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**Evaluation of Mesenchymal Stem Cell–Derived Exosomes Versus
Platelet-Rich Fibrin (PRF) in Post-Extraction Socket Healing: A
Randomized Controlled Clinical Trial**

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Abstract

Background: Post-extraction alveolar bone resorption remains a major challenge affecting implant placement and prosthetic outcomes. Platelet-rich fibrin (PRF) is widely used to enhance healing; however, its biological activity is variable and patient-dependent. Mesenchymal stem cell (MSC)–derived exosomes are cell-free nanovesicles rich in growth factors, cytokines, and microRNAs that promote angiogenesis, osteogenesis, and immunomodulation.

Study objective: To compare the effectiveness of MSC-derived exosomes versus platelet-rich fibrin (PRF) in enhancing soft tissue and bone healing of post-extraction sockets.

Methods: The study population will include 40 patients (20 per group), the sample will be selected conveniently to fulfil the inclusion criteria. Group A – MSC-Derived Exosome. Commercial or GMP-grade MSC-derived exosomes Group B – PRF Autologous PRF prepared using standard centrifugation protocol. Surgical Procedure (Standardized for All Patients) This study may establish exosome therapy as a superior regenerative alternative to PRF in oral surgery, contributing to safer, standardized, and more effective socket preservation techniques.

Introduction

The healing course after extraction is a complex biologic phenomenon, encompassing inflammation, angiogenesis, bone production, or rather bone generation, and tissue condensation.^(1,2) Uncontrolled bone resorption makes it necessary for the maintaining or rather preserve alveolar bone bulk.⁽³⁾ Platelet-rich fibrin (PRF) is a second-generation platelet concentrate, which is increasingly acknowledged as a regenerative biomaterial in the management of post-extraction sockets.^(4,5) PRF contains high platelet counts along with high levels of leucocytes and fibrin.⁽⁶⁾ Moreover, it provides a fibrin matrix to facilitate the release of growth factors, namely platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), and Vascular Endothelial Growth Factor (VEGF), to a greater extent.⁽⁴⁾ Several studies have provided evidence of its effectiveness in stimulating the healing of soft tissue, alleviating postoperative pain, and promoting early bone formation within the extraction socket.

More recently, a promising cell-free approach using mesenchymal stem cell (MSC) exosomes has appeared on the horizon.⁽⁷⁾ Exosomes are nanovesicles secreted by MSCs that are filled with bioactive cargo such as protein, cytokines, lipids, and micro-RNA.⁽⁸⁾ These structures are essential for cell-to-cell communication and can induce angiogenesis, modulate inflammation, and accelerate osteogenic differentiation and tissue regeneration.⁽⁹⁾ Exosomes isolated from dental and non-dental-derived MSCs showed encouraging preclinical regenerative outcomes for

bone and periodontal tissue regeneration, indicating their perceived usefulness in socket restoration following tooth extraction.⁽¹⁰⁾Currently, limited randomized clinical trials compare exosomes and PRF in oral surgery, making this study novel and clinically relevant.

Aim of the Study

To compare the effectiveness of MSC-derived exosomes versus platelet-rich fibrin (PRF) in enhancing soft tissue and bone healing of post-extraction sockets.

Objectives

Primary Objective

- To compare bone density and bone volume preservation at extraction sites treated with MSC-derived exosomes versus PRF.

Secondary Objectives

- To evaluate soft tissue healing quality
- To compare postoperative pain and swelling
- To assess complication rates (infection, dry socket)
- To evaluate patient satisfaction

Hypothesis

- Null hypothesis (H_0): There is no significant difference between MSC-derived exosomes and PRF in post-extraction socket healing.
- Alternative hypothesis (H_1): MSC-derived exosomes result in superior bone and soft tissue healing compared to PRF.

Study Design

- Type: Prospective, randomized, controlled, single-blind clinical trial
- Allocation: 1:1 ratio
- Blinding: Outcome assessor blinded
- Study duration: 6 months
- Study setting: El Salam University / oral and maxillofacial surgery department

Sample Size

- Total sample: 40 patients (20 per group)
- (Adjustable after power analysis; expected power 80%, $\alpha = 0.05$)

Study Population

Inclusion Criteria

- Patients aged 18–55 years
- Indicated for single non-infected tooth extraction
- Good systemic health (ASA I or II)
- Intact socket walls
- Willing to participate and sign informed consent

Exclusion Criteria

- Smokers (>5 cigarettes/day)
- Pregnancy or lactation
- Uncontrolled systemic disease (e.g., diabetes)
- Acute infection or abscess at extraction site
- History of radiotherapy or bisphosphonate therapy
- Immunosuppressive drug use

Randomization

- Computer-generated random sequence
- Allocation concealment using sealed opaque envelopes

Interventions

a-Group A – MSC-Derived Exosomes

- Commercial or GMP-grade MSC-derived exosomes
- Dosage: X µg exosomal protein suspended in sterile saline or hydrogel
- Applied directly into extraction socket immediately after extraction
- Socket closed with simple interrupted sutures

b- Group B – PRF

- Autologous PRF prepared using standard centrifugation protocol
- PRF membrane placed into extraction socket
- Socket closed with simple interrupted sutures

Surgical Procedure (Standardized for All Patients)

- Local anesthesia
- Atraumatic tooth extraction
- No flap elevation
- Socket irrigation with sterile saline

- Intervention applied according to group
- Suturing with 3-0 or 4-0 resorbable sutures

Postoperative Care

- Standard analgesics (paracetamol)
- No prophylactic antibiotics unless clinically indicated
- Chlorhexidine mouthwash (0.12%) twice daily for 7 days
- Postoperative instructions standardized

Outcome Measures

Primary Outcomes

- Bone density (HU) measured using CBCT at: Baseline (immediate post-extraction) 3 months
- Alveolar ridge width and height changes (CBCT)

Secondary Outcomes

- Soft tissue healing index (Landry score)
- Pain intensity (VAS scale) at days 1, 3, 7
- Facial swelling (linear measurements)
- Incidence of dry socket or infection
- Patient satisfaction questionnaire

Follow-Up Schedule

Time Point Assessment

- Day 1 Pain, swelling
- Day 7 Soft tissue healing, complications
- 1 month Clinical healing
- 3 months CBCT evaluation
- 14. Data Collection & Statistical Analysis
- Data analyzed using SPSS
- Independent t-test for quantitative variables
- Chi-square test for categorical variables
- Repeated measures ANOVA for follow-up comparisons
- Significance level set at $p < 0.05$

15. Ethical Considerations

- Approval from Institutional Ethics Committee
- Informed consent obtained from all participants
- Confidentiality maintained
- Adverse events monitored and documented

Expected Outcomes

MSC-derived exosomes will show:

- Greater bone density
- Improved ridge preservation
- Reduced postoperative inflammation
- Faster soft tissue healing

Significance of the Study

This study may establish exosome therapy as a superior regenerative alternative to PRF in oral surgery, contributing to safer, standardized, and more effective socket preservation techniques.

Potential Limitations

- Regulatory restrictions on exosome use
- Cost and availability
- Short follow-up period

Future Directions

- Long-term implant success evaluation
- Dose-response studies
- Combination therapy (Exosomes + PRF)

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