Purified Exosome Product (PEP) Enhances Skin Graft Donor Site Healing: A Phase 1b Clinical Trial

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OBJECTIVES

The objective of this study was to determine the safety of the first clinically used purified exosome product (PEP) for open wounds. This is the first FDA-approved clinical study evaluating the safety of a commercially available exosome product on human wounds.

METHODS

This was a phase 1b, prospective, open-label, controlled, randomized clinical trial of PEP in subjects with at least two equal sized Split-thickness skin graft (STSG) donor site wounds with one donor site treated with standard of care (SOC) and the other treated with PEP. Patients were divided into low-dose PEP-only group and high-dose PEP-only group.

The primary objective of this trial was to determine the safety and side effect profile of PEP. Safety markers included extent of exposure, laboratory assessments, vital sign measurements, and physical examination findings. The exploratory objective was wound re-epithelialization evaluated using Vancouver Scar Scale (VSS) and Photographic Wound Assessment Tool (PWAT) by a board-certified dermatologist and a plastic surgeon.

Clinical-grade PEP was manufactured by Rion Inc. Briefly, leukocyte-depleted human blood was pooled and subjected to a series of freeze-thaw, filtration, and lyophilization cycles according to U.S. patent 20160324A1. The resulting product was stable at room temperature for 24 months (Figure 1).

RESULTS

- A total of 7 subjects were enrolled in this study. All subjects (100%) completed the study without discontinuation.
- *Patient Characteristics:* The median age of the patients was 50.5 years (range, 19 to 79). Three male patients and four female patients were included. All subjects were White. Six subjects (85.7%) reported medical history findings that did not preclude subject enrollment or PEP treatment. All subjects (100%) reported using prior and/or concomitant medications that were not exclusionary per the protocol (Table 1). All patients (100%) required skin grafting in conjunction with other major plastic surgery procedures involving muscle flap coverage of the extremities or fasciotomy site closure.

FIGURE 1

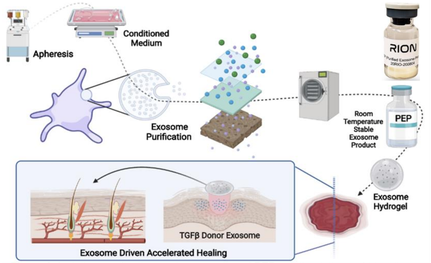

Figure 1. Isolation, purification, and preservation of PEP and the delivery of bioactive elements to the wound bed.

FIGURE 2

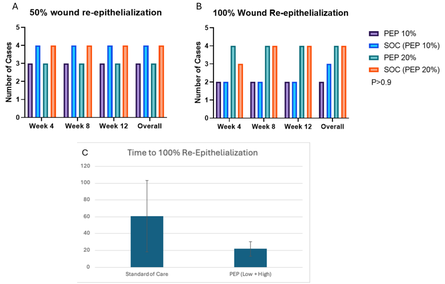

Figure 2. (A) Cases of achieving 50% wound coverage at different timepoints (B) Cases of achieving complete wound coverage at different timepoints (C) Mean days to 100% epithelialization in all SOC wounds and all PEP-treated wounds combined

RESULTS

TABLE 1: Characteristics of the Patients at Baseline

Statistic/Category	PEP-only low dose (N=3)	PEP-only high dose (N=4)	Total (N=7)
Age at Informed Consent (years)			
Mean±SD	58±33.81	42.8±24.35	49.8±28.4
Median (Min, Max)	76 (19, 79)	37 (22, 75)	50.5 (19, 79)
Gender, n (%)			
Female	1 (33.3)	3 (75.0)	4 (57.1)
Male	2 (66.7)	1 (25.0)	3 (42.9)
Race, n (%)			
White	3 (100)	4 (100)	7 (100)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3 (100)	4 (100)	7 (100)
Height (cm)			
Mean±SD	177.77±13.44	164.25±5.68	170.06±10.50
Median (Min, Max)	172.70 (167.6, 193.0)	162.50 (160.0, 172.0)	168.89 (160.0, 193.0)
Weight (kg)			
Mean±SD	86.50±7.09	76.85±26.10	81.58±18.22
Median (Min, Max)	84.40 (80.7, 94.4)	71.10 (52.3, 112.9)	82.55 (52.3, 112.9)
Body Mass Index, BMI (kg/m^2)			
Mean±SD	27.78±5.51	28.70±10.72	28.47±7.64
Median (Min, Max)	27.06 (22.66, 33.61)	25.75 (19.21, 44.10)	26.58 (19.21, 44.10)

FIGURE 3

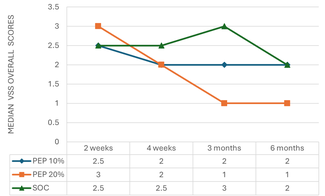

Figure 3. Median Vancouver Scar Scale (VSS) overall score over time

FIGURE 4

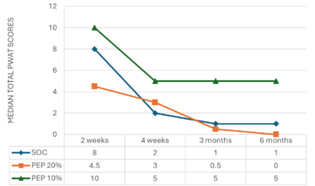

Figure 4. Median Photographic Wound Assessment Tool (PWAT) total score over time

FIGURE 5

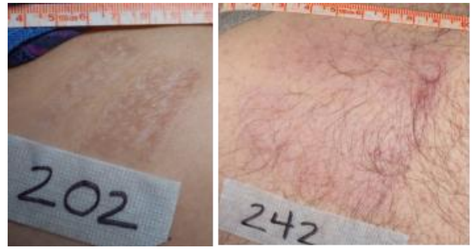

Figure 5. Representative photos of two subjects treated with PEP, showing their wounds 6 months after PEP administration, both achieving a PWAT score of 0.

RESULTS

- *Safety Profile:* There were no adverse events related to the treatments.
- *Efficacy in Wound Healing:*
  - The application of PEP significantly accelerated wound healing with the PEP-treated sites reaching 100% re-epithelialization in an average of 21.8 days, compared to 60.6 days for the SOC sites (P < 0.05).
  - By 4 weeks after treatment, all wounds reached 50% re-epithelialization (Figure 2A) and 6 (85.7%) of 7 subjects reached 100% re-epithelialization. (Figure 2B). PWAT scores demonstrated that the PEP-treated sites achieved 100% re-epithelialization significantly faster, with a mean of 21.8 days, compared to the SOC sites, which took an average of 60.6 days (P<0.05) (Figure 2C). Both the high-dose and low-dose PEP-only groups demonstrated a trend of decreasing VSS scores over time compared to SOC (Figure 3). At the 3-month and 6-month visit, the high-dose PEP-only group showed the lowest median VSS score of 1.The total PWAT score was significantly reduced in the high-dose PEP-only group compared to the low-dose PEP-only group at 3 months and 6 months after PEP administration (Figure 4).
  - All donor site wounds in the high-dose PEP-only group, including those treated with PEP and those receiving SOC, were closed with intact overlying skin indicated by PWAT=0. Representative photos of two subjects 6 months after PEP treatment were shown in Figure 5.

DISCUSSION

Our team has established the efficacy of PEP in promoting tissue repair and regeneration in various preclinical models. However, its use in human patients is still under investigation. This study marks the first completed trial of PEP application in wound healing, delivering satisfying results and showing that it is safe for patient use, with up to two vials administered at one time.

Currently there are 12 exosome-based interventional studies in the United States registered on ClinicalTrials.gov. Among them, 3 are related to Covid-19 or respiratory treatments, 3 on cancer research, and 4 are PEP clinical trials. This leaves only 2 other studies involving exosome therapies, which were designed to treat alopecia and thinning hair. These two clinical trials are testing two clinical-grade exosome products, which are Age Zero™ Exosomes (RESILIÉLLE Llc, Rochester, NY) derived from human umbilical cord mesenchymal stem cells63 and BENEV Exosome Regenerative Complex+ (BENEV, Inc., LA, CA) derived from human adipose stromal cells. Compared to PEP, Age Zero™ Exosomes requires storage at specific low temperatures and have a limited shelf life: -80°C for up to 15 months or -20°C for up to 6 months, while PEP can be stored at room temperature for up to 2 years. BENEV Exosome Regenerative Complex+ can be stored for up to 4 years under refrigeration, but it contains 0.5 to 1 billion lyophilized active exosomes per milliliter, whereas PEP contains 2 trillion regenerative exosomes per vial—approximately 200 billion exosomes per milliliter.

CONCLUSIONS

- PEP is a clinical-grade exosome product that can benefit wound healing with immediate clinical translation.
- Our results showed that a single application of PEP at a dose up to 20% (2 vials) was safe and support additional clinical investigation of PEP in wound management. Wound healing was significantly accelerated in the PEP-treated wounds compared to SOC, with a dose-response effect.
- Guided by the FDA, this study delivers exosome-based therapies to patients to achieve advancements in wound management safely, conveniently and efficiently. Further clinical efficacy studies are warranted.

LIMITATIONS

The major limitation is the small number of subjects. Even though we observed significant improvements in wound healing when comparing all PEP-treated wounds combined to SOC wounds, most of our results lack the statistical power needed for meaningful comparisons across different treatment groups. Second, we originally designed a second study arm for this clinical trial to evaluate PEP combined with an FDA-approved injectable surgical fibrin sealant (PEP-TISSEEL). Our previous studies demonstrated that while PEP applied alone to the wound site could not sustainably release active particles, combining it with TISSEEL allows PEP to maintain a 20% concentration release for up to two weeks. However, we missed the baseline data of the patient treated with PEP-TISSEEL, which excluded him from this trial. Third, our population was entirely white, which may limit generalizability to populations of other racial groups.