

Clinical Factors and Cost Effectiveness Associated with Healing of Venous Leg Ulcers with Dehydrated Human Amnion/Chorion Membrane Allografts

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Abstract

Purpose: Venous leg ulcers (VLU) are the most common wound of the lower extremity and are associated with significant medical costs due to their protracted healing periods. VLU-related treatment costs are directly related to the time to wound closure. We sought to identify clinical factors associated with healing of venous leg ulcers.

Design: Secondary analysis of data collected in a multicenter randomized clinical trial (RCT) examining venous ulcer healing rates over a four week period with adjunctive application of dehydrated human amnion/chorion membrane (dHACM) allograft in addition to standard multilayer compression therapy.

Methodology: Logistic regression analysis was performed to identify clinical factors associated with reduction in wound size of at least 40% over the four week study period. Healing rates with adjunctive dHACM therapy was modeled and number needed to treat (NNT) calculated.

Results: Ninety-three patients were enrolled in the RCT, 62 randomized to receive dHACM and 31 controls. All patients received multilayer compression. Logistic regression assessed gender, obesity, age, wound size, wound duration and dHACM treatment on the primary outcome. Wound size <10cm² (OR=3.97, 95% CI 1.07, 14.72, p=0.0394) and treatment with dHACM (OR=3.61, 95% CI 1.36, 9.57, p=0.0099) were both associated with >40% healing within 4 weeks. Based on status at 4 weeks, expected healing rates at 24 weeks were 50% and 26% for patients treated with dHACM vs. multilayer compression respectively. NNT calculations showed that 5 (CI 2-34) VLU would need to be treated with dHACM to achieve one additional wound closure within 24 weeks of treatment initiation, p=0.045.

Conclusion: Time to closure drives VLU treatment costs. Advanced treatments such as dHACM can accelerate VLU closure and are cost effective.

Background

- Venous leg ulcers (VLU) account for 80% of lower extremity wounds, with an overall prevalence of approximately 1% in the United States.¹
- The financial burden associated with VLU in the US is estimated at \$14.9 billion annually.²
- VLU-related treatment costs are directly related to the time to wound closure.
- Evaluating the efficacy of treatment for VLU is often difficult given the protracted study duration required before an endpoint of complete wound epithelialization can be achieved, thus intermediary outcomes may be reasonable, allowing for more rapid evaluation of treatment safety and potential benefits.
- In patients receiving standard wound care it has been demonstrated that the percent change in wound area of a VLU at the fourth week of care can serve as an important surrogate marker of complete wound healing within 24 weeks of care.³
- Early identification of patients unlikely to heal with aggressive compression therapy allows a clinician to employ advanced treatment modalities in an appropriate modification of the plan of care earlier in the treatment process and potentially reduce overall costs to the health care system.
- Calculation of the number needed to treat (NNT) allows for the comparison of clinical and cost effectiveness between advanced treatment modalities.⁴
- In a multicenter randomized controlled trial (RCT), VLU treated with PURION® Processed dehydrated human amnion/chorion membrane (dHACM) allograft had a significant improvement in healing at 4 weeks compared to multilayer compression therapy alone.⁵

Purpose of Current Study

Identify clinical factors associated with healing of VLU, and assess and compare the cost effectiveness of dHACM as an adjunctive treatment to multilayer compression in VLU management.

References

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Methods

- We performed a secondary analysis of data collected during an IRB approved multicenter RCT that examined rates of VLU healing during a 4 week study period with dHACM in addition to multilayer compression vs. multilayer compression alone (n=93).
- The RCT study population consisted of patients receiving care from physicians specializing in wound care and podiatric specialists at eight out-patient wound care centers in the United States (Pennsylvania, Massachusetts, Florida, Oklahoma, Indiana, and Texas).
- A long term follow-up study conducted to evaluate if the 4 week study outcome correctly correlated with rates of complete healing within 24 weeks, showing that 80% of patients with ≥ 40% healing at 4 weeks were completely healed within 24 weeks.⁶

Statistical analysis

- Logistic regression analysis was performed to identify clinical factors associated with reduction in wound size of at least 40% over the 4 week study period.
- Overall healing rates at 24 weeks were estimated at 80% of patients with at least 40% wound reduction at 4 weeks in the 93 patients enrolled in the RCT.
- To assess the potential cost implications of using adjunctive dHACM vs. compression therapy alone as a treatment for VLU, the NNT to achieve one additional healed VLU within 24 weeks was calculated.
- Cost estimates for use of dHACM as a treatment for VLU were compared to published cost data of another commonly used tissue-engineered skin substitute (T-ESS).⁷

Results

- Patients having a VLU ≤10 cm² or receiving at least one application of dHACM were almost 4 times likely to heal 40% or more within 4 weeks. (Table 1)

Table 1. Logistic Regression Results

Effect	Odds Ratio	95% Wald Confidence Limits		p-value
Gender (M/F)	1.376	0.517	3.663	0.5227
Obese (Y/N)	0.704	0.222	2.229	0.5509
dHACM (Y/N)	3.609	1.361	9.570	0.0099
65 or Older (Y/N)	1.182	0.405	3.444	0.7597
Wound Duration <1yr (Y/N)	2.853	0.944	8.624	0.0632
Wound ≤10 cm ² (Y/N)	3.968	1.069	14.720	0.0394

dHACM = EpiFix®, MiMedx Group, Inc., Marietta, GA
T-ESS = Apligraf®, Organogenesis, Canton, MA

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Results

- In the RCT 63% (39) of patients receiving dHACM and 32% (10) of patients receiving only multilayer compression achieved ≥ 40% wound closure at week 4. Estimated healing rates at 24 weeks and NNT calculations are presented in figure and Table 2 below.

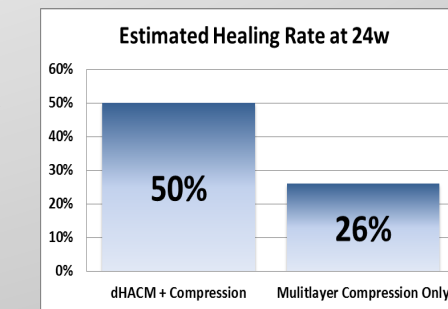


Table 2. NNT to Achieve 1 Additional Patient Success

Study Group	N	Healed at 24w*	NNT	95% CI	p-value
dHACM	62	50%	5	2-34	0.045
Multilayer compression	31	26%			

*Estimated. NNT = number needed to treat. CI = confidence interval.

- Estimated costs of dHACM and T-ESS treatment for VLU are presented in Table 3.
- Despite larger VLU size at treatment initiation, costs per patient were estimated to be more than 60% less for dHACM vs. T-ESS.
- At least 97% of each T-ESS graft was wasted compared with 6% wastage of dHACM.

Table 3. Cost Comparison

	dHACM	T-ESS ⁷
A NNT	5	6
B NNT 95% CI lower limit	2	3
C NNT 95% CI upper limit	34	24
D Mean wound size (cm ²)	5.6	1.3
E Graft size (cm ²)	6	44
F Grafts per application	1	1
G Cost per graft	\$1,300	\$1,664
H Mean number of grafts used	1.5	3
I Cost per patient (F x G x H)	\$1,950	\$4,992
J Cost per NNT (A x I)	\$9750	\$29,952
K Cost per NNT 95% CI lower limit (B x I)	\$3,990	\$14,976
L Cost per NNT 95% CI upper limit (C x I)	\$66,330	\$119,808

Conclusion

- VLU treated with only 1 or 2 dHACM allografts were almost 4 times likely to heal 40% or more in 4 weeks than VLU treated with compression alone.
- Advanced treatments such as dHACM can accelerate VLU closure and are cost effective compared with other T-ESS.
- With an NNT of 5, these data suggest that dHACM is an effective treatment for VLU.