A Pilot Randomized Clinical Trial on The Use of a Novel Polylactic Acid Dermal Matrix for Diabetic Foot Ulcer Closure

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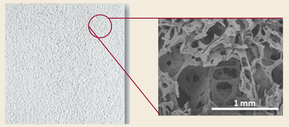
Background

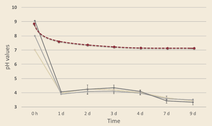
Objective:

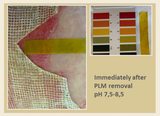
- To compare the performance of a **poly-lactic acid (PLA)** guided closure matrix vs. a collagen dressing to achieve 100% closure of diabetic foot ulcers.

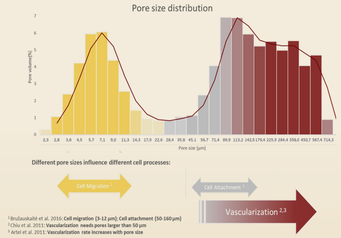
Background:

- Foot ulcers affect up to 35% of people with diabetes and represent a challenge for closure.
- Guided closure matrices are often required to accelerate the healing process.
- We recently developed a novel closure matrix made of PLA.
- PLA has demonstrated excellent closure outcomes for patients with acute wounds such as burns.
- The **lactate** released by the PLA matrix acts as a paracrine agent (lactormone) with potent signaling effects that include:
  - **Hypoxia mimicking** and triggering of **neo-angiogenesis**
  - **Cell survival and proliferation**
  - **Anti-inflammation**
- In addition, the lactate causes acidification of the wound bed and a **pH shift** to neutral values.

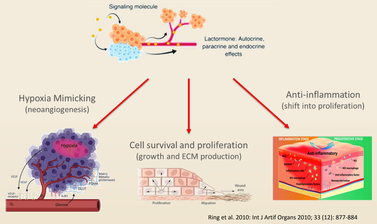








[1] Brulzauskaité et al. 2016: Cell migration (5-12 µm); Cell attachment (50-160 µm)
[2] Chiu et al. 2011: Vascularization needs pores larger than 50 µm
[3] Artel et al. 2013: Vascularization rate increases with pore size



Ring et al. 2010: Int J Artif Organs 2010; 33 (12): 877-884

Methods

- Patients with diabetes mellitus and a single foot ulcer of at least 3 months of evolution were **included** in the trial.
- **Exclusion criteria** were presence of active infection, uncontrolled diabetes mellitus or any other uncontrolled comorbidity, and use of drugs or medications that would affect wound healing.
- Patients were **randomized** to receive either the weekly applications of a PLA matrix or collagen dressings as adjuncts to the standard of care.
- All patients were enrolled in a **single high-volume center** and were treated by the same surgeon.
- The **primary objectives** of the trial was the number of weeks required to attain full closure of the wound.
- The **secondary objectives** included the odds of attaining closure by 12-weeks and the presence of complications, including infection, amputation, or treatment failure.
- Analysis of the data was performed blindly by an independent researcher.

Results

- No significant differences between patient groups were found at baseline:

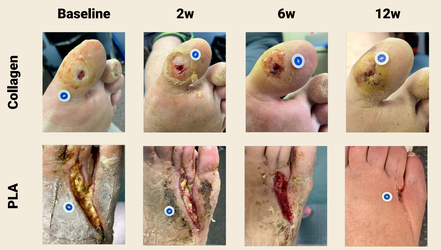
	Collagen (N=15)	PLA (N=15)	Total (N=30)	p-value
Age (years)				0.972[1]
Mean (SD)	63.800 (14.513)	64.000 (10.488)	63.900 (12.324)	
Range	41.000 - 88.000	49.000 - 78.000	41.000 - 88.000	
Gender				0.143[2]
Female	6 (40.0%)	5 (33.0%)	11 (36.0%)	
Male	9 (60.0%)	10 (67.0%)	19 (64.0%)	
BMI				0.675[1]
Mean (SD)	31.800 (8.904)	30.500 (3.719)	31.150 (6.675)	
Range	23.000 - 55.000	27.000 - 36.000	23.000 - 55.000	
Use of tobacco				0.438[2]
No	11 (74.0%)	9 (60.0%)	20 (67.0%)	
Yes	4 (27.0%)	6 (40.0%)	10 (33.0%)	
HbA1c (%)				0.200[1]
Mean (SD)	7.570 (0.886)	8.190 (1.179)	7.880 (1.064)	
Range	6.400 - 9.100	6.600 - 10.000	6.400 - 10.000	
Creatinine (mg/dL)				0.271[1]
Mean (SD)	1.201 (0.589)	1.312 (0.486)	1.265 (0.579)	
Range	0.900 – 2.170	0.814 - 2.310	0.814 - 2.310	
ABI				0.417[1]
Mean (SD)	1.049 (0.116)	0.994 (0.174)	1.022 (0.147)	
Range	0.840 - 1.210	0.740 - 1.290	0.740 - 1.290	

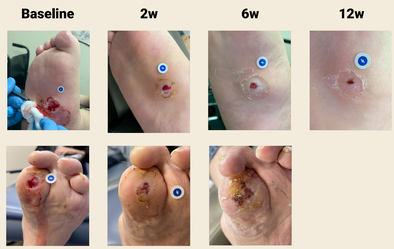
1. Linear Model ANOVA
2. Pearson's Chi-squared test

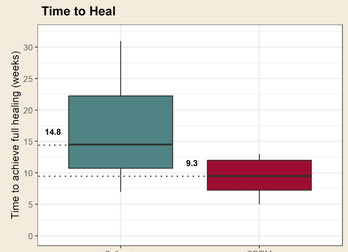
- No significant differences between wound characteristics were found at baseline:

	Collagen (N=15)	PLA (N=15)	Total (N=30)	p-value
Ulcer age (weeks)				0.636[1]
Mean (SD)	15.400 (3.748)	16.800 (8.390)	16.100 (6.365)	
Range	12.000 - 24.000	10.000 - 38.000	10.000 - 38.000	
Ulcer site				0.443[2]
Dorsum	6 (40.0%)	6 (40.0%)	12 (40.0%)	
Heel	2 (13.0%)	1 (06.0%)	3 (10.0%)	
Metatarsal	3 (20.0%)	3 (20.0%)	6 (20.0%)	
Plantar	4 (27.0%)	5 (34.0%)	9 (30.0%)	
Granulation tissue area (%)				0.108[1]
Mean (SD)	44.000 (25.906)	62.000 (21.499)	53.000 (24.942)	
Range	10.000 - 80.000	10.000 - 80.000	10.000 - 80.000	
Non-viable tissue area (%)				0.108[1]
Mean (SD)	56.000 (25.906)	38.000 (21.499)	47.000 (24.942)	
Range	20.000 - 90.000	20.000 - 90.000	20.000 - 90.000	
Depth (cm)				0.344[1]
Mean (SD)	0.338 (0.239)	0.473 (0.369)	0.406 (0.310)	
Range	0.100 - 0.800	0.100 - 1.200	0.100 - 1.200	
Area (cm^2)				0.120[1]
Mean (SD)	4.066 (2.186)	6.414 (3.984)	5.240 (3.352)	
Range	1.700 - 7.390	2.090 - 12.300	1.700 - 12.300	

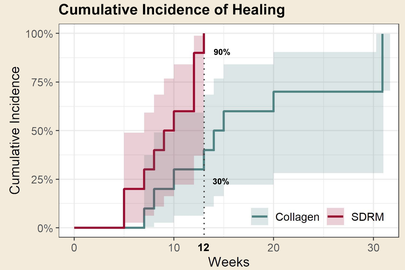
1. Linear Model ANOVA
2. Pearson's Chi-squared test







*Full healing of the wounds was achieved in 14.8 ± 8.1 vs. 9.3 ± 2.9 weeks (p=0.021) in the collagen vs. PLA group. This represents a **reduction of 44% of the time** needed to achieve full wound closure, compared to the standard of care.*



*The cumulative incidence for achieving full closure by 12 weeks with PLA matrices was **90%**. Compared to collagen, the **OR of achieving full closure by 12 weeks was 2.23** (95%CI 1.37 to 4.54, p = 0.004).*

- No complications or adverse events were recorded during the trial.

Discussion

- **PLA matrices are more effective** than active collagen dressings in promoting diabetic wound closure.
- Its use **reduces the time required to achieve full closure** and **increases the odds of achieving closure by 12-weeks**.
- Proposed **reasons** for this include controlled pore sizes that promote cell attachment, migration, and vascularization of the scaffolds; changes toward a neutral wound pH that may inhibit bacterial growth and promote cellular recruitment; and improved cellular signalling to promote neo-vascularization of the wound.

In summary, compared to standard of care, the use of a PLA guided closure matrix was more effective to promote closure of diabetic foot ulcers. Specifically, its use led to significant increases in granulation tissue and a reduction of 45% in the time required to achieve full closure of the wound.

References

1. Edmonds M, Manu C, Vas P. The current burden of diabetic foot disease. Journal of Clinical Orthopaedics and Trauma. 2021 Jun 1;17:88–93.
2. Mirhaj M, Labbaf S, Tavakoli M, Seifalian AM. Emerging treatment strategies in wound care. Int Wound J. 2022 Nov;19(7):1934–54.
3. Hundeshagen G, Collins VN, Wurzer P, Sherman W, Voigt CD, Cambiaso-Daniel J, et al. A Prospective, Randomized, Controlled Trial Comparing the Outpatient Treatment of Pediatric and Adult Partial-Thickness Burns with Suprathel or Mepilex Ag. J Burn Care Res. 2018 Feb 20;39(2):261–7.
4. Blome-Eberwein SA, Amani H, Lozano DD, Gogal C, Boorse D, Pagella P. A bio-degradable synthetic membrane to treat superficial and deep second degree burn wounds in adults and children - 4 year experience. Burns. 2021 Jun;47(4):838–46.
5. Ring A, Goertz O, Al-Benna S, Ottomann C, Langer S, Steinstraesser L, et al. Accelerated angiogenic induction and vascular integration in a novel synthetic scaffolding matrix for tissue replacement. Int J Artif Organs. 2010 Dec;33(12):877–84.