A Prospective, Randomized Comparative Study of Weekly versus Biweekly Application of Dehydrated Human Amnion/Chorion Membrane Allograft in the Management of Diabetic Foot Ulcers

Charles M. Zelen, DPM, FACFAS, FACFAOM, FAPWCA
Thomas E. Serena, MD, FACS, FACHM, MAPWCA
Robert J. Snyder, DPM, MSc, CWS

Professional Education and Research Institute, Roanoke, VA
SerenaGroup, Cambridge, MA
Barry University School of Podiatric Medicine, Miami Shores, FL

SAWC Spring Meeting, April 23-27, 2014 in Orlando, Florida
Poster # CR 055

Abstract

Objective: To determine if weekly application of dehydrated human amnion/chorion membrane (dHACM) allograft reduces mean time to healing versus biweekly application for treatment of diabetic foot ulcers (DFU).
Methods: A Western IRB approved and registered prospective, randomized, comparative, parallel group, single-center clinical trial was performed. Included were patients with non-infected DFU of at least four weeks duration having adequate arterial perfusion for wound healing. Patients were randomized to receive weekly or biweekly application of dHACM in addition to non-adherent based dressing with compressive wrapping. All wounds were offloaded using a removable cast walker. Primary study outcome was mean time to healing. Secondary outcomes examined were percentage of DFU completely healed by 2, 4, 6 and 12 weeks.
Results: Overall, during the 12 week study period, 37/40 (92.5%) of dHACM treated ulcers completely healed. Mean time to complete healing was 4.1 ± 2.9 vs. 2.4 ± 1.8 weeks (p=0.039) in the biweekly vs. weekly groups respectively. Within 2 weeks, 4 wounds (20%) in the biweekly group were completely healed vs.13 (65%) in the weekly group (p=0.009). By 4 weeks, 50% in the biweekly group and 90% in the weekly group (p=0.014) were completely healed, while by 6 weeks 70% in the biweekly group and 95% in the weekly group (p=0.091) were healed. Number of grafts applied to healed wounds was similar at 2.4 ± 1.5 and 2.3 ± 1.8 for biweekly vs. weekly groups respectively (p=0.841).
Conclusion: These results validate previous studies showing that dHACM is an effective treatment for DFU. Although similar numbers of grafts were used, wounds treated with weekly application of dHACM healed more rapidly than those with biweekly application. More rapid healing may decrease overall cost of care and prevent longer term medical complications including infection and amputation associated with more chronic wounds.

Introduction

Background

- In the US, 26 million people representing approximately 8.3% of the population have diabetes.[1]
- Patients with diabetes are at risk for the development of foot ulcers due to neuropathy.
- Approximately 25% of diabetic patients will develop a foot ulcer over their lifetime.[2,3]
- Diabetic ulcers are often slow to resolve; a large meta-analysis reported a weighted healing rate of only 24.2% after 12 weeks of treatment.[4]
- Given the clinical risks and high costs associated with treating lower-extremity ulcers, the development of treatment strategies to improve healing rates and reduce time to healing is warranted.[5,6]

Dehydrated Human Amnion/Chorion Membrane (dHACM)

- Commercially available allograft (EpiFix®, MiMedx Group Inc., Marietta, GA).[7]
- Shown to contain many growth factors that help in wound healing, including PDGF-AA, PDGF-BB, bFGF, TGF-β1, EGF, VEGF, and PlGF.[8]
- In addition to growth factors, cytokines including anti-inflammatory interleukins (IL-1ra, IL-4, IL-10) and the TIMPs (TIMP-1, TIMP-2, TIMP-4) which help regulate the matrix metalloproteinase (MMP) activity are also present in dHACM.[8]

Purpose

- Previous studies have established that biweekly application of dHACM allograft is an effective treatment for chronic diabetic foot ulcers (DFU).[9-11]
- Our objective is to compare time to complete wound closure and rates of healing with weekly versus biweekly application of dHACM allograft in patients presenting with a chronic DFU.

Methods

This was a Western Institutional Review Board approved, registered, prospective, randomized, parallel group, non-blinded clinical trial comparing time to healing in diabetic patients with a DFU treated with dHACM. The single center trial was performed between September, 2012 and October, 2013 in Southwest Virginia under the direction of a senior clinician with expertise in diabetic foot care with continuous enrollment of all eligible patients who wished to participate.

Included

- Patients with a history of type 1 or type 2 diabetes presenting for care of a non-infected DFU that failed to heal for at least 4 weeks
- After meeting initial eligibility criteria, patients were placed in a 2 week run in period
- At the end of the screening period if the wound failed to heal by 20% they were enrolled into the study

Study Groups

- Patients were randomized to receive weekly (n= 20) or biweekly (n=20) application of dHACM allograft

Treatment

- Minimizing waste, a wound-size-appropriate dHACM was applied weekly or biweekly following surgical debridement of all necrotic tissue according to group assignment
- A non-adherent dressing was used to cover the dHACM, followed by a moisture-retentive dressing and a compressive padded dressing
- All wounds were offloaded using a removable cast walker
- Follow-up visits were conducted weekly for dressing change and wound assessment
- When applicable, measurements and photographic evaluation were done after debridement
- Patients were seen by the investigator at day zero (day of first dHACM application) and at least once every 7 days (± 3 days) for up to 12 weeks or 1 week after complete healing, whichever occurred first

Study Outcomes

- Primary study outcome was mean time to healing
- Secondary outcomes were percentage of DFU completely healed by 4, 6 and 12 weeks in each group, and number of dHACM allografts used

Data Analysis

- Healing was defined as complete re-epithelialization of the wound without drainage or need for dressing
- Parametric and non-parametric statistics were used as appropriate to compare clinical characteristics between those receiving weekly applications of dHACM to biweekly controls

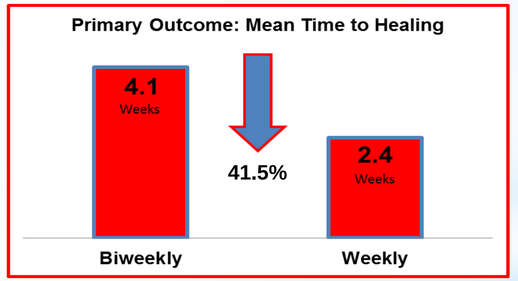
Results

Table 1. Clinical characteristics at study enrollment.

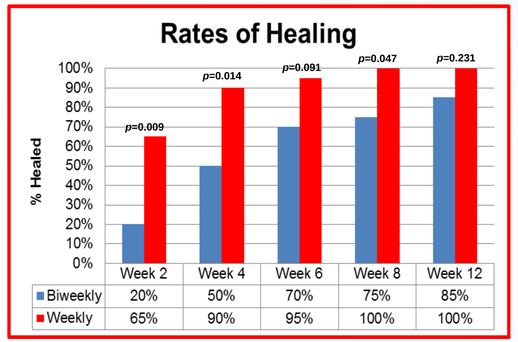
	Biweekly (n=20)	Weekly (n=20)	*P* value
Male gender (#/%)	10 (50)	9 (45)	1.000
Age (y)	59.6 ± 13.8	60.8 ± 10.9	0.758
Caucasian race (#/%)	19 (95)	16 (80)	0.342
Tobacco use (#/%)	1(5)	1(5)	1.000
Type 1 diabetes (#/%)	3 (15)	1 (5)	0.605
Body mass index	33.0 ± 5.8	36.8 ± 6.7	0.065
HbA1c	7.3 ± 1.5	8.7 ± 2.2	0.036
Ulcer duration (wks)	16.9 ± 21.7 9 (4, 99)	17.5 ± 14.5 11 (4, 50)	0.480
Baseline wound area (cm²)	2.4 ± 1.8 1.6 (1.1, 8.7)	2.0 ± 1.3 1.4 (1.1, 6.4)	0.303

Data presented as mean ± SD, median (min, max), or # (%) as indicated.

Results



- While a similar number of grafts were used on each healed wound (biweekly group = 2.4 ± 1.5, vs. 2.3 ± 1.8 - weekly group, p=0.841), those wounds receiving weekly dHACM healed 41.5% faster than those treated with dHACM biweekly, despite a greater mean HbA1c.



- Overall, after 1 dHACM application, mean wound size reduction was 76.4 ± 21.1%, and 22.5% (9/40) of wounds had healed completely.
- All but one patient (39/40, 97.5%) had >50% reduction in wound size within 4 weeks.

Results

Examples of Subjects Healed with dHACM

Male, 54 years of age with 6.4cm² plantar ulcer of 48 weeks duration. Randomized to receive weekly dHACM application. Complete healing occurred after 3 applications of dHACM. Wound reduced in size by 90.1% after first dHACM application.

Week 0	Week 1	Week 2	Week 3	Validation visit
Wound size 6.4cm² 2cm x 3cm dHACM	Wound size 0.63cm² 2cm x 3cm dHACM	Wound size 0.16cm² 16mm dHACM disk	Healed after 3 dHACM	Remained healed

Obese female, 51 years of age with 2.1cm² hallux ulcer of 5 weeks duration. Randomized to receive biweekly application of dHACM. Completely healed after 2 biweekly applications. Wound reduced in size by 47.6% after first dHACM application.

Week 0	Week 1	Week 2	Week 3	Validation visit
Wound size 2.1cm² 16mm dHACM disk	Wound size 1.1cm²	Wound size 1.0cm² 16mm dHACM disk	Healed after 2 dHACM	Remained healed

Conclusions

- Limitations of the current study are those inherent to small sample size. The lack of a standard care group not receiving dHACM can be perceived as a study weakness, although our intent was solely to examine rates of healing according to frequency of application and not compare to other treatment modalities, thus patients receiving biweekly application served as controls.
- DFU treated with weekly application of dHACM heal more rapidly than those treated with biweekly application.
- These results validate previous studies showing that dHACM allograft is an effective treatment for DFU.
- More rapid healing may decrease clinical operational costs and prevent longer term medical complications.

References

1. CDC - 2011 National Estimates - 2011 National Diabetes Fact Sheet - Publications - Diabetes DDT. http://www.cdc.gov/diabetes/pubs/estimates11.htm
2. Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, et al. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the ADA, with endorsement by the AACE. *Diabetes Care* 2008;8:1679-85.
3. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005 Jan 12;293(2):217-28.
4. Margolis D, Kantor J, Berlin J. Healing of neuropathic ulcers: results of a meta-analysis. *Diabetes Care* 1999;22:692-695.
5. Holzer SE, Camerota A, Martens L, et al. Costs and duration of care for lower extremity ulcers in patients with diabetes. *Clin Ther* 1998;20(1):169-81.
6. Harrington C, Zagari MJ, Corea J, Klitenic J. A cost analysis of diabetic lower-extremity ulcers. *Diabetes Care* 2000 Sep;23(9):1333-8.
7. Fetterolf DE, Snyder RJ. Scientific and clinical support for the use of dehydrated amniotic membrane in wound management. *Wounds* 2012;24:299-307.
8. Koob TJ, Rennert R, Zabek N, Massee M, Lim JJ, Temenoff JS, Li WW, Gurtner G. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. *Int Wound J* 2013 Oct;10(5):493-500. doi: 10.1111/iwj.12140. Epub 2013 Aug 1.
9. Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomized comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. Int Wound J 2013 Oct;10(5):502-7. doi: 10.1111/iwj.12097. Epub 2013 Jun 7.
10. Zelen CM. An evaluation of dehydrated human amniotic membrane allografts in patients with DFUs. J Wound Care 2013 Jul;22(7):347-8, 350-1.
11. Zelen CM, Serena TE, Fetterolf DE. Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: a long-term follow-up study. Wound Medicine, Available online 19 November 2013. http://dx.doi.org/10.1016/j.wndm.2013.10.008

PROFESSIONAL EDUCATION AND RESEARCH INSTITUTE, INC

EpiFix® - MiMedx®, Marietta, GA

Study sponsored by: MiMedx®, Marietta, GA

EP242.001