Assessing Placental Membrane Treatment Efficiency in DFUs: Processing for Retention Versus Lamination

Zwelithini Tunyiswa, BA[1] Wendy W Weston, PhD[2] , Robert Frykberg, DPM[1] and Ryan Dirks, PA[1]

[1] Open Wound Research, Puyallup, WA, [2] BioStem Technologies, Pompano Beach, FL

Abstract

Diabetic foot ulcers are a severe complication in diabetic patients, which significantly impact healthcare systems and patient quality of life, often leading to hospitalization and amputation. Traditional Standard of Care (SOC) treatments are inadequate for many patients, necessitating advanced wound care products (AWCPs) like human placental membranes. This study conducts a retrospective analysis to compare the effectiveness of two human placental membrane products, retention-processed (RE-AC) and lamination-processed (L-AC) in managing diabetic foot ulcers (DFUs). The study collected retrospective observational data from electronic health records (EHRs) of patients treated at three outpatient wound care centers. The analysis employed Bayesian estimation, utilizing an Analysis of Variance (ANCOVA) model with a Hurdle Gamma likelihood. Results indicated that RE-AC achieved a marginally higher expected Percent Area Reduction (xPAR) compared to L-AC at 12 weeks. RE-AC also required fewer applications, suggesting greater efficiency in general wound closure. The findings suggest that RE-AC offers overall better treatment efficiency, especially in reducing the frequency of applications. This efficiency can lead to improved patient comfort, reduced treatment costs, and optimized resource utilization in healthcare settings.

Methods

Since this was a deidentified retrospective review of previously collected data, IRB waiver was granted. Two wound care products were evaluated in managing DFUs: RE-AC (AmnioWrap2®) processed using the BioREtain®* method (BioStem Technologies, Pompano Beach, FL)) and L-AC (Epifix®) processed by the Purion lamination method (Mimedix, Marietta, GA).

1. A total of **41 subjects** were identified who met the study's inclusion criteria.
2. The researchers gained access to the electronic health records (EHR) of 41 identified subjects from **three outpatient wound care centers**.
3. The subjects were categorized into **two cohorts**: the **RE-AC** cohort (comprising 23 subjects) and the **L-AC** cohort (comprising 18 subjects.
4. The study team extracted **wound size** in square centimeters at **multiple time points** and **frequency of applications** for each product.

The researchers employed a **Bayesian regression analysis** in using PYMC (Probabilistic Programming in Python) estimating the **treatment efficacy** of RE-AC relative to L-AC. Given the data-generating process of the dependent variable (viz. wound area), which leads to either right-skewed continuous data, or zero (i.e. a closed wound), the researchers utilized a Hurdle Gamma Analysis of Variance (**ANCOVA**) model to estimate expected **Percent Area Reduction** (xPAR) from baseline. This is a more robust approach that returns posterior estimates for the probability of a closed wound and expected Percent Area Reduction (xPAR) for both the RE-AC and L-AC groups. The model was fit with PYMC using uninformative priors scaled to the range of the data and on the log and logit scales for the appropriate parameters. Four chains with a total of 4,000 draws were sampled. The resulting Markov Chain Monte Carlo (MCMC) summary is shown. The R-hat statistic shows that our chains converged well, and sampling showed no divergences. Our Effective Samples Statistics (ESS) show that our samples have high resolution, which shows good sampling efficiency. The mathematical notation for the model is as follows:

The Hurdle Component (the probability of a closed wound):

$$I(y_i > 0) \sim Bernoulli(\pi_i)$$

$$logit(\pi_i) = \alpha + \beta_{\times} group + \gamma \times pre_i$$

The Gamma Component (Expected Percent Area Reduction (xPAR)):

$$(y_i - pre_i) \mid I(y_i > 0) \sim Gamma(shape = k, rate = k/\mu_i)$$

$$log(\mu_i) = \theta + \delta group \times group_i + \varepsilon \times pre_i$$

Results

The statistical analysis revealed that the group receiving RE-AC had an xPAR that was on average 14.1 percentage points (95% credible interval: -1.0% - 30.12%) greater than the L-AC group at 12 weeks. Further, the probability of the full wound closure in the L-AC group was on average 0.017% percentage points greater (95% credible interval: -0.67%- 0.04%). This suggests RE-AC and L-AC groups are substantively similar in terms of complete wound closure, but that RE-AC has a greater general effect on wound closure when both full and partial closure are considered. Moreover, the average number of applications per wound in the RE-AC group was 7.9 versus 10.6 in the L-AC group, suggesting that RE-AC is more than 27% more efficient in terms of general wound closure efficiency in terms of applications required. The retrospective analysis revealed a significant finding that favored RE-AC over L-AC in terms of treatment efficiency for wound care. Patients who were treated with RE-AC required fewer applications of the product to achieve wound healing outcomes that were comparable with those treated with L-AC.

Table 1 Demographic Overview of Cohorts

		RE-AC	L-AC
Subjects		23	18
Age		71.0	58.6
		(11.7%)	(8.1%)
Sex	Female	5 (22%)	3 (17%)
	Male	18 (78%)	15 (83%)
Race	Asian	2 (9%)	0 (0%)
	Black	1 (4%)	1 (6%)
	Hispanic	8 (35%)	7 (39%)
	Native Hawaiian or Other Pacific Islander	1 (4%)	0 (0%)
	White	3 (13%)	2 (11%)
	Unknown	8 (35%)	8 (44%)

Table 2 Wound and Treatment Summary

		RE-AC	L-AC
Starting Area (in cm^2) *(Gamma Likelihood)*	Mean	16.5	14.2
		(10.9 - 26.1)	(8.4 - 24.9)
	Variance	0.8	0.8
		(0.5 - 1.3)	(0.4 - 1.3)
Product Applications *(Negative Binomial Likelihood)*	Mean	7.9	10.6
		(6.5 - 9.6)	(8.6 - 12.9)
	Variance	8.3	10.9
		(3.3 - 23.0)	(3.8 - 35)
Treatment Days *(Negative Binomial Likelihood)*	Mean	68.2	77.3
		(55.7 - 84.9)	(66.8 - 89.1)
	Variance	3.8	12.5
		(2.0 - 6.7)	(4.9 - 28.5)

Bayesian analysis was performed - estimates and 95% credible intervals (not confidence intervals) are reported

Figure 1 Markov Chain Monte Carlo (MCMC) Summary

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
Intercept	1.354	0.386	0.645	2.104	0.006	0.005	3924.0	2695.0	1.0
group[01_AW2]	-0.145	0.418	-0.961	0.616	0.006	0.006	4332.0	2897.0	1.0
pre	0.033	0.008	0.019	0.050	0.000	0.000	3707.0	2597.0	1.0
psi_Intercept	1.222	0.488	0.318	2.162	0.007	0.006	4782.0	2925.0	1.0
psi_group[01_AW2]	0.185	0.588	-0.867	1.300	0.009	0.008	4672.0	2967.0	1.0
post_alpha	0.690	0.135	0.442	0.934	0.002	0.002	4198.0	3006.0	1.0

Conclusions

This comparative analysis highlights the distinct advantages of BioREtain®-processed RE-AC, especially in terms of application efficiency and wound size reduction. RE-AC demonstrated a marginally higher expected Percent Area Reduction (xPAR) over 12 weeks, underscoring its effectiveness in managing wound size. Moreover, RE-AC required fewer applications than L-AC to achieve the same efficacy. RE-AC's reduced application frequency not only enhances patient comfort by lessening the need for repeated treatments but also signifies a more cost-effective and resource-efficient approach in clinical settings which positions it as a more advantageous option in many clinical cases. This study underscores the importance of evaluating both clinical outcomes and practical aspects of treatment in selecting the most suitable intervention for diabetic foot ulcers.

* Patent pending