A Multicenter Prospective Randomized Controlled Comparative Parallel Study of Dehydrated Human Umbilical Cord Allograft for the Treatment of Diabetic Foot Ulcers

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Abstract

To determine the safety and effectiveness of dehydrated human umbilical cord allograft* for the treatment of chronic, non-healing diabetic foot ulcers (DFUs). An IRB approved, multicenter, randomized, controlled trial was conducted at 11 centers in the United States. Individuals with diabetes and a 1-15 cm² DFU below the ankle for at least 30 days were eligible for the 14-day run-in phase with weekly debridement, moist wound therapy and off-loading. Those with ≤30% wound area reduction post-debridement were randomized in a 2:1 ratio to receive weekly application of allograft (n=101) or standardized therapy with alginate wound dressing, non-adherent silicone dressing, absorbent non-adhesive hydropolymer secondary dressing, and gauze (n=54). All DFUs were appropriately off-loaded. Study visits with debridement, wound photography, measurement, and treatment group specific dressings, were conducted for 12 weeks. Primary outcome was percent of DFUs with complete closure within 12 weeks. Data were evaluated using an intent-to-treat (ITT) analysis (n=155). Additional analysis was conducted on subjects completing the study per protocol (PP), (n=134) (allograft, n=86, alginate, n=48), and for those subjects receiving adequate debridement (allograft, n=67, alginate, n=40). ITT analysis showed that DFUs treated with allograft had higher healing rates within 12 weeks than those receiving alginate dressings, 71/101 (70%) versus 26/54 (48%) for allograft and alginate dressings respectively, p=0.0089. PP healing rates at 12 weeks were 70/86 (81%) for allograft-treated and 26/48 (54%) for alginate-treated DFUs, p=0.0013. For those DFUs with adequate debridement (n=107, ITT population), 64/67 (96%) of the allograft-treated ulcers healed completely within 12 weeks, compared with 26/40 (65%) of alginate-treated ulcers, p<0.0001. One-hundred-sixty adverse events were reported from 75 subjects. None were related to either allograft or alginate dressings. These results demonstrate the importance of adequate wound debridement and the safety and efficacy of dehydrated human umbilical cord allograft as a treatment for non-healing DFUs.

Background

- The estimated total cost of diagnosed diabetes is on the rise in the US with 2012 costs estimated at $245 billion.[1]
- Development of diabetic foot ulcers (DFUs) significantly influences costs related with managing a patient with diabetes.
- Given the high costs associated with treating DFUs, treatment strategies that promote more rapid and complete healing are warranted.[2]

Human Umbilical Cord

- Consisting of both amniotic epithelium and Wharton's jelly, human umbilical cord contains extracellular matrix composed of collagen, proteoglycans and hyaluronic acid, and provides a protective environment for the healing process.[3]
- Low immunogenicity of placental tissue[4] lends credence to its use as an allograft material for difficult to heal wounds.
- Dehydrated human umbilical cord (dHUC) allograft is a minimally manipulated, dehydrated, non-viable cellular umbilical cord for homologous use processed through a patented PURION® Plus process that provides an easy to use allograft stored at ambient conditions.
- A recent study established that dHUC allograft possesses biological properties that stimulate cellular responses important for soft tissue healing.[5]

Purpose and Study Design

- The purpose of this study was to determine the efficacy and safety of dHUC allograft for the treatment of chronic, non-healing DFUs.
- We conducted an IRB approved, multicenter, randomized, controlled trial at 11 centers across the US.
- The study period consisted of a 2-week run-in phase, 12-week treatment phase, and 4-week follow-up phase.

Methods

Patient Run-in Phase

- Individuals with Type 1 or Type 2 diabetes and a 1-15 cm² DFU below the ankle for at least 30 days were eligible for the 14-day run-in phase with weekly debridement, moist wound therapy and offloading.

Treatment Phase

- Subjects with ≤30% wound area reduction post-debridement were randomized in a 2:1 ratio to receive either weekly application of dHUC allograft (n=101) or standardized therapy with alginate wound dressing (n=54). Non-adherent silicone dressings, absorbent non-adhesive hydropolymer secondary dressings, and gauze were also applied.
- All DFUs were appropriately offloaded using an appropriate sponsor-approved device.
- Wounds were cleaned and debrided weekly as necessary, then photographed and measured using a Silhouette® camera.

Study Analysis

- The intent-to-treat (ITT) population (all randomized subjects) was used as the basis for the primary efficacy analysis (n=155).
- Additional analysis was conducted on subjects completing the study per protocol (PP), (n=134) (dHUC allograft, n=86, alginate, n=48), and for those subjects receiving adequate debridement (dHUC allograft, n=67, alginate, n=40).
- All randomized subjects meeting study inclusion criteria who received at least one application of dHUC allograft were used for the analysis of safety data. Subjects who discontinued the trial before their wound healed were categorized as treatment failures for the primary efficacy analysis and their last observation was carried forward.

Study Outcome

- Primary outcome was percent of DFUs with complete closure within 12 weeks.

Validation of Healing

- Complete healing was defined as 100% epithelialization of the wound.
- Adequate debridement was defined as exposure of healthy tissue in the ulcer bed with no significant eschar, callous, necrotic tissue, or foreign material present in or around the wound.
- To insure consistency across study sites all images taken before and after debridement with the Silhouette system were examined by a group of three wound care specialists who had not enrolled patients into the study and were blinded to group assignment, study sites, and treating clinician.

**Dehydrated human umbilical cord (dHUC) allograft = EpiCord®, MiMedx Group, Inc., Marietta, GA*
EpiCord® and PURION® PLUS are registered U.S. trademarks of MiMedx Group, Inc.
Study sponsored by MiMedx®, Marietta, GA

Results

- In the overall study population (n=155) 81.3% were male, 42.9% were smokers, 63.2% were obese, and 17.4% had a prior amputation.
- The two groups were well matched for demographic and clinical factors, as well as location, duration, and size of the study ulcer.
- ITT analysis showed that DFUs treated with dHUC allograft had higher healing rates within 12 weeks than those receiving alginate dressings, 71/101 (70%) versus 26/54 (48%), *p*=0.0089.
- Healing rates at 12 weeks for subjects treated PP were 70/86 (81%) for allograft-treated and 26/48 (54%) for alginate-treated DFUs, *p*=0.0013.
- For those DFUs with adequate debridement (n=107, ITT population), 64/67 (96%) of the allograft-treated ulcers healed completely within 12 weeks, compared with 26/40 (65%) of alginate-treated ulcers, *p*<0.0001.
- The median number of dHUC allografts applied per healed wound was 7 (range 2-12).
- Average cost per dHUC healed ulcer was $3,250.99 ± $2,898.48.
- Overall, 75 subjects experienced at least one adverse event, with a total of 160 adverse events recorded. There were no adverse events related to either dHUC allograft or alginate dressings.
- Of the 71 healed ulcers treated with EpiCord during the 12 week treatment phase, 68/71 (96%) remained closed at week 16 follow-up, while 22 of the 26 ulcers healed with alginate dressings (85%) had remained closed.

Figure 1. Primary study outcome. Complete healing within 12 weeks of treatment initiation (ITT population).

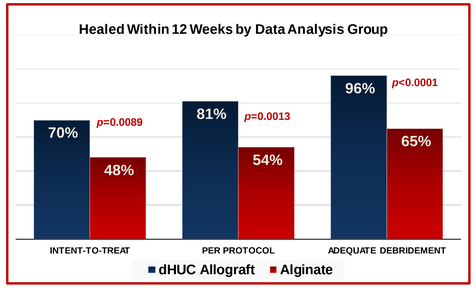
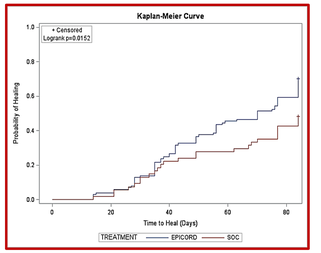


Figure 2. A Kaplan-Meier plot of time-to-heal within 12 weeks by study group (ITT population).



- A Kaplan-Meier plot of time-to-heal within 12 weeks by study group, demonstrated a superior wound healing trajectory for dHUC treated vs alginate treated (SOC) ulcers. The Log-Rank test of equality of the healing function over the 2 study groups produced a chi-square test statistic of 5.89, with a *p*=0.0152.

Conclusions

- This is the first RCT on the use of dHUC allograft as a treatment for DFUs.
- The results of this large, multicenter, randomized, controlled trial provide Level 1 evidence regarding the safety and efficacy of dHUC allograft as a treatment for non-healing DFUs.
- In addition, results illustrate the importance of adequate wound preparation and debridement which lies in the hands of clinicians.
- Both ITT and PP analysis showed significantly greater rates of healing with the use of dHUC allograft.

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