

Evaluation of a Surrogate Outcome Used in a Study of Dehydrated Human Amnion/Chorion Membrane for the Treatment of Venous Leg Ulcers

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Abstract

Evaluating the efficacy of treatment for venous leg ulcers (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 third or fourth week of care can serve as an important surrogate marker of complete wound healing after 12 or 24 weeks of care.¹⁻⁴ In a previously conducted multicenter randomized trial of VLUs treated with dHACM versus multilayer compression only, a surrogate endpoint of wound reduction of at least 40% after 4 weeks of treatment showed superiority of treatment with dehydrated human amnion/chorion membrane (dHACM).⁵ Our purpose is to evaluate long term outcomes of patients enrolled in the prior study and validate our use of a surrogate outcome. Records from 55 patients at 5 study sites were reviewed. Forty-seven without complete healing during the initial study were eligible. Three patients were lost to follow-up, yielding 44 evaluable records (80%). Of these 44, 20 (45.4%) had reduced wound size of $\geq 40\%$ and 24 (54.5%) $< 40\%$ during the initial study. After study conclusion, complete healing occurred in 16/20 (80%) and 8/24 (33.3%), $p=0.0027$. Complete healing occurred after a mean of 46 (n=16) or 103.6 (n=8) days for those with or without healing $\geq 40\%$ during the initial study period respectively. Similar to previous reports², overall correct correlation of status at 4 weeks and ultimate healing status of VLU was 72.7%. Although treatments received after the initial study period may have confounded patient outcomes, these results confirm that the surrogate measure used in our initial study is a viable predictor of ultimate VLU healing.

Background

- ❖ Venous leg ulcers (VLU) are associated with considerable morbidity and impaired quality of life with healing being a long and painful process.⁶
- ❖ Annually in the United States, the economic burden to payers for healthcare costs related to VLU is \$14.9 billion.⁷
- ❖ 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.¹⁻⁴
- ❖ A proprietary PURION® Process of advanced tissue stabilization and preservation has allowed for widespread clinical use of human amniotic membrane in the form of a dehydrated human amnion/chorion membrane (dHACM) allograft.⁸
- ❖ In a previously conducted multicenter randomized trial of VLUs treated with dHACM versus multilayer compression only, an intermediate endpoint of wound reduction of at least 40% after 4 weeks of treatment showed superiority of treatment with dHACM.⁵
- ❖ In that study (n=84), VLU treated with dHACM had a significant improvement in healing at 4 weeks compared to multi-layer compression therapy alone with 62% of wounds treated with dHACM and 32% of controls demonstrating a greater than 40% wound closure after 4 weeks ($p=0.005$).

Purpose

- ❖ Our purpose is to evaluate long term outcomes of patients enrolled in the prior study and validate our use of a surrogate outcome.

Methods

We conducted a retrospective follow-up study of patients previously enrolled in an IRB approved multi-center RCT⁵ which evaluated the use of dHACM for the treatment of VLU.

Included

- ❖ Records from 55 patients at 5 study sites were reviewed.
- ❖ Forty-seven patients without complete healing during the initial study were eligible.
- ❖ Three patients were lost to follow-up, yielding 44 evaluable records (80%).

Analysis

- ❖ Correct correlation between wound healing status at 4 weeks (reduction in size by $\geq 40\%$ yes or no) and healing within 24 weeks was determined.
- ❖ Patient characteristics were compared between those with and without correct correlation using parametric (Fisher's Exact Test, student's t test) and non-parametric (Mann-Whitney U) statistics as necessary.

Results

- ❖ Of the 44 patients, 20 (45.4%) had reduced wound size of $\geq 40\%$ and 24 (54.5%) $< 40\%$ during the initial study.
- ❖ Correct correlation between healing status at 4 weeks and 24 weeks, occurred in 32 of the 44 patients (72.7%).
- ❖ Wounds with reduction in size by at least 40% within the first 4 weeks of treatment were more likely to be completely healed within 24 weeks [16/20 (80%)] compared with those that did not have 40% healing the first 4 weeks [8/24 (33.3%)], $p=0.0027$. (Figure 1)
- ❖ Complete healing occurred after a mean of 46 (n=16) or 103.6 (n=8) days for those with or without healing $\geq 40\%$ during the initial study period respectively. (Figure 2)
- ❖ Comparison of clinical characteristics for patients with and without correct correlation of wound status at 4 weeks and complete healing within 24 weeks are presented in Table 1.

References

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Results

Figure 1. Rates of complete healing.



Figure 2. Mean days to complete healing.

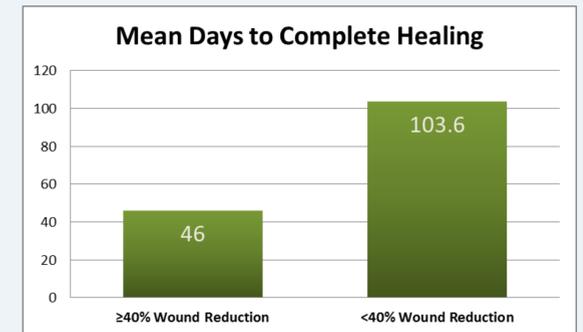


Table 1. Comparison of clinical characteristics for patients with and without correct correlation of wound status at 4 weeks and complete healing within 24 weeks.

	Correct Correlation with Status at 4 Weeks (n=32)	Incorrect Correlation with Status at 4 Weeks (n=12)	p-value
Age (years)	62.9 \pm 16.3	63.1 \pm 11.7	0.97
Male gender	17 (39%)	3 (7%)	0.17
Non-Caucasian	4 (9%)	1 (2%)	1.00
Body-mass index	38.0 \pm 13.4 35.7 (17.3, 80.7)	37.6 \pm 8.9 37.5 (26.3, 51.2)	0.78
Duration of wound at RCT enrollment (weeks)	18.1 \pm 24.3 5.5 (1, 96)	9.0 \pm 7.5 8.0 (0.9, 18)	0.35
Wound size at end of RCT (cm ²)	5.6 \pm 6.3 4.0 (0.1, 24)	3.1 \pm 1.8 2.8 (0.5, 5.4)	0.38

Data presented as mean \pm standard deviation, median (minimum, maximum), or number (percentage) as indicated.
RCT = randomized controlled trial.

Conclusions

- ❖ Intermediate endpoints that can predict the ultimate outcome of treatment are beneficial for researchers of new wound healing products or techniques allowing for more rapid evaluation of potentially promising innovations.
- ❖ The current follow-up analysis validates the intermediate outcome used in the initial RCT which showed that VLU treated with dHACM had greater reduction in wound size within the first 4 weeks of treatment than VLU treated with compression alone.