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

Introduction

Diabetes affects at least 6% of the population, or approximately 16 million people in the United States. Externally ulcerated ulcers are a serious complication for people with diabetes, developing in some 25% of individuals with the disease. 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-dressings, application of enzymatic agents, and the application of standard dressings. Advanced therapies and biologic dressings are often initiated after conservative treatments have failed.

Amenotic Membrane:
- Encapsulates the fetal compartments: composed of amnion and chorion layers
- Non-vascular tissue consisting of epithelial cells, basement membrane, a thin compact layer and fibroblast layer
- Fibrous layer contains cells anchoring collagen types IV, VI, and VII
- Biochemical properties help to reduce inflammation and enhance soft tissue healing
- Has antibacterial and anti-fungal properties, are self-gelling and mediate tissue repair via the contained growth factors

EpiFix® - A Dehydrated Human Amnion-Chorionic Membrane Allograft:
- A biologically active implant or graft for tissue regeneration application
- Amnionic membrane obtained from screened and tested donors to ensure safety
- Cleaned, dehydrated, sterilized and informed 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, with a diabetic foot ulcer (DFU) of at least 4 cm2 in size that failed to standard of care (SOC) was conducted. All patients had previously been enrolled in a prospective randomized trial of SOC versus EpiFix® (MiMedx, Marietta, GA) in a hospital-based, chronic diabetic foot ulcer with use of dehydrated human amniotic/chorionic membrane (dHACM) in patients failing standard treatment (2012). Methods: An R/B approved randomized clinical trial was conducted comparing SOC (n=12) to SOC+dHACM (n=12). Treatment with dHACM was initiated once patients were judged to be ready by the clinical investigators to start treatments. In 8 (67%) of patients, wounds were treated with dHACM after 6-8 weeks to the 11 patients treated. Wounds decreased in size on average of 28.6% ± 3.2% after 4 weeks of dHACM treatment compared to SOC. Conclusions: Use of dHACM provides superior rates of healing compared to SOC in patients with chronic DFU.

Methods

Results

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. Patients with DFU previously randomized to SOC (n=11) who failed to heal upon completion of the clinical trial (dHACM vs. SOC). Study Outcome:
- Ulcer size reduction at 4 and 8 weeks
- Proportion of ulcers healed during the study period
- Mean time to healing

Results

- Complete healing was achieved by 10/11 (91%) of patients once they received treatment with dHACM.

- The addition of dHACM to SOC significantly increased ulcer size reduction on average at 4 and 8 weeks. Complete healing was achieved in 87.6% ±16.0% at week 4 and 93.9% ±11.1% at week 8.

- The mean healing time was 3.0 ±5.0 weeks for wounds treated with dHACM compared to 9.9 ±7.4 weeks for wounds treated with SOC.

Limitations of the current study are inherent to those of a retrospective study design. A biologically active implant or graft for tissue regeneration application. In the initial study period while receiving SOC, cleaned, dehydrated, and sterilized by the proprietary PURION® process. Mean healing time was 3.0 ±5.0 weeks for wounds treated with dHACM compared to 9.9 ±7.4 weeks for wounds treated with SOC. Subsequent evaluation of clinical records was made with IRB approval.

Table 1: Mean percent reduction in wound size vs. baseline during each treatment period

<table>
<thead>
<tr>
<th>Treatment week</th>
<th>SOC Period (RCT)</th>
<th>After dHACM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1 (%)</td>
<td>21.4 ± 26.8</td>
<td>62.5 ± 29.5</td>
<td>0.013</td>
</tr>
<tr>
<td>Week 2 (%)</td>
<td>15.5 ±23.3</td>
<td>26.3 ±23.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Week 3 (%)</td>
<td>13.3 ±45.3</td>
<td>47.0 ±15.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 4 (%)</td>
<td>28.6 ±45.3</td>
<td>47.0 ±5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 5 (%)</td>
<td>6.7 ±6.5</td>
<td>29.5 ±12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Week 6 (%)</td>
<td>-16.5 ±6.8</td>
<td>39.3 ±11.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

In the initial study period while receiving SOC, only measurements of wound size were recorded at baseline. At week 4 and week 8 of dHACM applications, percent wound size reduction was noted week to week. (Figure 1) Wounds were reduced by >50% in 81.8% (n=9) by week 2 (1 dHACM application) and 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) Patients with Ulcer previously randomized to SOC (n=11) who failed to heal upon completion of the clinical trial (dHACM vs. SOC).

Table 2: Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61.3 ±16.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.6 ±5.4</td>
</tr>
<tr>
<td>Diabetes (≥2.9 kg/m²)</td>
<td>9 (81.8)</td>
</tr>
<tr>
<td>Smoker</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td>Wound size (cm²)</td>
<td>4.7 ±5.8</td>
</tr>
<tr>
<td>Wound duration (weeks)</td>
<td>21.1 ±12.4</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD.

Examples of Subjects Healed with dHACM

In the initial study period while receiving SOC, only measurements of wound size were recorded at baseline. At week 4 and week 8 of dHACM applications, percent wound size reduction was noted week to week. (Figure 1) Wounds were reduced by >50% in 81.8% (n=9) by week 2 (1 dHACM application) and 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) Patients with Ulcer previously randomized to SOC (n=11) who failed to heal upon completion of the clinical trial (dHACM vs. SOC).

Results

- Complete healing was achieved by 10/11 (91%) of patients once they received treatment with dHACM.

- The addition of dHACM to SOC significantly increased ulcer size reduction on average at 4 and 8 weeks. Complete healing was achieved in 87.6% ±16.0% at week 4 and 93.9% ±11.1% at week 8.

- The mean healing time was 3.0 ±5.0 weeks for wounds treated with dHACM compared to 9.9 ±7.4 weeks for wounds treated with SOC.

Conclusion

- In the current study, 11 patients with chronic diabetic foot ulcers that failed to heal with SOC were treated with dHACM. A total of 30% (n=9) of wounds were completely healed with 4 weeks of 4 applications of dHACM (n=9). Complete healing was achieved by 10/11 (91%) of wounds of their wound within 9 weeks of dHACM initiation.

- From the original 25 patients enrolled in the randomized trial, 23 (92%) were ultimately randomized to SOC. A total of 30% (n=9) of wounds failed to heal following standard of care treatment period. Wounds that failed to heal with SOC (n=9) with complete healing of their wound within 9 weeks of dHACM initiation.

- 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.

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

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

Study sponsored by MiMedx, Marietta, GA, EpiFix®, PURION®, and MiMedx® are registered trademarks of MiMedx Group, Inc.