Successful Non-Surgical Endodontic Treatment of Large Periapical Lesions using Platelet-Rich Fibrin and Mineral Trioxide Aggregate: Clinical Trial with Cone Beam Computed Tomography Evaluation

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Abstract: ***Plasma-Rich Fibrin (PRF) is a novel regenerative approach in dentistry, particularly for the treatment of periapical lesions. This study evaluates the effectiveness of PRF combined with Mineral Trioxide Aggregate (MTA) in non-surgical endodontic treatment. A clinical trial was conducted involving 35 patients with diagnosed periapical lesions, monitored over six months using Cone Beam Computed Tomography (CBCT). The results showed a significant healing rate, with 60% of cases achieving complete lesion resolution. The study concludes that PRF, when combined with MTA, is an effective treatment for periapical bone lesions, highlighting the importance of CBCT follow-ups for long-term assessment***

Keywords: Platelet-Rich Fibrin, CBCT, Periapical Lesions, Endodontic Healing, Mineral Trioxide Aggregate

1. Introduction

Platelets support important cellular activities and play a crucial role in hemostasis (1). They contain alpha granules that house various proteins, cytokines, and growth factors. When activated at injury sites, platelets release these substances, which promote chemotaxis, cell proliferation and differentiation, angiogenesis (2,3). Activated platelets also contain serotonin and histamine, which increase capillary permeability and facilitate the movement of leukocytes into sites of inflammation (4).

Platelet products have been used in dental tissue regeneration for over two decades and have proven to be an effective scaffold for pulp regeneration (5). Platelet-rich fibrin (PRF), a second-generation platelet concentrate, is a natural autologous fibrin matrix that contains trapped platelets and leukocytes, resulting in the extended release of growth factors and cytokines (6). However, its solid-state design restricts its applicability (7). In 2014, injectable platelet-rich fibrin (I-PRF) was created as a liquid blood derivative with high concentration of platelets, leukocytes, and growth factors (8). I-PRF is a three-dimensional fibrin dynamic gel including platelets, leukocytes, type I collagen, osteocalcin, and growth factors that may modify inflammatory processes, inhibit bacteria and biofilms, and stimulate osteogenesis (9). Compared to PRF, I-PRF promotes bone regeneration, treats gingival recession problems, and eliminates endodontic infection (10,11).

Fibrinogen plays a crucial role in fibrin assembly, heparin binding, and cell-matrix interactions (12). Fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF) bind to fibrinogen, potentiating endothelial cell proliferation (13). Cytokines like interleukin (IL)-1, which participates in the inflammatory response, also bind to fibrinogen, and enhancing the stimulated activity of endothelial cells in the bound form (12,14).

Regenerative procedures involve using materials to heal and repair the pulp dentin complex after restoring diseased tooth tissue. They include pulp implantation, revascularization, and postnatal stem cell therapy Regenerative endodontics plays a crucial role in overcoming root canal treatment failure and post treatment complications by preventing aggressive invasive instrumentation and radiographic exposure (15).

PRF is used in bone grafts to promote bone growth and vascularization, leading to osteoblast proliferation and bone formation (16). Cytokines released by PRF play a significant role in blood vessel formation and immune system stimulation. PRF prepared by using low centrifugal forces has been found to have a high concentration of leukocytes and growth factors. When combined with biomaterials, PRF's revitalization power increases and is more suitable for defected tissue as in cleft alveolar ridge defects or orthodontic needs (17).

Apical periodontitis (AP) is a prevalent inflammatory lesion affecting the jaw, with 50% of the adult population having at least one tooth with AP (18). Treatment modalities of AP include non-surgical root canal treatment (RCT), periradicular surgery, or extraction of the tooth (19).

Furthermore, Various clinical approaches involving nonsurgical endodontic treatment have been developed, including antimicrobial agents like sodium hypochlorite, chlorhexidine, and calcium hydroxide to eliminate bacteria from the root canal, using chemical irrigation with sodium hypochlorite. However, a two-visit treatment may risk temporary filling leakage, potentially causing canal reinfection and impeded healing (20–23).

Additionally, these agents also face limitations, such as the development of bacterial resistance and flare-ups caused by bacteria forming biofilms within the root canal. Alternative therapies, such as regenerative endodontics, biological medications, antioxidants, probiotics, and specialized pro-resolving lipid mediators, have been recently tested to combat the immune-inflammatory response (24).

PRP gel has become a valuable adjunct in dental and oral surgery procedures, facilitating easier handling of graft material and promoting wound healing and bone maturation. AP is typically diagnosed and monitored after treatment using periapical radiograph. Recently Cone-beam computed tomography (CBCT) allows for the earlier identification and more precise assessment of AP Another benefit of CBCT is its capacity to accurately assess the complete scope of AP in regard to other anatomical structures, enabling the clinician to choose an appropriate treatment approach and providing a more dependable follow-up (25–27).

The aim of the present study is to evaluate the healing process of PRP and Mineral Trioxide Aggregate (MTA) in the non-surgical management of periapical lesions through a clinical trial, using CBCT over six months' period of time.

This study is significant as it explores a minimally invasive endodontic approach that could reduce the need for surgical interventions while improving treatment outcomes for periapical lesions.

Subjects and Method

A randomized clinical trial was undertaken in a dental clinic in Benghazi. Thirty-five otherwise healthy individuals were included in the study. They had a total of thirty-five permanent teeth that were diagnosed with preapical lesions.

The teeth were anaesthetized using local anesthesia containing epinephrine. Following isolation with the rubber dam, access cavity preparation and removal of decayed tissue was done. Irrigation using sodium hypochlorite (2.5% NaOCl) and normal saline was performed during instrumentation. After the bleeding has stopped, working length was determined followed by cleaning and shaping. Subsequently, the canal was dried with paper points and was filled with calcium hydroxide powder in combination with distilled water as a paste. During the subsequent appointment after 2 weeks, intracanal dressings were removed and irrigation was done with 5% NaOCl after that canal was dried with paper points. After 2 weeks, no evidence of exudate was noticed from the canal, and hence, the tooth was considered suitable for formation of an artificial plug. A PRF membrane was inserted in the apical 1-2 mm space of the canal which formed a primary stoppage.

To prepare PRF, 10mL of intravenous blood was drawn from the antecubital vein and was collected in a 10 mL sterile tube without anticoagulant which was centrifuged immediately at 3000 rotations per minute for 10 min. This allowed formation of the fibrin clot in the middle of the tube between the red blood cells and acellular plasma layer (Figure. 1). This was followed by the placement of MTA mixed in the ratio of 1:3 and condensed in small increments in the canal using a hand plugger gently until a barrier thickness of 4-5 mm was established, where the MTA acted as the secondary apical barrier

The teeth were restored with composite and teeth were followed up with periapical radiograph and CBCT. The patients were recalled for clinical and radiological assessment and subsequent follow up every 3 months over a span of 6 months. Preoperative and 6-month postoperative CBCT imaging was conducted.The radiolucency evaluation of the periapical area was based on the CBCT-Periapical Index (CBCT-PAI)) developed by Estrela C. et al(28).

The statistical analyses were conducted using IBM SPSS Statistics for Windows version 26 (IBM Corp, New York, USA) .

Compliance with ethical standards

There was no use of identifying information for the included patients. Written or verbal consent was sought from patients during procedures. The study adhered to the ethical standards set by the research ethics committee in Benghazi, Libya.

Figure 1: Collection of the i-PRP after centrifugation (800 rpm, 3 min)

Case 1: 19 years old male Libyan patient (Figure.1).

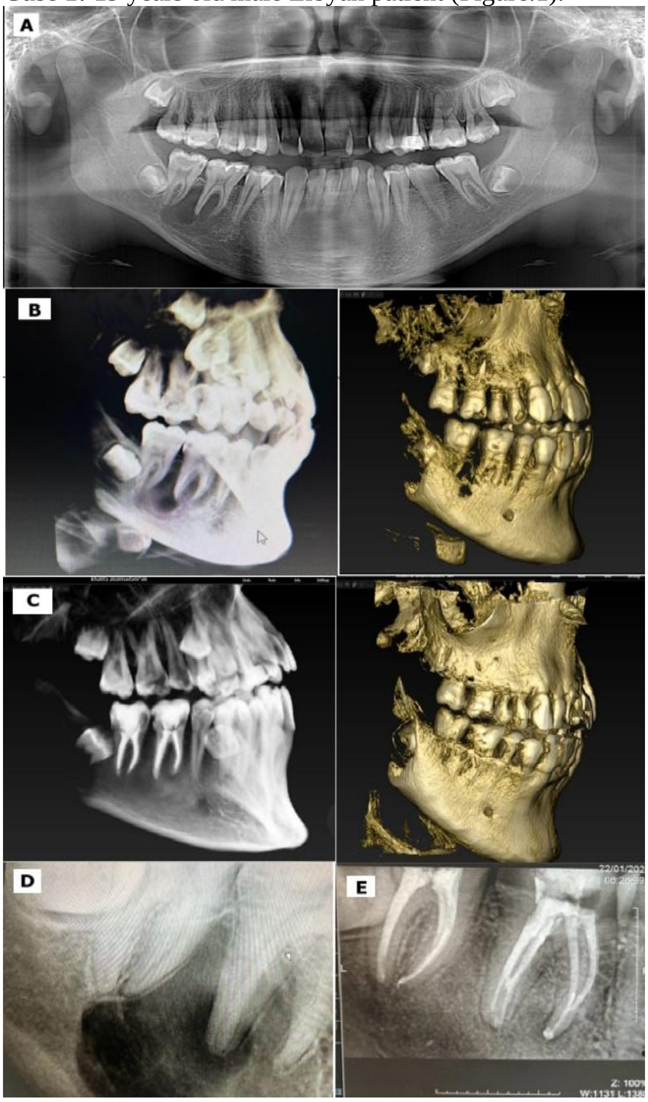
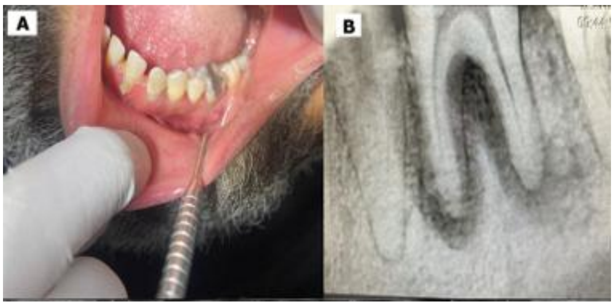


Figure 2: (A) Preoperative OPG shows big radiolucency related to roots of right lower molar. **(B)** Preoperative CBCT image show the bone defect related to the offending tooth. **(C)** Postoperative CBCT shows complete healing of the bony defect at 6-month follow-up. **(D)** Intraoral radiogaphe shows the bony defect related to the distal root. **(E)** Postoperative intraoral radiograph shows complete healing of the bony defect at 6-month follow-up**.**

Case II: 33 Old Libyan male patient (Figure. 2)



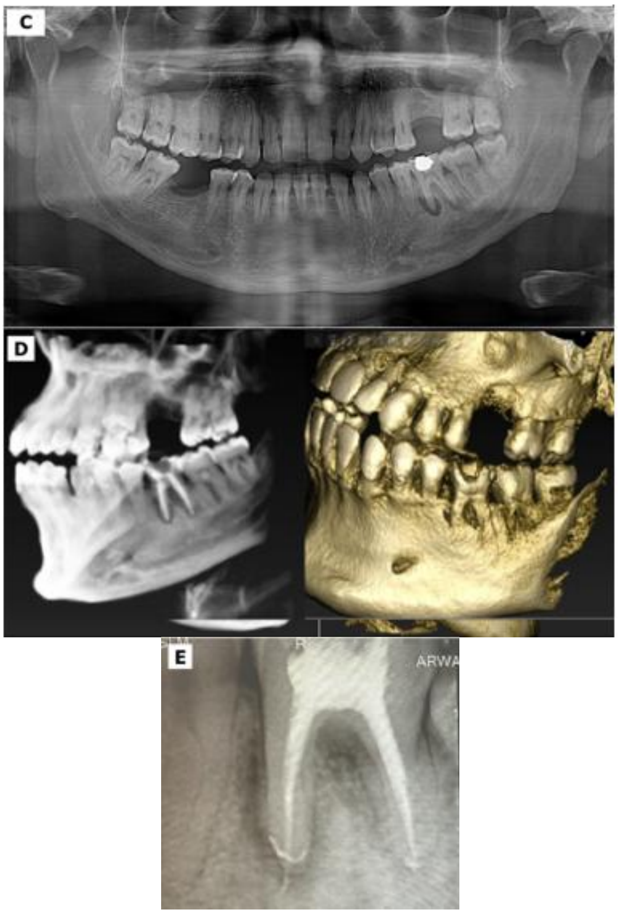


Figure 3: (A) clinical view of the dentoalveoalr abscess with two sinuses in the left mandibular region**. (B)** Intraoral radiograph shows the sinuses relate to roots of first molar. **(C)** preoperative OPG shows big radiolucency related to roots of left lower molar. **(D)** Postoperative CBCT shows considerable healing of the bony defect at 6-month follow-up. **(E)** Intraoral radiograph shows the roots with apical seal and healed periapical tissues at 6-month follow-up.

Case III: 33 Old Libyan male patient (Figure. 4).

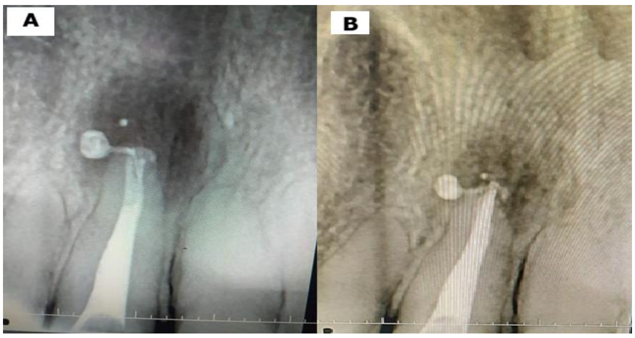


Figure 4: (A) Intraoral radiograph shows root canal treated upper right incisor immmediatly after injection of i-PRP. **(B)** Another radiogrph shows gross diminsion of the bony defect at 3 months folow-up.

Case IV: 37 Old Libyan male patient (Figure. 5)

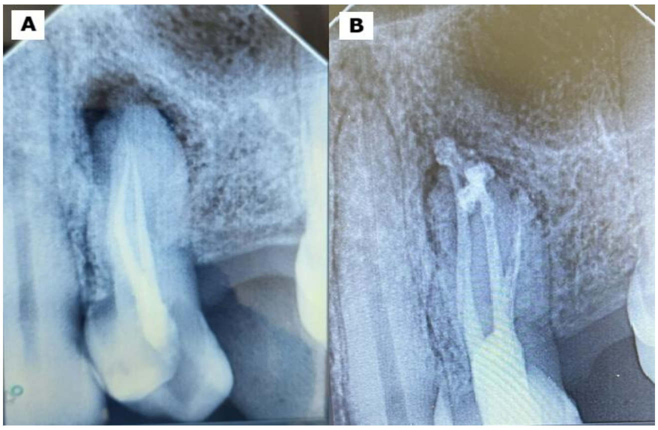


Figure 5: Preoperative intraoral radiograph showing Upper left premolar **(A)** endodontic treatment failure , **(B)** following an MTA PRF injection.

Case V: 33 Old Libyan male patient (Figure. 6)

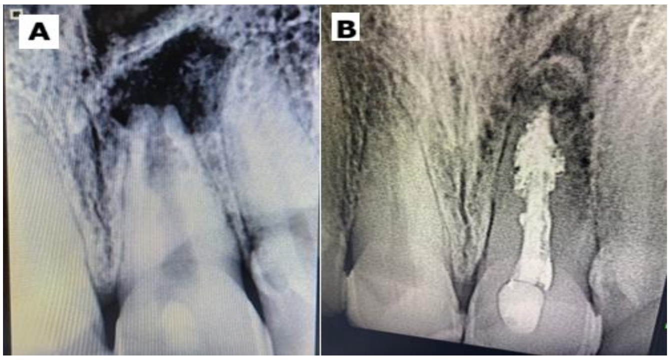


Figure 6: (A) Intraoral radiograph shows root canal treated upper left incisor immmediatly after injection of i-PRP. **(B)** Another radiogrph shows gross diminsion of the bony defect at 3 months folow-up.

2. Results

A total of 35 individuals participated in the study The majority were female (62.9%). In contrast, males accounted for 37.1% of the sample. The average age of the participants was 38.88 years, with the age range spanning from 16 to 70 years old (Table 1). Maxillary teeth included 7 incisors, 2 canines, and 6 premolars. while mandibular teeth comprised of 3 incisors, 2 canines, 1 premolar, and 14 molar of molars.

Table 1: Base line characteristics of the study sample.

Character		N (%)
Sex		13male (37.1%) 22female (62.9%)
Age average (range)		38.88 (16-70)
Tooth		
Maxillary	Incisor	7 (20%)
	Canine	2 (5.7%)
	Premolar	6 (17.1%)
	Molar	-
Mandibular	Incisor	3 (8.6%)
	Canine	2 (5.7%)
	Premolar	1 (2.9%)
	Molar	14(40%)

As illustrated in Table 2, the results of the CBCT-PAI healing assessment showed a significant improvement in the periapical bone structures over the course of six months. At baseline, the periapical bone structures were undisturbed, but after six months, 60% of cases demonstrated complete healing. The diameter of periapical radiolucency also decreased over time, with no cases of radiolucency greater than 1-2 mm at the six-month follow-up visit compared to baseline.

Table 2: Results of CBCT-PAI healing assessment.

Healing Assessment	Base line	3 months follow up	6 months follow up
Undisturbed periapical bone structures	0	0	21 (60%)
Diameter of periapical radiolucency > 0.5–1 mm	0	8 (22.9%)	13 (37.1%)
Diameter of periapical radiolucency > 1–2 mm	0	18 (51.4%)	0
Diameter of periapical radiolucency > 2–4 mm	13(37.1%)	6 (17.1%)	0
Diameter of periapical radiolucency > 4–8 mm	5(14.3%)	2 (5.7%)	0
Diameter of periapical radiolucency > 8 mm	17(48.6%)	0	0

Complete healing was observed in lower incisors, premolars, and upper canines (100%). Although the lower canines showed high improvement in the size of the lesion (Diameter of periapical radiolucency > 0.5–1 mm), a complete recovery was not achieved (**Figure 1**).

66.7% of the upper incisors and premolars, as well as 50% of the lower molars, had a complete healing. However, a total of 33.3% of the upper incisors and premolars, together with 50% of the lower molars, exhibited a dimensioned lesion size to 0.5–1 mm.

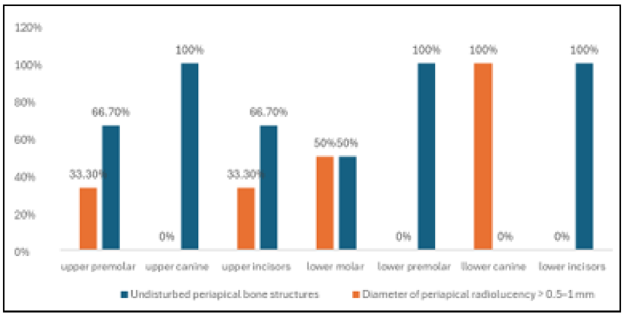


Figure 7: Chart showing the various Healing rate according to tooth type.

3. Discussion

The regeneration capacity of platelets has been discussed thoroughly in the literature. Platelets produce growth factors that get stuck inside the fibrin matrix after being activated. These substances are known to stimulate mitogenic response in the periosteum and play a crucial role in bone regeneration throughout the process of normal wound healing. The enhanced comprehension of the physiological characteristics of platelets in the process of wound healing has resulted in their increased use for therapeutic purposes. However, there are still concerns over the protocols used in the manufacturing of autologous fibrin adhesives (R). In addition, there have been legislative limitations on the manipulation of concentrated platelet rich plasma. To address these issues, there was a consideration to create a new group of platelet concentrates, known as platelet rich fibrin (PRF) (35–38).

Consequently, further exploration of the field led to replacement of the fibrin glue with platelet concentrates, which was first described by Whitman et al. (29). Consequently, PRF as a tool for tissue regeneration in medicine was introduced in 2001 (30). The concept was extrapolated from the first-generation platelet concentrate, i.e., platelet-rich plasma (PRP). Its efficacy in various medical fields was astounding despite the setback of inhibiting the coagulation cascade because of adding an anticoagulant to the preparation (31,32)

PRF has several uses in regenerative endodontics, the process of revascularization included intentionally introducing a blood clot into the root canal space, which considered a significant success in clinical practice (45,55). As a result, platelet concentrates were used as a scaffold made from the patient's own cells to support the process of revascularization (34). Bains et al. used this agent for repairing iatrogenic perforation of the pulpal floor of the mandibular molar when combined with MTA (35). PRF is an excellent option for restoring blood flow to immature permanent teeth with necrotic pulps by providing a high concentration of substances that promote the development of cells and their specialization. It serves as a framework for the development of tissues (36). Moreover, the controlled release of growth factors throughout the resorption of the fibrin matrix guarantees a consistent healing process (37). Shivashankar et al. reported that the application of PRF on a tooth with pulpal necrosis and open apex resulted in gradual thickening of dentinal walls, lengthening of the root, regression in the periapical lesion, and closure of the apex (38).

Consistently, Rudagi and Rugadi reported effective healing and apexification using a combination of MTA as an apical barrier and autologous PRF membrane as an interior matrix (39).

Researches have shown that performing pulpotomy in young permanent teeth using PRF has had positive outcomes (40). PRF stimulated the growth of dental pulp cells, increased the activity of alkaline phosphatase, and upregulated the expression of osteoprotegerin according to the duration of exposure (41). The use of a combination of PRF and a biomaterial (β-TCP) presents a superior therapeutic option for faster healing. It has been documented that more consistent and expected regrowth of bone tissue, as shown by radiographic and clinical analysis (64, 65).

Cases of traumatic immature teeth with necrotic pulp usually treated with calcium hydroxide, which stimulate the formation of a calcific barrier. However, this treatment also weakened the organic support of the dentin in the root, making it more susceptible to fracture. PRF is the most effective option for preventing fractures and maintaining the vitality and strength of teeth (36).

According to our findings, the CBCT-PAI healing assessment showed a significant improvement over the six-month period. The majority of patients had undisturbed periapical bone structures at the six-month follow-up (60%). Additionally, there was a noticeable decrease in the diameter of periapical radiolucency overtime in most of the recruited cases.

Periapical lesions undergo healing in a sequential manner, starting from the outer edges and gradually reducing in size as fresh bone is formed in the vicinity of the affected area to substitute any bone that was injured by the infection (19,43,44). The process of new bone deposition can be observed on subsequent radiographs as the periapical lesion gradually diminishes in size and ultimately vanishes completely (45).

Consistent with our study, healing of the lesions should be assessed between 6 and 12 months after root canal treatment (46,47). Our finding was highlighted by the previous literature, in study of Orstavik, half of cases experienced complete healing at the 6-month visit, and after 12 months, 88% of the cases were completely healed (47).

In another study, the teeth treated by PRP showed at the end of 12^{th} month resolution of signs and symptoms pain, swelling, fistulas, and sensitivity to percussion, and 93% of teeth in the PRP group showed various degrees of increased root length or apical closure (48).

According to our findings, the success rate of RPR root canal treatments was significantly higher in teeth with single canal compared to those with multiple canals. This suggests that the complexity of the root canal system may play a role in the overall success of the treatment.

Jayalakshmi et al. used PRF in combination with beta tricalcium phosphate (β-TCP) bone graft for treating periapical cysts, achieving progressive, significant, and predictable clinical and radiographic bone regeneration (49). Simonpieri et al (50). reviewed advantages of the use of PRF as it acts as a stabilizing sheath and offers mechanical sustenance.

In regard to regenerative endodontic procedures with PRF, it is assumed that some amounts of human dental pulp cells present in the apical papilla usually remain vital even in case of a large periapical lesion. After the regression of the inflammation and under the influence of epithelial root sheath of Hartwig, these cells differentiate into odontoblasts like cells. osteoprotegerin and Alkaline phosphatase expression are generally regarded as markers of odontoblastic differentiation. The only disadvantage associated with PRF is its manipulation to place inside the canal. Clinical trials are crucial to equate the effect of PRF in the revitalization of tooth with necrotic pulp and open apex on a long term basis (51).

Hiremath et al. reported affirmative results with pulpotomy using PRF, but suggested that long-term trials with larger sample sizes are required to justify the use of PRF for pulpitis treatment. Overall, PRF satisfies many criteria as an ideal physical scaffold for pulpal regeneration and tooth revitalization (40).

Our study concludes that PRP is an effective method for treating periapical bone lesions. The findings underscore the importance of regular follow-up using CBCT to confirm complete recovery. Further research is recommended to investigate factors that may influence healing rates across different tooth types and to refine treatment strategies for improved outcomes.

4. Conclusion

This study highlights the effectiveness of Platelet-Rich Fibrin (PRF) combined with Mineral Trioxide Aggregate (MTA) in the non-surgical treatment of periapical lesions. The six-month CBCT follow-up demonstrated significant healing, emphasizing the role of regenerative endodontic therapies in clinical practice. Future research should focus on long-term outcomes and potential applications of PRF in broader endodontic treatments.

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