Original Article

Histological Evaluation of Local Application of Peripheral Blood Mesenchymal Stem Cells and Platelet-Rich Fibrin Matrix on Bone Healing of Rats

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Abstract

Background: Bones are more than just the framework that binds the body together. Bones exist in diverse forms and sizes and serve a variety of functions. Repairing defects in bones remains a significant clinical medical problem. Bone is a highly vascularized tissue, meaning it relies on the close spatial and temporal interaction between blood vessels and bone cells to maintain skeletal integrity. **Objective:** The purpose of this research was to examine the effects of using platelet-rich fibrin matrix (PRFM) (supercell and glue) and peripheral blood stem cells to promote bone repair at the site of injury. **Materials and Methods:** This research will include the use of 20 male albino rats, with weights ranging from 300 to 400 g and ages between 6 and 8 months. These rats will be subjected to controlled conditions in terms of temperature, drinking, and food utilization. The animals will be subjected to an intrabony defect in the maxillary diastema. In the control group, consisting of 10 rats, the maxillary diastema bony defect will be left untreated. Simultaneously, the experimental group consisting of 10 rats will be subjected to treatment using a PRFM infused with stem cells at a dosage of 1 mg. The rats were euthanized at 2 and 4 weeks postsurgery, with five animals per time point for each group. **Results:** The histological examination reveals that the bone defect treated with a PRFM, including stem cells, exhibits a rapid creation of osteoid tissue, characterized by a large number of cells involved in bone formation, including osteoblasts, osteocytes, and osteoclasts. **Conclusion:** The use of PRFM combined with stem cells has shown the potential to enhance bone healing and augment osteogenic ability. This evidence supports the notion that these aims may be achieved, hence providing valuable insights for future clinical treatment.

Keywords: Bone, bone healing, platelet-rich fibrin matrix, stem cells

Introduction

The skeletal system is a complex organ that serves the dual purpose of providing structural support and facilitating mobility. Additionally, it serves as a reservoir for blood cells, including both adaptive and innate immune cells. The preservation of structural and functional integrity is maintained by the equilibrium between bone creation and bone resorption, which is impacted by mechanical stresses, signaling pathways, and the milieu of the tissue.[1]

Bone is a mineralized connective tissue with four cell types: osteoblasts, bone lining cells, osteocytes, and osteoclasts. Bone is a rigid biological tissue composed of cells embedded inside a compact extracellular matrix. The primary constituents of this material are collagen and calcium phosphate.[2]

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Bone is composed of approximately 28% type I collagen and 5% noncollagenous matrix proteins, such as bone sialoprotein, which play an essential role in bone metabolism.[3] Bone contains a variety of proteins, including osteocalcin, osteonectin, osteopontin, and proteoglycans, as well as growth factors and serum proteins. Substituted hydroxyapatite (Ca10[PO4]6[OH]2) is the target of this organic matrix, which necessitates the remaining 67% of bone.[4]

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Bone defects are often occurring lesions to the skeletal system that need an inflammatory reaction, the recruitment of stromal progenitor cells, proliferation and differentiation of chondrogenic or osteoblastic cells, as well as their maturation, and the synthesis and remodeling of a substantial amount of extracellular matrix.[5] The process of osseous healing involves the participation of several components, including the cortex, periosteum, bone marrow, and external soft tissues.[6] A range of hormones and local variables influence bone healing, modeling, and remodeling.[7]

Stages of bone healing[8]

A. Reactive phase: Inflammatory response and the creation of a hematoma. Formation of granulation tissue.
B. Rehabilitative phase: Soft callus formation. Formation of a hard callus.
C. Bone remodeling: Platelets possess significant potential in the context of bone regeneration due to their capacity to store growth factors and cytokines, which are crucial for the processes of bone regeneration and the maturation of soft tissues, such as VEGF, which recruits and activates osteoclasts and stimulates osteoblast chemotaxis, differentiation, and matrix mineralization. They are involved in intramembranous ossification.[9]

Mesenchymal stem cells (MSCs) are multipotent stromal cells that have strong regeneration abilities. MSCs are multipotent stem cells with the ability to self-renew and differentiate in multiple directions. MSCs possess several characteristics, such as the ability to differentiate into multiple cell lineages and their capacity to regulate the immune system. These attributes make them a very intriguing candidate for cell-based therapies in the context of inflammation, immunological disorders, and organ transplantation. MSCs have been recognized as a distinctive therapeutic modality for the management of cancer in recent times.[10]

The need for aspirating bone marrow from the patient will result in donor-site discomfort and morbidity. It would be very handy if peripheral blood MSCs could be extracted and grown in sufficient quantities while maintaining their osteogenic ability for a clinically allowed duration.[11]

Platelet-rich fibrin (PRF) or leukocyte-PRF (L-PRF) is a kind of platelet-rich plasma (PRP) that consists of autologous platelets and leukocytes embedded inside a sophisticated fibrin matrix. This formulation is designed to enhance the process of healing in both soft and hard tissues, making it valuable in many applications, such as tissue engineering, wound healing, and bone repair.[12]

The field of PRP has seen notable progress, leading to the development of an innovative substance called PRFM matrix, characterized by a more compact and pliable composition. PRFM is the latest iteration of platelet concentrate, characterized by the inclusion of a fibrin matrix that encompasses platelets.[13]

PRFM and PRP both displayed high efficacy in bone creation, although A-PRF had a faster regenerating ability than PRP.[14]

The PRF membrane has remarkable density, elasticity, flexibility, and strength because of the 3D design of the fibrin matrix, making it ideal for handling, manipulating, and suturing.[15]

PRF has garnered significant attention as a biocompatible regenerative substance in the fields of dentistry and medicine. PRF is a naturally occurring biomaterial generated from fibrin that is easily accessible. It may be obtained from human blood without the use of an anticoagulant. The primary aim of using PRF technology within the context of tissue regeneration is to gather a comprehensive assortment of growth factors that facilitate the process of tissue regeneration by accelerating the healing mechanisms derived from the patient's own blood.[16]

Materials and Methods

All experimental procedures were conducted in adherence to the ethical guidelines set out by the College of Dentistry at Baghdad. For this study, a sample of 20 male albino rats weighing between 300 and 400 g and aged between 6 and 8 months will be used. The rats will be subjected to controlled settings regarding temperature, access to drinking water, and consumption of food. The animals were exposed to an intrabony defect in the maxillary diastema, and in the control group (10 rats), the bony defect in the maxillary diastema was not treated. Simultaneously, the experimental group consisting of 10 rats will be given a PRFM containing stem cells (1 mg). The rats were slaughtered 2 and 4 weeks following surgery (five rats were sacrificed each time for each group). PRFM—Merisis™ super cell glue kit—Dental (DiponEd intelligence company), PRFM—Introducing PRFM kit (DiponEd intelligence company) were the items linked in the study.

Preparation of stem cells

Merisis super cells kit from DiponEd bio intelligence firm, equipment for autologous stem cell concentration preparation. Each rat in the matching group had a 3-ml blood sample taken from the orbital sinus.[17]

Using a cell separator gel (thixotropic gel) in a collecting tube. Mix the blood 2–3 times to ensure that no anticoagulant is present. The centrifuge is thereafter used to spin the tube for a duration of 5 min at a rotational speed of 3000 revolutions/min. The process involves the separation of the supernatant plasma and stem cell suspension from the blood.

The presence of red blood cells is seen underneath the cell separator gel. The stem cells located directly above the gel, with a volume ranging from 0.2 to 0.3 mL, are preserved for potential future applications. The uppermost layer of plasma should be carefully eliminated, and the stem cells located directly above the gel should be promptly collected, specifically targeting a volume range of 0.2–0.3 mL. The tube should be inverted in order to facilitate the combination of the cells present on the surface of the gel with the plasma. Retrieve a volume of plasma ranging from 0.2 to 0.3 mL, which contains the supercell, and transfer it into a separate tube for further utilization.[11]

Preparation of PRFM glue

For the glue preparation, use the Merisis PRFM kit from the DiponEd bio intelligence business gel separator tube. A small amount of blood (1 ml whole blood) is taken and placed in a collecting tube with a gel separator.

In the gel separator tube, the previously produced stem cells are combined with whole blood. The blood is centrifuged for 6 min at 3400 rpm to separate the plasma and platelets into the supernatant. The red blood cells are found beneath the gel. PRF is generated after centrifugation owing to fibrin polymerization. Using sterile tweezers, the PRF clot was quickly removed from the tube. The PRF clot was then put between two layers of sterile gauze and gently squeezed to extract fluids, yielding the PRF membrane.[18]

Surgical procedure

The animals will be undergoing surgery (maxillary diastema bone defect). The procedure will be conducted in a sterilized environment using a gentle manner.

Injectable intramuscular doses of 2% xylazine and 10% ketamine hydrochloride (50 mg/kg BW) are used to induce deep unconsciousness during the surgical procedures.

The operating field was adequately wrapped after anesthesia with sterile cloths. Before the surgery, all surgical tools and surgical cloths were sterilized in an autoclave at 121°C at a pressure of 15 bar/cm^2 for 30 min.[19]

For all rats (1.5–2.5 cm), surgical incisions were created along the alveolar crest to create an edentulous area between the incisors and molar teeth in the maxillary arch (upper diastema).

To expose the alveolar cortical bone on the buccal side, a full-thickness mucoperiosteal flap was reflected. A slow 800 rpm round bur (no. 012) chilled by a continuous stream of sterile normal saline was used to execute the opening in the bone, then the cavity was deepened with a fissure bur (no. 010). The prepared cavity measures around 2 mm in diameter and 3 mm in depth. Each rat has an intrabony hole created on the buccal side of the upper diastema.

Histological specimen preparation

The specimens were immersed in a 10% formalin solution for about 24 h. During that period, the specimens were subjected to formic acid in order to induce decalcification. Additionally, these specimens may have undergone dehydration before embedding in wax (paraffin). It is possible that a portion of 4–5 m underwent modifications in accordance with conventional architectural practices. Additionally, staining with hematoxylin and eosin may have been performed. The use of a light magnifying lens may have been employed for the purpose of assessing histological examinations.

Statistical analysis

Calculate the number of bone cells in a histological study using the mean, standard deviation, minimum, maximum, *F*-test, and probability values. SPSS (Statistical Package for the Social Sciences) version 26 was used to analyze the data. At the 0.05 level, statistical significance is assumed.

Ethical approval

The experimental methodologies and animal handling procedures adhered to the ethical guidelines for animal experiments established by the College of Dentistry at the University of Baghdad in Iraq (Ref. number: 2021, project no. 275).

Results

Histological finding

Following a duration of 2 weeks, the perimeter of the trabeculae exhibited the presence of newly formed bone trabeculae that included a substantial quantity of osteocytes and osteoblasts, which were unevenly dispersed. The reversal line serves as a demarcation between the pre-existing bones and the newly formed ones [Figure 1].

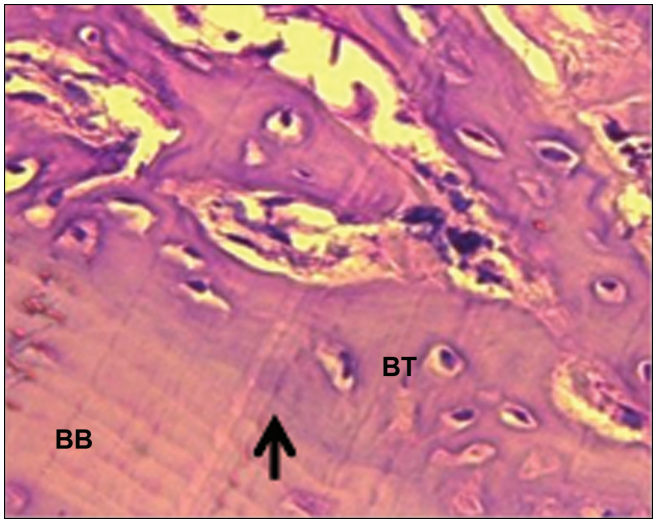

Figure 1: A view of 2 weeks of the control group shows bone trabeculae (BT) demarcated from basal bone (BB) by reversal line (arrow) H&E ×40

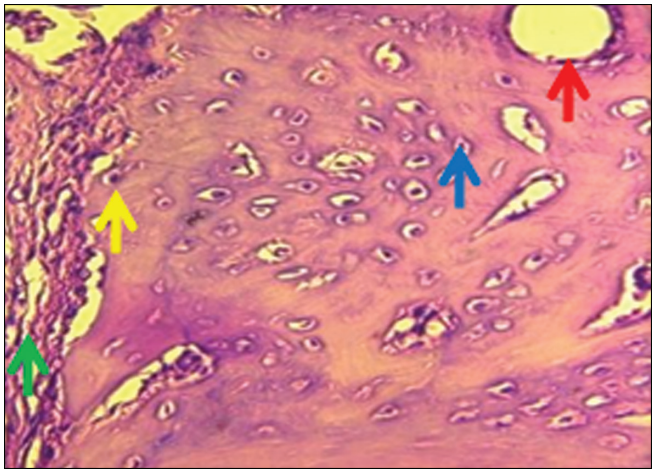

Figure 2: A view of the defect site of the control group after 2 weeks, bone trabeculae infiltrated with osteocytes (blue arrow), osteoblasts (red arrow) were shown on its periphery, osteoclast (yellow arrow), and inflammatory cells (green arrow) H&E ×40

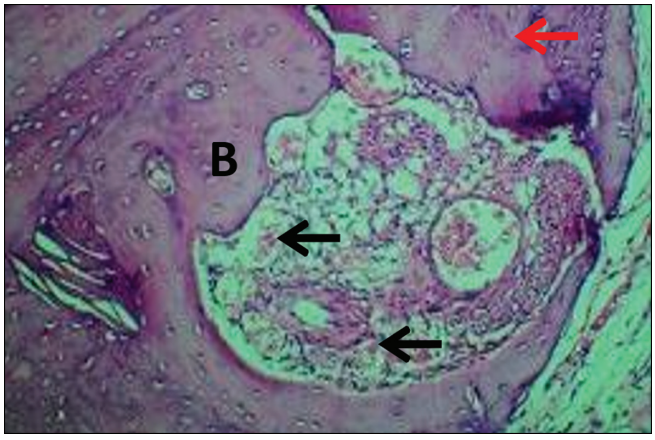

Figure 3: A view of the control group after 4 weeks shows immature bone (B), numerous blood vessels (black arrows), reversal line (red arrow), H&E ×20

Over the course of the 4-week duration, the surgical site exhibited a substantial influx of immature bone, accompanied by the presence of osteoblasts and osteocytes. Additionally, a demarcation line, known as the reversal line, was seen to distinguish between the old and newly formed bone. Furthermore, a significant number of capillaries were identified inside the area [Figure 2].

The presence of osteoclast cells with active woven bone formation and reversal line in the experimental group during the 2-week study period demonstrated primitive bone growth (woven bone) surrounded by active osteoblast cells and osteocytes trapped in bone matrix [Figure 3].

After 4 weeks, the defect site had a thick bone, osteocytes were organized in a predictable fashion around the havrersian canal, and osteoblasts were evident at the bone's perimeter [Figure 4].

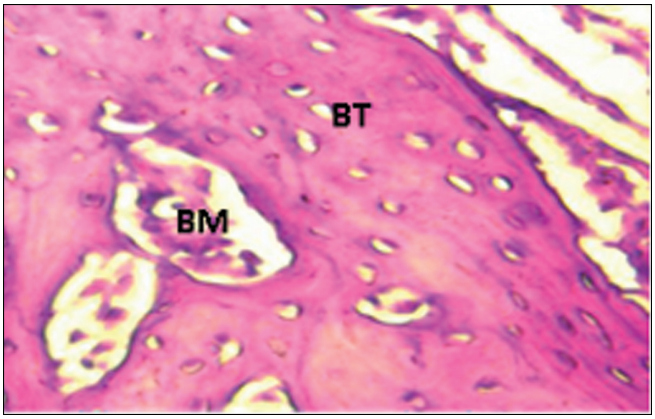

Figure 4: A view of the control group after 4 weeks shows thick bone trabeculae (BT) surrounding large and numerous bone marrow (BM). H&E ×20

Analysis of statistical data: Histological analysis

Histological analysis and statistical study of the mean number of bone cells for osteoclast, osteoblast, and osteocytes for 2 and 4-week intervals show that the PRFM groups have a growing mean quality with profoundly crucial differences when compared to control groups [Tables 1 and 2].

Discussion

In this study, we showed that stem cells and PRFM may work in harmony to promote bone repair. According to the research, PRFM may encourage cell migration, proliferation, and osteogenesis. The PRFM was utilized in prior studies to treat three-walled intraosseous periodontal anomalies in the human maxillary sinus, which sped up bone healing and improved the amount of new bone formation, according to the results. Using PRF as an autologous graft material may be a successful strategy for accelerating clinical bone growth.[10]

The process of preparing the PRFM yields a gel-like matrix that exhibits notable characteristics, including the presence of functioning and intact platelets encapsulated inside a fibrin matrix. This matrix demonstrates the ability to consistently release growth factors at a reasonably stable concentration.[20]

MSCs have the capability to undergo differentiation along many lineages and originate from diverse sources. MSCs are essential for immunomodulation, hematopoiesis, and tissue repair. The intercellular matrix, other cells, cytokines, and humoral components are sometimes referred to as the cell's microenvironment. It is also a site of cell contact. The microenvironment's stability is critical for sustaining cell proliferation, differentiation, metabolism, and functional activities.[21]

Microscopic evidence of new bone formation was seen via the appearance of several bone trabeculae and an increase in the number of osteoblasts, as compared to a control group. Based on histological findings

Table 1: Descriptive statistics on the number of bone cells (H&E) and the variance between groups for each time period

Duration	Cells	Groups	Descriptive Statistics				Comparison	
			Mean	S.D.	Min.	Max.	F-test	P- value
Two weeks	OB	Cont.	35.8250	3.23355	33.00	40.30	3.360	0.055 S
		Experimental group	39.4250	4.36530	35.20	45.70		
	OC	Cont.	23.7750	.96393	22.80	25.10	31.832	0.000 HS
		Experimental group	26.2500	1.49332	24.70	28.20		
	OCL	Cont.	1.8917	.60697	1.25	3.00	3.042	0.053
		Experimental group	1.7917	.79273	.75	2.60		
Four weeks	OB	Cont.	30.2500	4.64579	24.00	35.00	4.597	0.023 S
		Experimental group	25.5000	4.65475	19.00	30.00		
	OC	Cont.	35.1250	1.26062	33.70	36.50	48.838	0.000 HS
		Experimental group	37.8000	1.96129	35.80	40.10		
	OCL	Cont.	.6250	.34022	.10	.90	2.323	0.106
		Experimental group	.4633	.28821	.10	.70		

Table 2: Descriptive statistics of T-area (H&E) and groups' differences at 14 and 30 days duration (ANOVA test)

Duration	Groups	Descriptive statistics				Comparison	
		Mean	S.D.	Min.	Max.	F-test	P-value
Two weeks	Cont.	.3300	.05701	.25	.40	4.565	0.017
	Experimental group	.3580	.11367	.20	.50		
Four weeks	Cont.	.5420	.11735	.35	.65	6.223	0.005
	Experimental group	.6300	.05099	.57	.69		

and histomorphometric analysis of bone architecture parameters, the utilization of autologous platelet-rich fibrin matrix in areas with bone defects offers advantages in terms of facilitating the organization of formative cells (osteoblasts), promoting neovascularization formation, and expediting the process of bone matrix apposition and mineralization.[22]

In comparison to the control, there was an increase in the number of trabecular bone, osteoblast, osteocyte, and blood vessels, as well as an increase in trabecular breadth. Because the differences were so significant, it could be explained that PRFM with stem cells can integrate as a fibrin network and facilitate cellular migration and differentiation, particularly osteoprogenitor cells and endothelial cells, which recorded a large number of blood vessels (neoangiogenesis).

More blood supplementation to the healing area accelerates and potentiates inflammation regulation by the presence of leukocytes and cytokines in the fibrin matrix and from blood and provides an environment for osteo differentiating and effects for their migration to the healing area, activating its biological role.[10]

Two weeks healing duration

The current study's histology findings showed that both the experimental and control groups developed new, irregular bone trabeculae, albeit at differing rates of bone deposition and remodeling. The newly formed bone trabeculae featured osteocyte-containing lacunae scattered throughout. In contrast, osteoblasts bordered the trabeculae's edges. Fibrovascular marrow was found between the newly formed trabeculae [Figure 5].

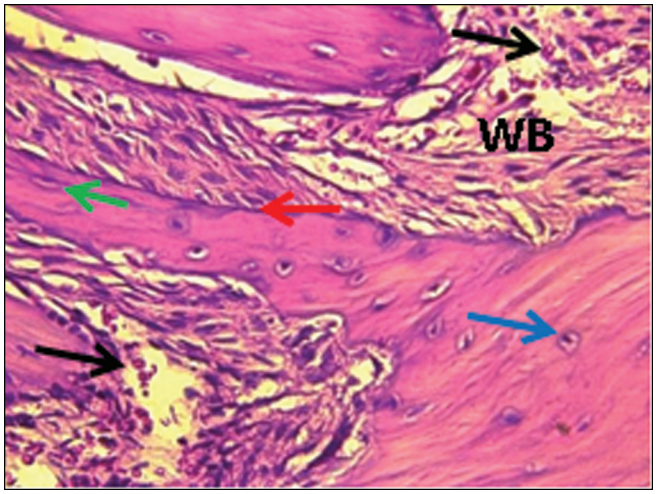

Figure 5: A view of 2 weeks of the PRFM group shows woven bone (WB), blood vessels (black arrow), stem cells (green arrow), osteocyte (blue arrow), and rimmed by osteoblast (red arrows) H&E ×40

Two weeks after starting treatment with the PRFM, microscopical investigation demonstrated a significant elevation in the number of osteoblasts in comparison to the control group [Figure 6]. This outcome is congruent

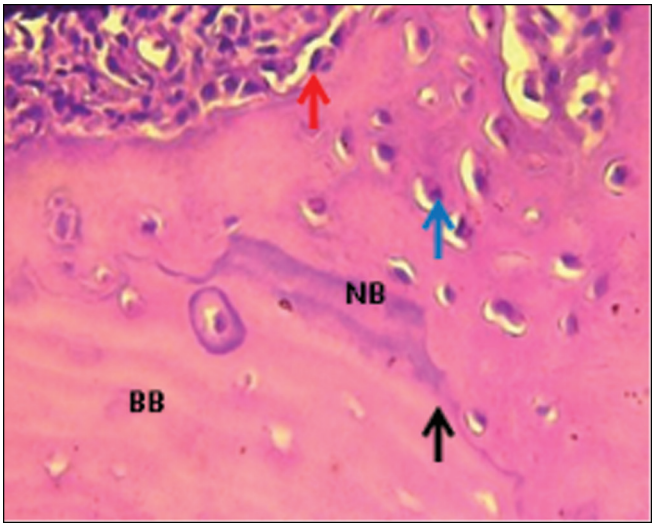

Figure 6: A view of 2 weeks of PRFM group shows basal bone (BB) coalesce with new bone (NB) matrix, reversal line (black arrow), osteocyte (blue arrow) and rimmed by osteoblast (red arrows) H&E ×40

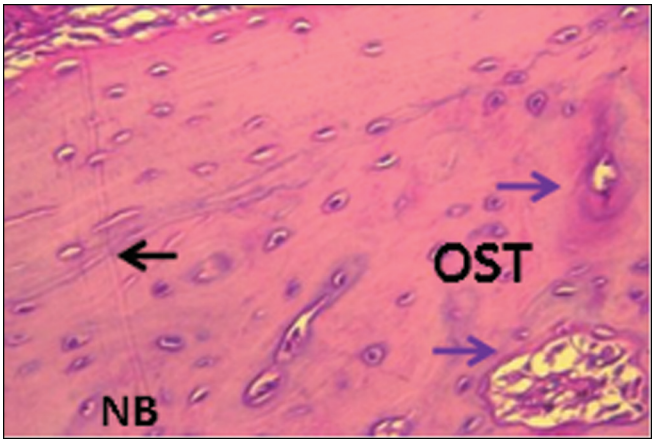

Figure 7: A view of the PRFM group after 4 weeks shows mature bone (NB) with osteon (OST) (purple arrows) and the remnant of reversal line (black arrow) separating basal bone (BB) from new bone (NB). H&E ×20

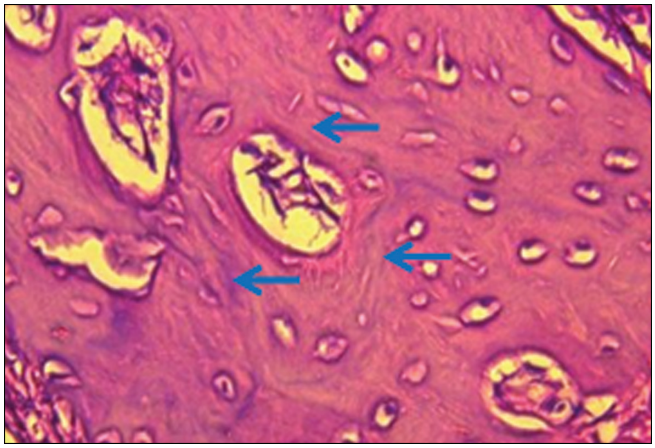

Figure 8: A view of the PRFM group after 4 weeks shows osteon (purple arrows), which is lined with regularly arranged osteocytes (blue arrow). H&E A view 40

with the findings of Salih *et al.*,[23] who discovered that applying PRFM to rabbit fracture regions improved osteoblastic proliferation and activity.

The current investigation discovered a significant rise in trabecular number and breadth, cortical width, and osteoclast number as the experimental area period progressed to bone trabeculae formation, apposition, maturation, and establishment to ideal thickness requirements for time. This outcome is congruent with the findings of Alhijazi and Mohammed,[24] who studied the effects of PRFM on bone rabbit healing in the dental socket after tooth extraction.

Four weeks healing duration

In this study, histological sections taken after 4 weeks of healing revealed an increase in trabecular area compared to 2 weeks of healing in all groups at varying rates. There were also denser bone trabeculae filled with osteocytes than in the preceding 2 weeks of recovery [Figure 7].

The microscopical findings of the PRFM group at 4 weeks postoperatively indicated an increase in bone trabecular area, an increase in bone mineral density, and a decrease in bone marrow area when compared to the control group [Figure 8].

This conclusion was similar to the findings of Nour and Aggour,[25] who found that defects filled with PRFM exhibited superior new bone formation compared to defects filled with L-PRF and empty defects. Additionally, both the PRFM and L-PRF groups demonstrated increased bone density compared to the control group after a 21-day evaluation period.

Microscopical findings of bone defects treated with, when compared to the control group, PRFM demonstrate an increase in trabecular area and a decrease in osteoblast mean value with an increase in osteocyte mean number 4 weeks postoperatively.

This finding is consistent with that of Serwa (2018), who investigated the effectiveness of PRFM treated with silver nanoparticles in promoting fracture healing in a rabbit model. The findings revealed that 4 weeks after the surgical procedure, there was a notable presence of thick trabecular bone lining by osteoblasts, which extended from both sides of the fracture site. This resulted in the filling of the gap cavity and the formation of haversian canals of different sizes, which were lined with a significant number of osteocytes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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