Effectiveness of a novel polylactic acid matrix for diabetic foot ulcer closure: Results from a single center interim analysis

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Background

Objective:

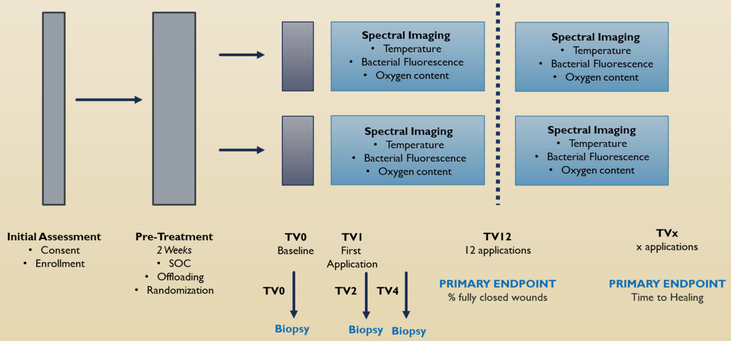
- To compare the performance of a **poly-lactic acid (PLA)** guided closure matrix vs. a collagen dressing to achieve 100% closure of diabetic foot ulcers.

Background:

- A recent pilot RCT demonstrated a **44% reduction in time** for achieving diabetic foot ulcer (DFU) healing when using a novel polylactic acid (PLA) wound closure matrix compared to collagen dressings. [1]
- Building on those results, here we present results on a single center interim analysis of a larger RCT.
- PLA matrices have a biological effect through the release of **lactate**, which 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**
  - **pH shift** to neutral values.

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.
- Multispectral imaging data, thermography, and bacterial fluorescence were **recorded on each visit**.
- Ten patients from each arm were randomized to receive **tissue biopsies at baseline, 2, and 4 weeks** of treatment. Biopsy data includes gene expression analysis and histology assessment.
- The **primary objectives** of this trial were the proportion of wound fully closed by 12 weeks and the time required to attain full closure of the wound.
- The **secondary objectives** included changes in the imaging and biopsy data.
- Analysis of the data was performed blindly by an independent researcher.

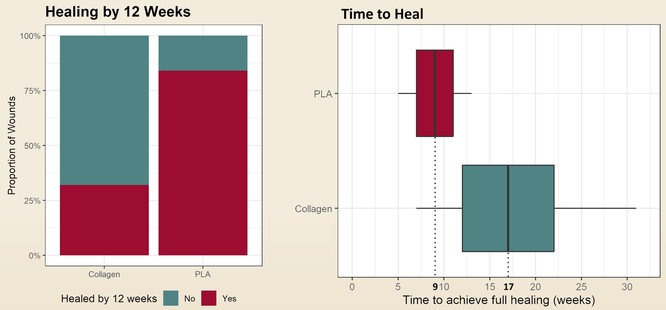


Results

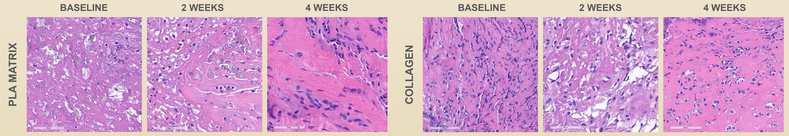
- A total of 50 patients, 25 per treatment arm, are included in this analysis.
- No significant differences between patient or wound characteristics or were found at baseline:

		Collagen (N=25)	PLA (N=25)	Total (N=50)	p value
Age	Mean (SD)	60.600 (13.339)	63.640 (10.078)	62.120 (11.800)	0.368[1]
Gender	Male	14 (56.0%)	15 (60.0%)	29 (58.0%)	0.774[2]
	Female	11 (44.0%)	10 (40.0%)	21 (42.0%)	
BMI	Mean (SD)	31.600 (8.150)	32.520 (4.709)	32.060 (6.604)	0.627[1]
Use of Tobacco		12 (48.0%)	9 (36.0%)	21 (42.0%)	0.390[2]
HbA1c (%)	Mean (SD)	7.682 (1.145)	7.856 (1.166)	7.771 (1.142)	0.661[1]
ABI	Mean (SD)	1.055 (0.122)	1.012 (0.153)	1.033 (0.139)	0.373[1]
Wound Area (cm^2)		4.920 (2.722)	6.221 (3.235)	5.571 (3.031)	0.130[1]

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



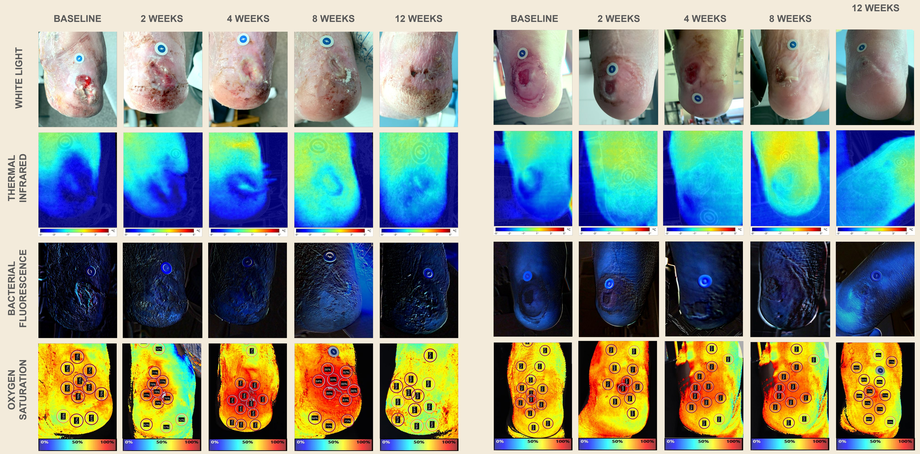
*By 12 weeks of treatment, **84% of the wounds treated with PLA matrices were fully healed**, as compared to only 32% of those treated with collagen dressings (p <0.001). The median time required to obtain full closure in the PLA group was 9 weeks (range 4 to 13) and 17 weeks (range 7 to 32) in the collagen group (p <0.001).*



H&E staining

- Histology data showed better organized tissue, with higher blood vessel density in the PLA group.
- Molecular data evaluated the expression of RNA wound healing biomarkers in response to treatment. The marker categories included ECM and cell adhesion molecules, inflammatory cytokines and chemokines, growth factors, and signal transduction molecules. Subjects who received PLA treatment had increased cellular adhesion, proliferation, angiogenesis, and ECM biomarker expression with the restoration of the immune balance by week 4.
- A detailed analysis of the histological and gene-expressions results is presented in poster ***(CR-052 (RPT-006)) Polylactic acid matrices directly promote neo-angiogenesis and immune balance in diabetic foot ulcers***

PLA Matrix **Collagen Dressing**



*Two representative wounds with similar healing trajectories are presented. While the clinical (white light) images show a very similar pattern, spectral imaging captures stark differences between the wounds. **Infrared thermal images** capture the heat in the tissue as a proxy to blood flow. In the baseline images, the wound can be observed colder than the surrounding tissues. As they are treated and the blood flow is restored, the thermal asymmetry between the wound bed and surrounding tissues disappears. In the PLA treated wound, the wound bed becomes hotter throughout the treatment period and is even identifiable as a bright spot by 12 weeks. This suggests a more metabolically active tissue with a higher vascularity. **Fluorescence images** take advantage of the autofluorescence of bacterial proteins (heme factor - red or pyoverdines - cyan) at critical thresholds. As expected, most wounds did not show positive fluorescence during the study period. However, faint red and cyan signals can be observed at the baseline image of the PLA group that disappeared after treatment. In contrast, the baseline image of the collagen group does not show fluorescence, but the 2 week image does. This faint pink signal indicates subsurface bacteria in the periwound area and significant contamination at this time point. In the PLA group, **tissue oximetry** shows a relative symmetry in the oxygen content of the periwound at baseline. After treatment, a localized increase in the oxygen saturation in the wound and periwound area that peaks at 4 weeks is evident. In contrast, in the collagen group the onset of this oxygen content increase is delayed until after the 4th week and peaks at the 8th week. Even after wound closure at 12 weeks, a local oxygen content increase is easily identifiable in this group.*

White light, thermal, and fluorescence images were acquired with a Ray-1 imaging device (Swift Medical, Toronto, ON). Oxygen content images were acquired with a Kent Snapshot device (Kent Imaging, Calgary, AB)

Discussion

- **PLA matrices are more effective** than active collagen dressings in promoting diabetic wound closure.
- Its use **increases the odds of achieving closure by 12-weeks** and **reduces the time required for full closure**.
- Spectral, histological, and gene data analysis demonstrate an increase in **cell attachment, migration, vascularization, and remodelling** of the tissue produced in response to the PLA matrices.

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 blood flow, vascularity, granulation tissue content, and a reduction in the time required to achieve full closure of the wound.

References

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