Umbilical Cord and Amniotic Membrane Product for Chronic Wounds

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18th Annual Conference
May 31 - June 02
THE PERIPHERAL EVENT OF THE YEAR
Disclosures

- I have used a lot of these products
Amniotic Sac

- Placenta
- Amniotic sac
- Chorion
- Amnion
- Amniotic fluid
- Umbilical cord

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Placental Cross Section
Benefits of Amnion

Human amniotic membrane has been used to treat a variety of wounds for over 100 years.

Many useful components important for dynamic reciprocity of healing:

Membrane and extracellular matrix components:

- Growth factors and cytokines such as:
  - PDGF, VEGF, TGF-B, and FGF, EGF, IL-4, 6, 8, and 10
  - TIMPs 1, 2, 3 and 4, which inhibit matrix metalloprotease degradation of new tissue

There are multiple studies that show various dehydrated amniotic products retain these key components.
Clinical Benefits

Promotion of epithelialization

Angiogenesis (neovascularization)

Promotion of cellular differentiation and adhesion

Inflammatory regulation effects

Anti-scarring/anti-adhesive activity

Low immunogenicity/ low antigenicity

How it Works

Enhanced expression of growth factors such as KGF, b-FGF, HGF and TGF-β
bFGF, PDGF, TGF-β1

VEGF promotes formation of new capillaries and proliferation/migration of endothelial cells

Collagen types IV, V and VII are contained within the matrix

Suppressed pro-inflammatory cytokines IL-1α and IL-1β
Produces TIMPs 1, 2, 3 and 4

Reduced protease activity via TIMPs, in turn reducing fibrotic effect
Down-regulated TGF-β, prevents adhesion and reduces fibroblast expression

Minimized expression of histocompatibility antigens A, B, C D, R; β2 microglobulin; and MHC Class II antigens
History of Placental Product Use

- Initially for burn use going back to the early 1900’s
- Ophthalmology use started in the 1970’s
- First published use in wounds was in the late 1980’s in France were VLU’s. Taken fresh from Labor and Delivery
All placental based HCT/Ps (Human Cellular and Tissue-Based Product) are all regulated under Section 361 of the Public Health Service Act and are governed by the FDA Center for Biologics Evaluation and Research (CBER).

They meet the following regulatory criteria:
1. They must be minimally manipulated
2. Intended for homologous use
3. Does not involve the combination of the cells or tissue with other articles, except for water, crystalloids, sterilizing, preserving or storage agents
4. Does not have a systemic effect
<table>
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<th>Product (Supplier)</th>
<th>Preparation</th>
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37 Listed
Healing Neuropathic Ulcers: Results of a Meta-analysis

This data provide clinicians with a realistic assessment of their chances of healing neuropathic ulcers.

Even with good, conventional wound care, healing neuropathic ulcers in patients with diabetes continues to be a challenge.

Weighted Mean Healing Rates

- 12-week end point (N=450): 24.2%
- 20-week end point (N=172): 30.9%

FIRST AMNIOTIC DFU RCT

dHACM: EpiFix - Mimedx
“A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers”

dHACM (Dehydrated Human Amnion Chorion Membrane) EpiFix, MiMedx Group Inc., Marietta, GA
Second Amniotic RCT

HVWM: Grafix - Osiris
“The efficacy and safety of Grafix (R) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial” **
Lavery L, Fulmer J, Shebetka KA, Regulski, Vayser D, Fried D, Kashefsky H, Owings TM,. Int Wound J 2014; 11:554-60

hVWM (human viable wound matrix)
Third Amniotic RCT

DAMA: AMNIOEXCEL® - Derma Sciences
“A Prospective, Randomized, Multicenter and Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft (DAMA) compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcers”
Robert J. Snyder, DPM, MSc; Kenneth Shimozaki, DPM; Arthur Tallis, DPM; Michael Kerzner, DPM; Alexander Reyzelman, DPM; Dimitrios Lintzeris, DO; Desmond Bell, DPM; Randi L. Rutan; and Barry Rosenblum, DPM - WOUNDS 2016; 28(3): 70-77

DAMA (Dehydrated Amniotic Membrane Allograft)
Aseptically Processed Placental Membrane Improves Healing of Diabetic Foot Ulcerations: Prospective, Randomized Clinical Trial

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Dennis P. Orgill, MD, PhD
Robert D. Galiano, MD
Thomas E. Serena, MD
Marissa J. Carter, PhD, MA
Jarrod P. Kaufman, MD
Nathan J. Young, DPM
Charles M. Zelen, DPM

Background: Allogeneic grafts derived from amnion/chorion are known to be efficacious in healing chronic diabetic foot ulcerations (DFUs). The goal of this study was to compare aseptically processed dehydrated human amnion and chorion allograft (dHACA) versus standard of care (SOC) in facilitating wound closure in nonhealing DFUs.

Methods: Patients with DFUs treated with SOC (off-loading, appropriate debridement, and moist wound care) after a 2-week screening period were randomized to either SOC or wound-size-specific dHACA (AmnioBand, Musculoskeletal Transplant Foundation, Edison, N.J.) applied weekly for up to 12 weeks plus SOC. Primary endpoint was the percentage of wounds healed at 6 weeks between groups.

Results: At 6 weeks, 70% (14/20) of the dHACA-treated DFUs healed compared with 15% (3/20) treated with SOC alone. Furthermore, at 12 weeks, 85% (17/20) of the DFUs in the dHACA group healed compared with 25% (5/20) in the SOC group, with a corresponding mean time to heal of 36 and 70 days, respectively. At 12 weeks, the mean number of grafts used per healed wound for the dHACA group was 3.8 (median 3.0), and mean cost of the tissue to heal a DFU was $1400. The mean wastage at 12 weeks was 40%. One adverse event and 1 serious adverse event occurred in the dHACA group; neither was graft related. Three adverse events and 1 serious adverse event occurred in the SOC group.

Conclusion: Aseptically processed dHACA heals diabetic foot wounds significantly faster than SOC at 6 and 12 weeks with minimal graft wastage. (Plast Reconstr Surg Glob Open 2016;4:e1095; doi: 10.1097/GOX.0000000000001095; Published online 12 October 2016.)
Amnion Membrane in Diabetic Foot Wounds: A Meta-analysis

Alexandra M. Haugh, BA*
Jacqueline G. Witt, BS*
Adam Hauch, MD, MBA†
Michael Darden, PhD†
Geoffrey Parker, PhD‡
Warren A. Ellsworth, MD¶
Joseph F. Buell, MD, MBA†

Background: Amniotic membrane is tissue obtained from human placenta rich in cytokines, growth factors, and stem cells that possess the ability to inhibit infection, improve healing, and stimulate regeneration.

Methods: A meta-analysis was performed examining randomized controlled trials comparing amniotic tissue products with standard of care in nonhealing diabetic foot ulcers including PubMed, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews.

Results: A search of 8 databases identified 596 potentially relevant articles. Application of selection criteria led to the selection of 5 randomized controlled trials. The 5 selected randomized controlled trials represented a total of 311 patients. The pooled relative risk of healing with amniotic products compared with control was 2.7496 (2.05725–3.66524, \( P < 0.001 \)).

Conclusions: The current meta-analysis indicates that the treatment of diabetic foot ulcers with amniotic membrane improves healing rates in diabetic foot ulcers. Further studies are needed to determine whether these products also decrease the incidence of subsequent complications, such as amputation or death, in diabetic patients. (Plast Reconstr Surg Glob Open 2017;5:e1302; doi: 10.1097/GOX.00000000000001302; Published online 25 April 2017.)
Fig. 1. As shown in this figure, the RR of wound healing is significantly greater with the use of amniotic products when compared with SOC.
The evidence on amniotic and placental membrane products for the treatment of diabetic lower-extremity ulcers includes several RCTs compared HAM to SOC or to an established advanced wound care product. All of these industry-sponsored studies included evaluation of wound closure as the primary outcome measure, and some included power analysis, blinded assessment of wound healing, and ITT analysis. For the amniotic membrane products evaluated in RCTs (e.g., AmnioBand Membrane, EpiFix, Grafix), results indicated improved outcomes compared to SOC, and outcomes that are at least as good as the advanced wound care product Apligraf.
Thank You
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