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Topical Human Mesenchymal Stem Cell-Derived Exosomes for Acceleration of Wound Healing Following Tissue Trauma and Aesthetic Procedures: A Case Series

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ABSTRACT

Background: In the Aesthetics Practice, measures to accelerate wound healing and minimize downtime following procedures have been largely restricted to topical serums and platelet-rich plasma (PRP), which can have varying levels of success. Here, the authors present a case series of patients treated in clinical practice with cell-free exosomes derived from human placental mesenchymal stem cells (Exovex™, Exocelbio, Doylestown, PA). Topical administration of exosomes after either aesthetic treatment or traumatic injury (a dog bite) had a marked effect on healing. Effects were assessed visually and case-study images are shared. Individuals demonstrated significantly accelerated recovery and wound healing within hours to days, depending on the procedure. Patients who had undergone the same aesthetic procedure prior without exosomes reported satisfaction with reductions in pain, swelling, redness, and post-procedure downtime. No adverse events were reported by patients after treatment. Together, these case series suggest that exosome treatment can accelerate wound healing safely and effectively and support topical use in an office-based setting. These findings also highlight the need for more formal evaluation of the effects of exosomes on wound healing in reducing aesthetic procedure recovery times for surgical and non-surgical interventions.

Significant Finding: The case series presented here illustrates the potential for exosomes to be a versatile and important part of clinical care, especially in situations where expedited healing is central to patient safety and/or satisfaction. These results provide strong support for additional research.

Meaning: Topical administration of cell-free exosomes has the potential to improve patient care and satisfaction with aesthetic interventions. Early experience, illustrated by the presented case studies has been remarkably positive and treatment has the potential to dramatically improve the standard of care.

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INTRODUCTION

While surgical and non-surgical aesthetic technologies continue to evolve, there remains an unmet need for effective wound healing therapy in clinical practice. Although PRP has been widely and safely used in the clinic,[1,2] there are multiple limitations to its use as a wound healing therapy, including its extensive collection and preparation process and potential for decreased effectiveness in more mature patients.[3-5]

Exosomes, also known as extracellular vesicles (EVs), are lipid bilayer membrane micro-vesicles secreted by almost all eukaryotic cells.[6-8] Native exosomes target and repair damaged tissue at sites of inflammation through the delivery of lipids, proteins, and nucleic acids to recipient cells via paracrine signaling.[7,8] Their contents may also include cell-signaling proteins and/or growth factors relevant to all four phases of wound healing. The safe use of exosomes derived from a variety of cell types has been extensively reported for numerous therapeutic applications and their anti-inflammatory and immunomodulatory properties are well documented.[7,9]

The ability of exosomes to influence angiogenesis and the differentiation, proliferation, and apoptosis of target cells has made these micro-vesicles the subject of particular interest in wound healing and regenerative medicine.[10] In addition, many studies have demonstrated a role for certain miRNAs in the promotion of scar removal, skin rejuvenation, pigmentation regulation, and hair growth.[10]

MATERIALS AND METHODS

Exosome Source and miRNA Content

Cell-free exosomes were pre-clinically isolated from mesenchymal stem cells derived from human placental tissue according to good manufacturing practice (GMP) guidelines.[7]

Routine quality control (QC) testing (ie, nitriloacetic acid [NTA], next-generation sequencing [NGS], and multidimensional identification technology [MudPIT]) was performed to determine the quantity, size, miRNA contents, and purity of the exosomes.

Intervention/Preparation of Intervention

Exosomes (Exovex™, Exocelbio, Doylestown, PA) are a cell-free preparation in pre-diluted vials of serum at 1 of 4 ready-to-use concentrations: 5 x 10^9 exosomes in 2 mL of serum, 12 x 10^9 exosomes in 2.5 mL of serum, 25 x 10^9 exosomes in 5 mL of serum, and 100 x 10^9exosomes in 5 mL of serum. Vials are stored at -20 °C until use and must be thawed without shaking before application. In each of the cases detailed below, exosome serum was applied topically. All patients presented here were treated in accordance with the principles outlined in the Declaration of Helsinki, and each patient consented to treatment and photography.

RESULTS

Case Study Patient 1: A 31-year-old woman with acne, mild acne scarring, and melasma who received fractional non-ablative laser treatment (Novel 1,927 nm Fractional Thulium Laser, LaseMD Ultra by Lutronic). The patient received

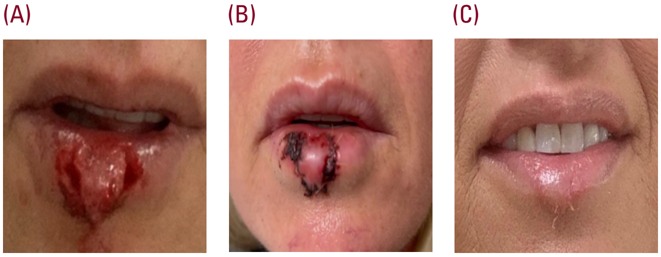
FIGURE 1. A 31-year-old female immediately after treatment with fractional non-ablative laser therapy for melasma (A-D) and 1 hour (E-H), 4 hours (I-L), and 24 hours (M-P) after topical exosome application.

treatment at a moderate-to-high laser temperature (7 Joules) set for hyperpigmentation/melasma treatment (ie, random laser application to prevent overheating of the skin) to the face, chest, and back with 6 passes per treatment area.

After the last pass, the patient was assessed for discomfort and reported a pain level of 8 out of 10 for heat discomfort, stinging, and burning. After the assessment, a total of 3 mL of the 5 x 10^9 concentration of exosome serum was applied across the treatment areas. Immediately after application, the patient reported a reduction in severity of discomfort to a pain level of 4 out of 10. As observed in Figure 1, erythema and swelling recovery time was also reduced.

Case Study Patient 2: One drawback of PRP is that the bioactivity of platelets and growth factors isolated from older individuals may be less efficient than in younger counterparts, impacting the clinical effectiveness.[5] Therefore, comparing the efficacy of PRP vs exosome therapy in older patients is of particular clinical interest. In Figure 2, a 72-year old female patient is shown following after treatment with CO2 fractional laser therapy followed by PRP. The patient demonstrated erythema and swelling with PRP that continued for a week after treatment (Figure 2A). After receiving the same treatment, 4 years later, followed by 2.5 mL of the 12.5 x 10^9 exosome serum solution, the patient's skin showed reduced swelling at 4 days after treatment with minimal erythema and an overall reduction in peak post-treatment severity (Figure 2B). The reduced downtime, swelling, and discomfort contributed to increased patient satisfaction with the procedure.

FIGURE 3. A 49-year-old female immediately following a dog bite (A) and at 20 hours (B) and day 10 (C) after topical exosome application. Wound closure is aesthetically pleasing with minimal scarring.



Case Study Patient 3: A 49-year-old female patient who suffered a dog bite in the lower lip (Figure 3A) was treated by an emergency room physician (non-plastic surgeon) and presented for treatment 20 hours after wound stitching (Figure 3B). At this time point, the wound was cleaned with a hypochlorous acid solution, and 2.5 mL total of the 12.5 x 10^9 exosome solution was slowly applied, a few drops at a time, over 10 minutes using a 32 G ½" needle, allowing each aliquot of serum to be absorbed by the skin before the subsequent application. Wound healing could be observed as early as 18 hours after exosome application. Although the emergency room estimate for healing of this type and location of traumatic injury was estimated to be 6 months, by day 10 (Figure 3C), the wound was completely closed, with no evidence of fibrotic tissue, and with minimal scarring and well preserved sensory and motor function. Within this time period, lip function was entirely restored, and evidence of scaring is nearly absent.

FIGURE 2. A 72-year-old female 4 days after treatment with CO_2 fractional laser followed by topical PRP (A) or topical exosomes (B). The photograph in panel B was taken four years after the image in panel A.

CONCLUSIONS

PRP is an autologous concentrate derived from a patient's own serum and its acquisition is a multi-step process that requires access to specific equipment and carries handling and contamination risks.[3] Furthermore, PRP can contain variable numbers of platelets and growth factors, which can affect bioactivity.[5] For more mature patients, PRP may not be able to provide enough of the cellular factors necessary, which is problematic as these are the patients who need healing and accelerated recovery the most. In contrast, harvesting and preparation of exosomes in a laboratory and according to GMP guidelines controls for variability in efficacy and removes the need for further manipulation in the clinic, allowing their application with no interruption in workflow and the expectation of a predictable level of bioactivity across patient populations and between batches.

The discovery of the ability of exosomes to act as carriers of genetic messages between cells has caused an explosion of interest in these micro-vesicles.[7] In 2020, exosomes carrying some of the same genetic material contained within the exosomes used in these case studies (miRNA 425-5p and 142-3p; Exovex™) were demonstrated to promote wound healing and to reduce scarring, potentially through the inhibition of transforming growth factor (TGF)-β1expression within injured tissue, suggesting a potential mechanism for their effects in promoting accelerated recovery time and traumatic injury.[11] Indeed, a clinical study investigating the safety and efficacy of human placental mesenchymal stem cell-derived exosomes in the acceleration of wound healing after infection was recently (June 2022) initiated, further evidence of the interest in their clinical potential.[12]

In these case studies, exosomes rapidly and dramatically accelerated recovery times for a range of patients with no reported adverse effects. For those patients who prioritize or require minimized downtime, exosomes are a valuable complement to treatment. For patients with the potential for scarring, this type of therapy may be invaluable, in particular for post-surgical scarring. That the patient in Figure 3 demonstrated dramatically accelerated wound healing (10 days to complete wound closure vs 6 months predicted) displayed no scarring or fibrosis is a testament to the potential therapeutic application of these vessels that is further backed by in vitro findings and recognition that exosomes can promote healing through various pathways at multiple stages in wound healing.[11,13] Taken together these case studies emphasize the need for further clinical study of these potentially significant modifiers of infection, inflammation, and wound healing following both trauma and surgical procedures.

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DISCLOSURES

Dr Peredo is a trainer for Galderma and an Advisory Board Member for Exocel Bio. Dr Shivananjappa is a Scientific Advisor for Exocel Bio.

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