A Prospective, Multicenter, Randomized, Controlled Study Confirming the Efficacy of Dehydrated Human Amnion/Chorion Membrane Allograft in the Management of Diabetic Foot Ulcers

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Background

- Diabetic foot complications, such as ulcerations, infections, and gangrene, are a common cause of hospitalization, amputations and disability among diabetic patients.
- Routine ulcer care, treatment of infections, amputations, and hospitalizations cost billions of dollars every year in the US alone and place tremendous burdens on health care systems worldwide.[1,2,3]
- Over their lifetime, up to 34% of people with diabetes may develop lower extremity ulcers and an estimated 12% of those patients will ultimately require lower extremity amputation.[4,5]
- Guidelines suggest that advanced wound therapies be incorporated into the treatment plan if an ulcer does not reduce in size by at least 40% after 4 weeks of standard wound therapy.[6]

Dehydrated Human Amnion/Chorion Membrane (dHACM)

- Level 1 evidence examining the efficacy of dehydrated human amnion/chorion membrane (dHACM) as a treatment for diabetic foot ulcers in addition to wound offloading, has reported statistically significant superior rates of complete healing and a more rapid time to healing when dHACM is incorporated into the treatment plan, compared to standard wound care and offloading alone.[7]
- Two additional Level 1 comparative effectiveness studies have shown superiority of dHACM when compared with another bioengineered skin substitute, and a standard care group for healing at 6 weeks[8] and at 12 weeks.[9]

Purpose

- The purpose of the present study is to further confirm the efficacy of using the dHACM allograft as a treatment for chronic diabetic lower extremity ulcers.

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Methods

- An IRB approved, randomized, controlled, multicenter clinical trial was conducted at 14 wound care centers in the US.

Patient Screening and Eligibility

- Patients with Type 1 or Type 2 diabetes with a lower extremity ulcer of at least 4 weeks duration were entered into a 2-week study run-in and treated with alginate wound dressings and offloading (cam walker, offloading boot, shoe, or complete contact cast).
- Those with <25% wound closure at run-in completion entered the treatment phase.

Treatment Phase

- Randomized in a 1:1 ratio to receive weekly application of dHACM (dHACM group), or standard wound dressings without dHACM (no-dHACM group).
- Sharp debridement performed weekly (if wound had not healed).
- In the dHACM group, a wound size appropriate allograft was applied to the debrided wound bed, hydrated if necessary, and then dressed with a non-adherent silicone dressing, an absorbent non-adhesive hydropolymer secondary dressing, and wrapped with gauze.
- Subjects in the no-dHACM group had their wounds cleansed, debrided and dressed with a standard alginate dressing, an absorbent non-adhesive hydropolymer secondary dressing, and wrapped with gauze.
- Appropriate offloading continued in both study groups.
- Ulcer measurements were performed after cleansing and debridement using the SilhouetteStar™ camera and Silhouette Connect® system.
- Patients were followed weekly for 12 weeks, with final follow-up at week 16.

Study Analysis

- Data from 110 patients (n=54 in dHACM group, n=56 in no-dHACM group) meeting study inclusion and exclusion criteria were analyzed in the Intent-to-Treat (ITT) cohort. ITT analysis requires enrolled patients, who met the inclusion/exclusion criteria, to be included even if they did not complete the study or fully adhere to the protocol.
- A total of 98 patients (n=47 in dHACM group, n=51 in no-dHACM group) completed the study Per-Protocol (PP) cohort. In comparison, in a PP analysis, only patients who completed the entire clinical trial according to the protocol are counted towards the final results.

Study Outcome

- Primary outcome was percent of study ulcers completely healed within 12 weeks.

Results

- No statistically significant differences were observed in the patient demographics. Plantar ulcers were less prevalent in the dHACM group than in the no-dHACM group (48% vs 74%, *p*=0.0190).
- Rates of complete healing are presented in Figure 1.
- The median number of grafts applied per healed wound was 5 (range 1-12).
- Median cost per dHACM healed ulcer was $2,252.33 (range $306.95 - $12,394.02).
- At final 16 week follow-up, 95% of dHACM healed ulcers and 86% of healed ulcers in the no-dHACM group remained closed.

Figure 1. Primary outcome: healing rates at 12 weeks.

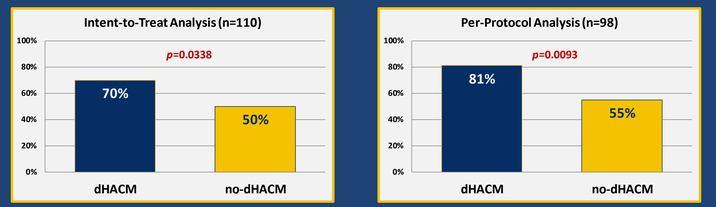
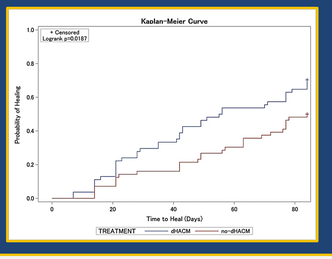


Table 1. Refined Cox regression results after eliminating stepwise covariates with descending *p*-values (ITT population).

Variables	*p*-Value	Hazard Ratio	95% CI for HR	
			Lower	Upper
Treatment - dHACM	0.003	2.15	1.30	3.57
Race - Caucasian	0.008	3.01	1.33	6.80
Hx of Recurring DFU - Yes	0.029	0.42	0.20	0.92
Baseline Ulcer Size ≥ 2.2cm^2	0.003	0.44	0.26	0.75
Inadequate Debridement	0.022	0.36	0.15	0.86
Ulcer Location - Toe	0.013	3.29	1.29	8.38
Ulcer Location - Forefoot	0.043	2.12	1.02	4.39
Ulcer Location - Midfoot	0.095	2.20	0.87	5.55

- Adjusting for co-variates associated with healing, Cox regression analysis showed subjects treated with dHACM were more than twice as likely to heal completely within 12 weeks than those not receiving dHACM (HR: 2.15, 95% confidence interval 1.30-3.57, *p*=0.003), and subjects identified as having inadequate debridement were 64% less likely to heal within 12 weeks.

Figure 2. A Kaplan-Meier plot of time-to-heal within 12 weeks by study group (ITT population).



- Kaplan-Meier analysis showed significantly improved time-to-healing with use of dHACM, Log-Rank *p*=0.0187).

Conclusions

- The results of this multicenter, randomized, controlled study support and confirm that dHACM is an efficacious treatment for lower extremity ulcers.
- A unique feature of the current study is evaluation of the thoroughness of debridement and its influence on healing outcomes. Patients were 3x more likely to heal at 12 weeks with adequate debridement. These results support the importance of adequate wound debridement on rates of healing.
- Both ITT and PP analysis showed significantly greater rates of healing with use of dHACM.
- These results provide additional Level I evidence regarding the efficacy of dHACM, they are useful to clinicians who are determining which advanced wound care product to choose when caring for their patients, and they offer additional data points for healthcare policy makers in both the United States and globally who are challenged to evaluate the benefits of available advanced wound care products compared with costs.

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