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Impact of Platelet Rich Fibrin Application on Healing of Periapical Bony Defects After Endodontic Peri-radicular Microsurgery: A One-Year Clinical study

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ABSTRACT

Purpose: This clinical study was performed to evaluate the clinical effect of Platelet Rich Fibrin (PRF) application on healing process of periapical bony defects after endodontic peri-radicular microsurgery. **Material and methods:** Twenty-eight teeth in 25 patients were included in this study. They were divided into 2 equal groups, each including fourteen teeth. After retrograde filling was completed, the bony crypt was grafted with Platelet Rich Fibrin in the study group (Group A, n=14) and no graft in the control group (Group B, n=14). Patients were recalled at 12 months postoperatively for examination. **Results:** After one year of clinical and radiographic follow up, Group A showed higher success rate (81.8%), While Group B showed the lower success rate (45.4%). Significant difference in results was found between the two groups ($P < 0.05$). **Conclusions:** Within the limitation of this study, application of PRF in bony crypt after endodontic peri-radicular microsurgery showed higher long-term success rate and hence it may be considered as an adjunct autologous material to endodontic peri-radicular microsurgery.

KEYWORDS

Keywords: Platelet Rich Fibrin, Endodontic microsurgery, Healing.

INTRODUCTION

Peri-radicular Surgery (also termed endodontic surgery, (peri) apical surgery, apicectomy, surgical re-treatment) is a procedure that any endodontist should be able to perform as the last option to save a tooth before extraction. Healing following this surgery is a very complex process that involves a consecutive series of reactions including clotting, inflammation, granulation tissue formation, collagen synthesis and tissue remodeling. However, many scientists are interested especially in the factors that delay or hinder it [1,2]. Tissue regeneration

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guided by using different bone grafting materials and/or membrane barriers following peri-radicular tissue destruction by pathological processes, has an important bearing on the success of endodontic peri-radicular microsurgery [3].

Guided tissue regeneration (GTR) is an updated technique(s) aimed to enhance and direct cell growth for regeneration of specific periodontium tissues that have been damaged by either periodontal or pulpal diseases [4]. In endodontic surgery GTR principles have been applied to reestablish damaged bone and periodontal tissues by placing various bone filling biomaterials and/or different barrier membranes. The GTR concept was firstly based on excluding faster epithelial cells (ten times) from migration to the wound site as long as possible so that other cell types with regenerative potential (as osteoblasts), become settled, established and achieve regeneration that can be accomplished by introducing various barrier membranes and/or bone grafts [5,6].

The purpose of a "space making technique" application in endodontic peri-radicular microsurgery is similar to those in periodontology and implantology: (A) creating favorable environment (stable and protected wound) for enhancing tissue regeneration; and (B) exclude non-desired fast-proliferating cells that hinders desired tissue regeneration [7].

Nowadays, using of platelet concentrates has been suggested as an adjunct for promoting bone and epithelial tissues regeneration in dental surgical procedures [7-13]. Many in-vitro studies, proposed that platelet concentrates may have a great positive effect in triggering bone and soft tissue regeneration, and decrease inflammatory response, postoperative pain and undesired side effects [8-13]. The clinical impact of platelet-rich fibrin in oral surgery is uncertain as mentioned in various clinical applications. This was reported by some updated systematic reviews and meta-analysis emphasizing the clinical effect of using platelet concentrates in oral surgical procedures [14-23].

Thereby, it may be of great value to evaluate the clinical effect of Platelet Rich Fibrin (PRF) application on the healing process of periapical bony defects after endodontic peri-radicular microsurgery.

MATERIAL AND METHODS

The clinical design and protocol of this study was conducted according to the principles embodied in World Medical Association Helsinki Declaration of 1975 for biomedical research involving human subjects, as revised in 2000 (World Medical Association Declaration of Helsinki 2000). Ethical approval was obtained from the Institutional Review Board of our institution number, (A27100221). All patients underwent endodontic treatment in Endodontic Department and in a private practice clinic. All patients were informed of the nature of the study and signed a written consent. Patients undergoing endodontic peri-radicular surgical treatment were recalled within one year for follow up and clinical examination.

Patient selection:

Case selection was done according to the following inclusion criteria[24]: Patients classified according to the American Society of Anesthesiologists into ASA-I or ASA-II (free from systemic contraindications for dental surgical procedures). Patients suffering from one or more teeth with a periapical lesion of definite endodontic origin (chronic apical periodontitis). Patients with bony defects of 5-15 mm diameter, as determined from periapical radiographs. Recorded cases of previous orthograde re-treatment failure or inapplicable orthograde re-treatment (such as obstructed canal proven not to be removable, too great damage risk if orthograde re-treatment will be done, and cases with extruded obturating material over a long period of time). Teeth with proper permanent restorations and at least 6 mm of their apical root canal systems were free from a post. Absence of spontaneous swelling, pain and sinus tract. Both anterior and posterior teeth were included in our study. The exclusion criteria of this study included: Patients with

neuropsychiatric disorders, presence of any pathosis accompanied with vertical fracture of the root; perforation in the lateral canal walls or in the bifurcation area; history of dental trauma; probing depth was more than 5 mm detected with a periodontal probe (moderate to severe periodontal bone loss).

Allocation to Groups

25 patients with 28 treated teeth were included in the current study. The choice of using Platelet Rich Fibrin for each patient was done randomly by the aid of a computer-generated randomized table. Before the beginning of each surgical operation, a closed opaque envelope containing the indication of group allocation was opened. The 28 treated teeth in 25 patients were divided into 2 groups (n=14) according to the type of bone graft material as the following:

Group A: The bony crypt was filled with Platelet Rich Fibrin.

Group B: The bony crypt received no bone graft material to serve as control group.

Surgical Procedure [25]

For each patient, two to three sessions of oral hygiene instructions with scaling and root planning were performed, if necessary, to reduce gingival inflammation and minimize any primary periodontal disease. Antiseptic mouth wash rinse containing 0.2% chlorhexidine digluconate was used preoperatively to decrease the risk of surgical field contamination. Preoperative radiographs and photos were taken for the teeth or tooth to be treated. Local anesthesia with articaine 2% and epinephrine 1:100,000 was administered. In 6 very anxious patients, sedation was arranged by using intra-venous midazolam (0.02-0.03 mg/kg) in conjunction with local anesthesia.

Using a microsurgical blade mounted on a rounded handle allowing a pen-like grip, a full mucoperiosteal tissue flap design was performed with a horizontal papillary-based incision, involving 4–5 papillae, and a vertical releasing incision placed on tooth distal to the tooth being treated. The flap was reflected using Molt periosteal elevator by the undermining elevation technique, with careful retraction by maintaining the Minnesota retractor on cortical bone throughout the procedure. Frequent irrigation of the flap with sterile saline to decrease the risk of periosteal dehydration. Erosion of the cortical bone was usually observed in most moderate to large lesions based on typical peri-radicular lesions, which are distinguished by their location, extension, or pathway of infection [26].

A zumax OMS 2350 surgical microscope (with magnification ranges between 2.8 and 25.6) or magnification loupes (Zeiss EyeMag Pro S 4.5X) and a headlight were used for hard tissue management (according to availability). When necessary, a low-speed round bur was used to gain accessibility to the root apex through cortical bone. The size of the osseous window depended on the size of the lesion and the proximity of the window to normal anatomic structures (such as roots and neurovascular bundles). The peri-radicular lesion was completely enucleated with sharp bone micro-curettes. The concave surface of the curette was always kept in contact with the osseous surfaces of the bone cavity. The removed pathologic tissue was inserted in formalin solution of 10% concentration for pathological diagnosis. The bony cavity was carefully inspected after irrigation with sterile saline and any residual fragments of soft tissue within the cavity were removed with micro-curettes. A micro-explorer was used for sounding the cortical plate in advance of surgery and probing the root-end.

Following the root end exposure, a handpiece with a straight fissure bur was placed perpendicular to the long axis of the root cutting 3 mm of its end, starting from the apex and proceeding in a coronal direction. The root end surface was smoothed and flattened by moving the bur from mesial to distal at a small bevel angle (less than 10 degrees) or with almost no bevel. In some cases where there is a proximity to nerve or sinus, it is strongly recommended to start cutting of the root end 3 mm short of the apex.

For obtaining local hemostasis before root-end preparation, one more anesthetic carpule was injected inside the bony crypt followed by using two or three gauze pledgets soaked in local anesthetic agent containing vasoconstrictor, applied under pressure and fixed with finger pressure for two minutes. Afterwards remove one or two of the superficial gauze pledgets leaving the last pledget in position without disturbing until after retrograde filling. This was usually enough for finishing of the procedure.

Root-end cavity preparation was done by using of a zirconium nitrate retro-tip (Dentsply Maillefer Instruments, Ballaigues, Switzerland) driven by an ultrasonic device unit (Piezon Master 400; EMS, Nyon, Switzerland) under copious irrigation of sterile water to preclude overheating. The 3-mm long retro-tips offered well-defined parallel preparation of 3 mm depth (Fig 2). In case there was a post inside the canal, the retrograde preparation was never extended to the apical end of the post. Using a paper cone, the retrograde cavity was dried, then filled with mineral trioxide aggregate (ProRoot MTA; Dentsply Maillefer) using MAP System (Micro-Apical Placement System). Micro-pluggers were used for compacting retro-filling material. Excess filling material was removed by a fine diamond bur. Throughout the procedure, a micro-mirror was used for retro-preparation and filling.

Preparation and Application of Platelet Rich Fibrin

Before the administration of local anesthesia, 20 ml of peripheral blood was drawn and collected in 5-mL glass laboratory tubes (plain vacuum tube A-PRF™; Process for PRF, Nice, France). Some cases with more than two teeth required more blood withdrawal, according to the lesion size. An A-PRF™ DUO centrifuge (Process for PRF™, Nice, France) was used for 8 min at 1300 rpm (208g) centrifuge speed. Special tweezers and scissors were used to extract the obtained fibrin clots from the tubes, precluding the red blood component below the buffy coat. Then the fibrin clot was placed in a sterile container (PRFBOX, Process for PRF™, Nice, France) with controlled pressure for standardizing the membrane thickness and retrieving the plasma exudate that is rich in fibrinogen and adhesive proteins. This protocol guaranteed asepsis of the fibrin membranes throughout the surgery [27]. (Fig 1)

In cases related to group A, the defect was filled with PRF. While in cases of group B, only modern endodontic microsurgery without bone graft was performed.

Reflected tissues were re-approximated, compressed and stabilized, then sutured with 5-0 non-absorbable silk (Ethicon Inc, Johnson & Johnson, Piscataway, NJ). Root-end filling was performed with an endoscope for adequate visual access to all the phases of root-end management directly on a monitor.

Postoperative Instructions

After the surgery, the patients received both verbal and written routine instructions. They were instructed to avoid mouth wash, hot drinks, hard and hot food, heavy physical work, and tooth brushing in the surgery day. After surgery, ice packs were supplied (10–20 minutes every one hour). Mouth rinse with chlorhexidine digluconate 0.2% (Curasept) twice daily was prescribed for plaque control up to 10 days after surgery. For both pain relief and control of inflammation, ketoprofen was prescribed as a nonsteroidal anti-inflammatory drug after the surgical procedure. Antibiotics were not prescribed. Patients were recalled for monitoring post-surgical healing and sutures removal 5 days after the surgery. For each case, the clinical and radiographic findings were recorded at 12 months recall period.

Criteria for healing assessment

The patients were followed up for one year. Clinical examination and periapical radiographs were routinely done at 12 months post-operative recalls visits for healing monitoring and evaluation. A preoperative periapical radiograph for each case was taken before surgery. Another periapical

radiograph was taken at each scheduled clinical visit up to one year. All periapical radiographs were taken using film holders by the paralleling technique for reproducibility. In one case only, panoramic radiograph was taken since the periapical radiograph was not applicable for proper visualization of a large lesion in mandibular anterior area. Healing was evaluated by radiographs taken at 12 months post-surgery. All periapical radiographs at 12 months postoperatively were scored according to the following classification: [28,29]

1. **Complete healing:** Full regeneration of bone, the width of periapical periodontal ligament is normal or with slight increase (not wider than twice the periodontal ligament space on the lateral aspect of the tooth). The peri-radicular rarefaction should be eliminated with normal osseous pattern and lamina dura. No evidence of root resorption. The treated area should be comparable to an area of the tooth with normal lamina dura.
2. **Incomplete healing**: Periapical radiolucency is reduced, with signs of bone healing at the periphery of the defect. Formation of scar tissue (fibrous connective tissue produced by the body as a reparative response) is characteristic feature of this type of healing. Sometimes exploratory surgical flap may be needed to confirm scar tissue formation.

Clinical success	The tooth must be functional. Absence of signs and symptoms related to the tooth. Not tender to palpation and percussion and normal mobility. No signs of a sinus tract or periodontal pocket. No evidence of infection or swelling. No complaint of any discomfort.
Clinically questionable status	Vague symptoms, may include: mild discomfort or a feeling of pressure and fullness around the treated tooth.
Clinical failure	Presence of a sinus tract or swelling. Discomfort to palpation and percussion. There may be persistent subjective symptoms which may not allow the tooth to function adequately or root fracture.

3. **Uncertain healing:** Periapical radiolucency is reduced with one or more of the following signs: the radiolucency width was more than twice that of the periodontal space and was surrounded by a structure such as hard lamina, it had a circular or semi-circular periphery, or was present symmetrically 'cone-like' around the apex as an extension of the periodontal space.
4. **Unsatisfactory:** showed either no changes, or an increase in periapical radiolucency.

Any evidence of signs and/or symptoms was recorded (subjective discomfort, loss of function, mobility, tenderness to percussion or palpation, periodontal pocket formation or sinus tract formation, postoperative complications), in accordance with the following guidelines [27]:

Cases were grouped according to the clinical assessment and radiographic presentations 12 months post-surgery, as follows:

		Clinical assessment	Radiographic classification
1. Successful		Absence of signs/ symptoms (clinical success).	Complete healing
2. Doubtful	**D1**	Clinical success	Incomplete healing
	D2	Presence of clinical signs/symptoms (clinically questionable)	Incomplete healing
	D3	Clinical success.	Uncertain healing
	D4	Presence of clinical signs/symptoms (clinically questionable)	Uncertain healing
	D5	Presence of clinical signs/symptoms (clinically questionable)	Complete healing
3. Failure		Presence clinical signs/ symptoms (clinical failure)	Unsatisfactory healing.

Statistical Analysis

Differences between the two groups were statistically assessed by Fisher's exact test. The tooth was regarded as the unit of analysis. A probability of P = .05 indicates the level of significance.

RESULTS

25 patients with 28 treated teeth from 2015-2017 were included in this study. This study included 13 females (16 teeth) and 12 males (12 teeth) with an age range of 20–64 years (mean, 52 years). All patients attended at the scheduled follow-up visits and could be evaluated for up to one year. Among the teeth evaluated at one year, 15 were located in the maxilla (5 incisors, 4 canines, 2 premolars, 4 molar) and 13 in the mandible (5 incisors, 2 canines, 2 premolars, 4 molar) as shown in Table 1

At one-year follow-up, 17 teeth showed successful healing (60.7%), eight exhibited doubtful healing (28.5%), and three were classified as failures (10.7%), as showed in Table 2. Of the 17 teeth that were classified in successful group: three maxillary incisors and three mandibular incisors; three maxillary canines and one mandibular canine; one maxillary premolar and one mandibular premolar; and three maxillary molars & two mandibular molars. Of the eight teeth that were classified in the doubtful healing group: D1, one mandibular incisor and one maxillary molar; D2, one maxillary premolar; D3, one maxillary canine and one mandibular premolar; D4, one mandibular canine and two mandibular molars. Further follow-up visits for 3 years later were scheduled for cases classified as doubtful healing. Of the three teeth that were classified in the failure healing group: there were two maxillary incisors and one mandibular incisor as reported in Table 1.

Of the 14 teeth enrolled for Group A: 12 teeth showed successful healing (4 teeth of the same patient were found in mandibular incisor region with a large lesion involving incisor teeth) with an overall success rate of 85.7%; and two showed doubtful healing and no failure outcome was found. Of the 14 teeth enrolled for Group B: five teeth showed successful healing with an overall success rate of 35.7%; six showed doubtful healing; and three showed failure as reported in Table 2.

Investigators found there is a significant difference between test Group A (85.7% success) and control Group B (35.7% success). Representative periapical radiographs of successful healing outcome for Group A (Fig 3, 4).

Table (1) *Distribution of treated teeth (1 year)*

		Success	Doubtful	Failure	Total, n (%)
Maxilla	Incisors	3	0	2	5 (17.8)
	Canines	3	1	0	4 (14.2)
	Premolars	1	1	0	2 (7.1)
	Molars	3	1	0	4 (14.2)
	Subtotal Maxilla, n (%)	10 (35.6)	3 (10.7)	2 (7.1)	15 (53.5)
Mandible	Incisors	3	1	1	5 (17.8)
	Canines	1	1	0	2 (7.1)
	Premolars	1	1	0	2 (7.1)
	Molars	2	2	0	4 (14.2)
	Subtotal Mandible, n (%)	7 (24.9)	5 (17.8)	1 (3.5)	13 (46.4)
Total, n (%)		17 (60.7)	8(28.5)	3 (10.7)	28 (100)

Table (2) *Summary of outcomes according to treatment groups*.

Treatment Group	Successful	Doubtful	Failure	Total	Success %
Group A	12	2	0	14	85.7
Group B	5	6	3	14	35.7
Total	17	8	3	28	60.7

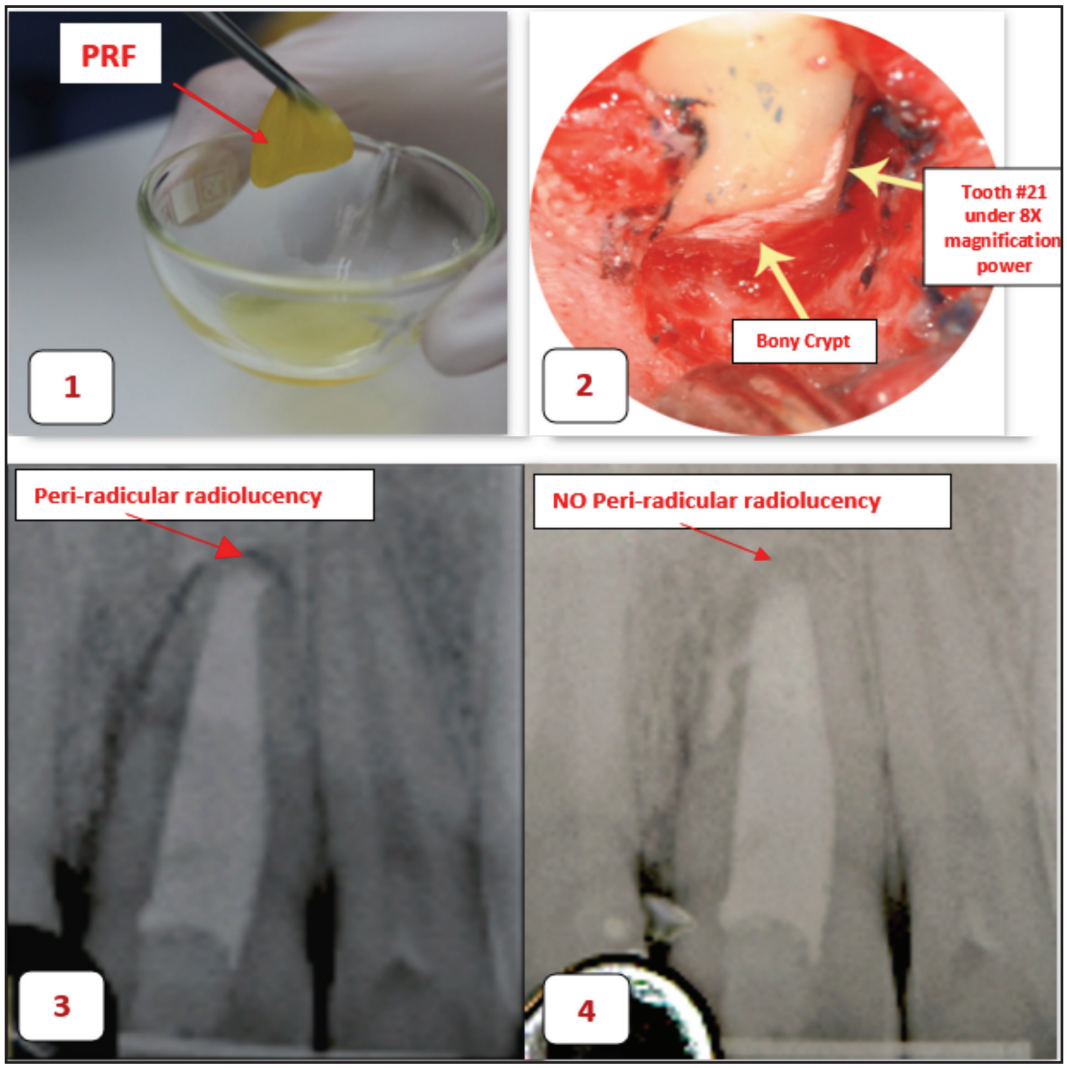

Figure (1): PRF preparation (Group A).
Figure (2): Retro-cavity preparation and filling of the bony defect.
Figure (3): Pre-operative preapical x-ray (Group A).
Figure (4): 12-months post-operative periapical x-ray (Group A).

DISCUSSION

Platelet-rich fibrin (PRF) is the second generation of platelet concentrates [31]. The first generation of platelet concentrates requires the addition of biochemical blood handling, while PRF preparation is simple, time-saving and inexpensive [10].

PRF is a complicated fibrin scaffold with entrapped white blood cells, platelets, glycanic chains, and structural glycoproteins [16]. This network further serves as a reservoir for slow and gradual of various growth factors which could be continuously released for 10 to 14 days [32]. These components play an important role in healing by promoting angiogenesis, cell proliferation and differentiation, which leads to subsequent new bone and tissue regeneration [32]. The vascular endothelial growth factor (VEGF) can control growth, migration and differentiation of epithelial cells and so it is the most powerful agent for angiogenesis [7].

The molecular fibrin network is the most characteristic feature of PRF as it forms a uniform three-dimensional structure with long-term effect on tissue regeneration by slow delivering of cytokines [7, 30]. Cytokines within the PRF have both pro- (IL-1b, IL-6, TNF-a) and anti-inflammatory (IL-4) action, which are superior to plasma concentrates. Both interrupting the inflammation process and promoting angiogenesis explain cytokines role in promotion of healing [30]. In addition, the platelet-derived growth factor (PDGF), one of the main angiogenesis soluble factors, binds to fibrin with high affinity [33, 34].

Our results agreed with a clinical study that reported promising results in stimulating bone regeneration after 2 and 3 months around periapical surgical defects and in reducing postoperative pain after PRF application in endodontic periradicular microsurgery [33]. This also comes in accordance with another study that reported faster bone healing after endodontic periradicular microsurgery when the bony crypts were filled with platelet rich plasma (PRP) and Hydroxyapatite compared to control group without bone grafts [34].

However, our results disagreed with another clinical study that reported that the PRF application to the surgical cavity may not necessarily improve outcomes and showed no significant benefit regarding to bone healing when periapical surgery was done on perio-endo lesion with apico-marginal defects [35]. This result may be due to periodontal communication that allow bacterial ingress from the marginal periodontium unlike our present study that evaluate healing effect after PRF application in pure endodontic lesions. Other disagreements between the clinical results of our study and the others may be related to the size of the osseous cavity, retro-filling material, and PRF preparation technique.

The endodontic microsurgery triad including: high magnification, illumination and micro instruments, was firmly established over the past decade.[36] In our study, surgical microscope and/or loops with enhanced magnification and illumination was utilized for hard tissue management throughout the clinical operation. This allowed for atraumatic smaller osteotomy atraumatic as well as more precise root end resection and cavity preparation, compared to the traditional procedures [37-40].

Micro- surgical instruments were used for inspection, flab reflection and retraction, curettage, and root-end preparation and filling. Using the microsurgical approach, roots could be resected at a shallow bevel angle, almost perpendicular to the long axis of the tooth, sacrificing less tooth structure, and exposing fewer dentinal tubules. Ultrasonic tips were then utilized for the preparation of a root end cavity, again inspected and subsequently filled with a root end filling material, as a result of the microsurgical techniques, patients experience less trauma and faster postsurgical healing [37, 40].

Our study has some limitations. Only one year follow up period was done for evaluation of peri-radicular healing; however, it may be better to increase the follow up period since the uncertain category may revert to success or failure. The lack of histologic evidence is another limitation of the study. CBCT evaluation in addition to pathologic evaluation might be the best method for determination of the nature of the healing process in tissues. However, it is unethical to obtain post-operative healed tissue from patients to compare pathologic findings with CBCT scans.

Finally, the present study recommends using of autologous PRF in peri-radicular bone defects after endodontic peri-radicular surgery as it has significant beneficial outcomes on the rate of peri-radicular bone healing one year postoperatively. More clinical and histologic studies with larger sample sizes and longer recall rates with standardized clinical protocols are required to confirm these findings.

CONCLUSION

Within the limitation of this clinical study, the adjunct implication of PRF in endodontic peri-radicular microsurgery may be of great significance as it dramatically improves healing and success rates.

RECOMMENDATIONS

According to the results of the current study, it is recommended to use PRF in periapical bony defects after endodontic peri-radicular microsurgery. Additional clinical and histologic studies with larger sample sizes and longer follow up rates are needed to confirm these results.

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