collagen-alginate dressing. The study was conducted at three outpatient centers in the state of Virginia (USA) and was approved by Western IRB (WIRB) and pre-registered in ClinicalTrials.gov (NCT01921491).

References

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Methodology

Included

- Type 1 or Type 2 diabetic patients presenting for care of a lower extremity ulcer.
- Ulcer duration of ≥4 weeks with ulcer size ≥1cm^2 and <25cm^2.
- Inclusion/exclusion criteria were used to determine patients eligible to enter the two week study run-in period prior to study enrollment and randomization.
- Patients demonstrating a reduction in wound size of 20% or less after the 2 week run-in period and who still met all study inclusion/exclusion criteria were enrolled and randomized to one of 3 study groups (BSS, dHACM, or SOC) in a 1:1:1: ratio.

Study Groups

- 20 patients in dHACM arm; 20 patients in the BSS arm; 20 patients in SOC arm

Study Outcomes

- Primary study outcome was the percentage of wounds completely healed after 4 and 6 weeks of treatment.
- Secondary outcomes included percent change in wound area per week, velocity of wound closure, and a calculation of amount used and cost of dHACM or BSS.

Treatment

- Patients were seen by the investigator at least once every 7 days (± 3 days) for up to 12 weeks, or until one week after complete healing, whichever occurred first.
- Procedures conducted at each study visit included: ulcer debridement if required and cleansing with a sterile normal saline solution, weekly application of graft if required, ulcer measurement and photography, assessment for adverse events, wound dressing and offloading with removable cast walker.
- Wound surface area was calculated by width x length, and depth, and an acetate tracing of the wound was also performed.

Data Analysis

- The null hypothesis was that the proportion of wounds that achieve complete healing within 6 weeks is the same for dHACM or BSS treated subjects.
- Parametric and non-parametric tests were used as appropriate.
- Adjusted two-sided p-values <0.05 were considered significant.
- SAS® 9.4 (SAS Institute, Inc., Cary, NC) was used to perform statistical testing.

Results

- Clinical characteristics were similar between the study groups (Table 1).
- The primary study outcome is presented in Figure 1 showing significantly higher rates of wound healing at 4 and 6 weeks in patients receiving dHACM.
- Velocity of wound closure is presented in Figure 2 illustrating that wounds treated with dHACM had more rapid healing compared to wounds treated with BSS.
- Median time to healing was significantly faster (all adjusted p-values ≤0.001) with dHACM-13 days compared to BSS-49 days or SOC-49 days.
- Mean number of grafts and amount of graft material used is shown in Figure 3. Overall due to available graft size, 5297 cm^2 of BSS vs. 86 cm^2 of dHACM was discarded.
- Cost per patient (Figure 4) was lower in the dHACM group at 2.15 grafts at cost of $1669 versus the BSS group at 6.2 grafts at cost of $9216.

dHACM = EpiFix®. EpiFix® is a registered trademark of MiMedx Group, Inc., Marietta, GA
BSS = Apligraf®. Apligraf® is a registered trademark of Novartis
Study sponsored by: MiMedx®, Marietta, GA

Results

Table 1. Clinical characteristics at study enrollment (*all p>0.05*).

	BSS (n=20)	dHACM (n=20)	Standard Care (n=20)
Mean Age, in years (SD)	65.2 (11.7)	63.2 (13.0)	62.2 (12.8)
Age ≥ 65 years (n, %)	11 (55.0%)	11 (55.0%)	9 (45.0%)
Male Gender	9 (45.0%)	10 (50.0%)	9 (45%)
Race			
Caucasian	18 (90.0%)	19 (95.0%)	17 (85.0%)
African-American	2 (10.0%)	1 (5.0%)	3 (15.0%)
Mean BMI (SD)	32.7 (8.56)	35.0 (7.5)	35.8 (9.7)
Obese BMI ≥ 30 (n, %)	13 (65.0%)	14 (70.0%)	14 (70.0%)
Mean HbA1c (SD)	8.0 (1.9)	7.4 (1.5)	8.0 (1.8)
HbA1c ≥ 9% (n, %)	6 (30.0%)	2 (10.0%)	5 (25.0%)
Smoker (n, %)	3 (15%)	5 (25%)	5 (25%)
Mean Duration of Index Ulcer in weeks (SD)	18.5 (13.8)	15.6 (12.7)	16.2 (13.5)
Median (Min, Max)	13 (6, 54)	11 (5, 54)	9 (6, 52)
Mean Baseline wound size, in cm^2 (SD)	2.6 (1.8)	2.7 (2.4)	3.3 (2.7)
Median (Min, Max)	2.1 (1.0, 6.8)	2.0 (1.0, 9.0)	2.0 (1.0, 9.0)

Data presented as mean (standard deviation), median (minimum, maximum), or number (percent) as indicated. BMI= body mass index.

Figure 1. Primary study outcome - rates of complete wound healing at 4 and 6 weeks.

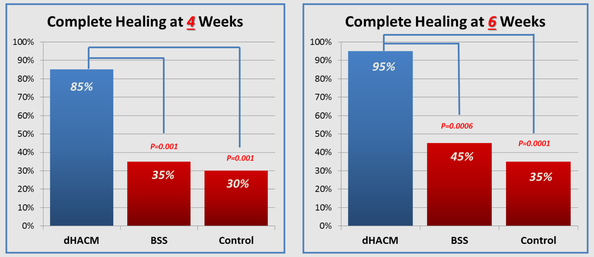
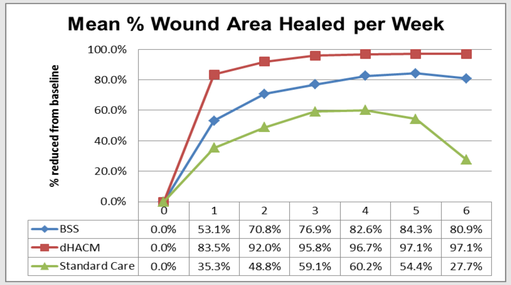


Figure 2. Percent wound size reduction per week.



	0	1	2	3	4	5	6
BSS	0.0%	53.1%	70.8%	76.9%	82.6%	84.3%	80.9%
dHACM	0.0%	83.5%	92.0%	95.8%	96.7%	97.1%	97.1%
Standard Care	0.0%	35.3%	48.8%	59.1%	60.2%	54.4%	27.7%

Figure 3. Product usage.

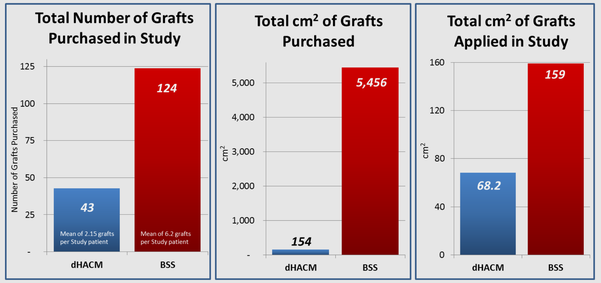
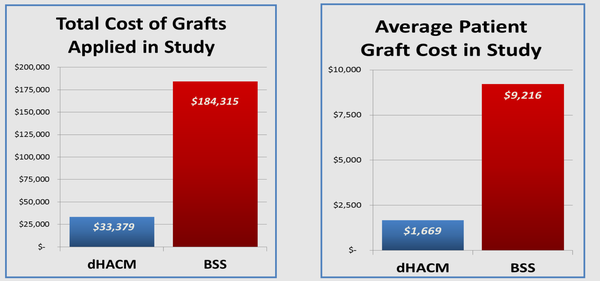


Figure 4. Costs of grafts.



Conclusions

- Wounds treated with dHACM were more likely to heal completely and reduce in size more rapidly, with less graft material used and at less cost compared to wounds treated with BSS, indicating that dHACM allografts are more clinically and cost effective than BSS for the treatment of lower extremity ulcers in patients with diabetes.
- This is the first multi-center randomized comparative effectiveness study examining side by side the performance, outcomes, and utilization of two advanced wound care products as a treatment for chronic lower extremity diabetic ulcers.