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Effect of local administration of injectable platelet-rich fibrin on root resorption during orthodontic tooth movement in dogs

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ABSTRACT

Background: This study aimed to assess the effect of local administration of injectable platelet-rich fibrin (i-PRF) on root resorption during orthodontic tooth movement in dogs.

Materials and Methods: This animal study was conducted on 4 adult male mongrel dogs. The right and left maxillary first premolars of the dogs were extracted, and a Nickel-Titanium closed coil spring was used to connect the canine to the second premolar with 150 g load. Next, 0.5 cc of i-PRF was injected in one quadrant of the maxilla around the second premolar into the periodontal ligament. The other quadrant of the maxilla served as the control group and received saline injection. Injections were performed at 1, 21, and 42 days, and the dogs were sacrificed after 63 days. Histological sections were prepared and cementum resorption, secondary cementum formation, and number of cementoblasts and cementoclasts were compared between the two groups by the Friedman test, Wilcoxon test, and Mann–Whitney test ($\alpha = 0.05$).

Results: The mean percentage of cementum resorption (17.75% ± 5.56%) and secondary cementum formation (14.50% ± 6.65%), and the mean number of cementoblasts (10.25 ± 2.36) and cementoclasts (9.75 ± 4.71) were insignificantly higher in the i-PRF group than the corresponding values (13.75% ± 4.34%, 8.50% ± 2.88%, 7.75 ± 1.25, and 6.50 ± 3.10, respectively) in the control group ($P > 0.05$).

Conclusion: Administration of i-PRF insignificantly increased the percentage of cementum resorption, secondary cementum formation, number of cementoblasts, and number of cementoclasts.

Key Words: Dental cementum, platelet-rich fibrin, tooth movement techniques

INTRODUCTION

Orthodontists have always been in search of modalities to accelerate orthodontic tooth movement (OTM) and prevent complications associated with the long course of orthodontic treatment. OTM is in fact a biological response to a physical stimulus. Acceleration of OTM prevents the occurrence of common iatrogenic side effects such as development of white spot lesions, caries, root resorption, and periodontal problems. Adequate volume of alveolar bone and adequate root length are the main prerequisites for successful OTM and stability of treatment results.[1]

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Root resorption during OTM is a major problem that can lead to irreparable defects.[2] No definite reason has been identified for the occurrence of root resorption in the course of OTM.[3] Application of heavier and uncontrolled orthodontic forces and prolongation of the treatment course are significantly correlated with a higher rate of root resorption.[4] Hormonal changes and genetic factors can also lead to root resorption.[2]

Recently, a great focus has been given to autologous blood products such as platelet-rich plasma (PRP), which is prepared from the patient's own blood to benefit from the beneficial effects of growth factors in tissue regeneration. Such effects are related to the release of growth factors from the alpha granules of platelets, which mediate the tissue healing process.[5] PRP can serve as a source of chemical mediators in the process of inflammation and release of growth factors.[6]

Platelet-rich fibrin (PRF) is a modified form of PRP. PRF or the second-generation platelet aggregate was first introduced by Choukroun[7] in France. It is an autogenous fibrin matrix that contains growth factors, platelets, leukocytes, and cytokines. Some pulpal cells survive even in extensive periapical lesions. PRF induces the proliferation of such cells, and following disinfection of the root canal system and resolution of inflammation, these cells differentiate into odontoblasts.[8]

The pattern of release of growth factors such as transforming growth factor-beta (TGF-B), and platelet-derived growth factor (PDGF) varies between PRP and PRF. In PRP, the release of TGF-B and PDGF considerably decreases after the 1st day of application while PRF shows a considerable sustained release of TGF-B and PDGF for up to 2 weeks.[9] Dohan Ehrenfest *et al*.[10] confirmed a difference in release profiles of vascular endothelial growth factor (VEGF) derived from leukocytes in PRP and PRF. Evidence shows that PRF membranes can probably release higher amounts of growth factors over longer periods of time.[11] PRF is also available in injectable form (injectable PRF [i-PRF]) which is prepared by compaction of PRF membranes between metal sheets. Furthermore, i-PRF can be coagulated right before injection to form biomaterials or can be combined with other biomaterials to form covalent bonds.[7]

Application of mechanical orthodontic forces causes OTM. The main parameter causing OTM on application of orthodontic forces is the inflammation developed in the periodontal ligament (PDL) and alveolar bone.[12] The dominant cells in this inflammatory process affect the activity of osteoblasts and osteoclasts and accelerate PDL and alveolar bone remodeling as such. Normal remodeling of bone depends on the balance between bone formation and bone resorption. Bone resorption is regulated by the receptor activator for nuclear factor K-B and receptor activator for nuclear factor KB ligand (RANKL), which are members of the tumor necrosis factor family, as well as osteoprotegerin (OPG).[13]

PRF has advantages over PRP such as easier preparation and not requiring a coagulant. In addition, PRP requires bovine thrombin or calcium sulfate for activation, and bovine thrombin can elicit unwanted reactions such as hemorrhage, thrombosis, autoimmune reactions, and conditions such as systemic lupus erythematosus.[14]

Considering the increasing use of PRP and PRF for acceleration of OTM, this study aimed to assess the effect of local administration of i-PRF on root resorption during OTM in dogs.

MATERIALS AND METHODS

This animal study was conducted on 4 adult male mongrel dogs. The study was performed in accordance with the guidelines for the care and use of laboratory animals. The study protocol was approved by the Ethics Committee of the School of Dentistry, Islamic Azad University, Khorasgan Branch (IR. IAU. YAZD. REC.1401.006).

Sample size

The sample size was calculated to be 4 in each group according to a previous study[15] assuming alpha = 0.05, beta = 0.2, and study power of 80% to find a significant difference two times the standard deviation.

Eligibility criteria

The inclusion criteria were male dogs between 10 and 12 months of age, and with 15–20 kg weight.

Intervention

The dogs were sedated with intramuscular injection of 10% ketamine (20 mg/kg; Alfasan, Netherland) and 0.5 mg/kg acepromazine (Alfasan, the Netherlands), and general anesthesia was induced by isoflurane (Alfasan, the Netherlands) inhalation (0/75%–3% per Liter). The right and left maxillary

first premolars of the dogs were extracted, and a Nickel–Titanium closed coil spring (G and H wire Co.) was used to connect the canine to the second premolar with 150 g force. A groove was created in the canine tooth by a diamond disc and high-speed hand-piece, the closed coil spring was attached to the created groove by a ligature tie (0.14 Orthotechnology, USA), the closed coil spring was fixed with composite resin, and the force applied by the spring was measured by a force-meter (Dentaurum, Germany) to ensure application of 150 g force [Figure 1].

To ensure the presence of a healthy PDL around the teeth, periapical radiographs were obtained from the teeth. Next, one quadrant of the maxilla was randomly selected for injection of 0.5 cc of i-PRF and the other maxillary quadrant served as the control group. In the test quadrant, i-PRF was injected into the PDL around the second premolar at 8 points of mid-buccal, mid-lingual, distobuccal, distolingual, mid-distal, mesiolingual, mesiobuccal, and mid-mesial. In 2 randomly selected dogs, the right quadrant served as the test and the left quadrant served as the control group while in the remaining 2 dogs, the left quadrant served as the test and the right quadrant served as the control group. During the intervention, the dogs only received soft food to prevent displacement or deformation of orthodontic appliances.

Preparation of platelet-rich fibrin

Blood samples were collected from the cephalic vein of dogs and centrifuged in 10 cc test tubes without anticoagulant at 700 rpm (Intraspin System, Intra-lock) and 60 g relative centrifugal force for 3 min. After centrifugation, 0.5 cc of the supernatant (PRF) was collected by a syringe and injected into the PDL at the aforementioned 8 points around the second premolar in the test quadrant. In the control quadrant, 0.5 cc of sodium chloride (saline) was injected. Injections were performed at 1, 21, and 42 days. After 63 days, the dogs were generally anesthetized and sacrificed by succinylcholine overdose.

To prepare histological sections, the maxillae of the dogs were resected and fixed in 10% formalin (Merck, Germany) for 48 h. They were then placed in 10% formic acid (Merck, Germany) for 1 week, embedded in paraffin, and sectioned into 5-µm slices by a microtome (Leica, RM 2035, Germany). Five slices with 5-µm thickness were obtained from each premolar tooth (a total of 20 test and 20 control slides). The slides were stained with hematoxylin and eosin (Merck, Germany) and inspected under a

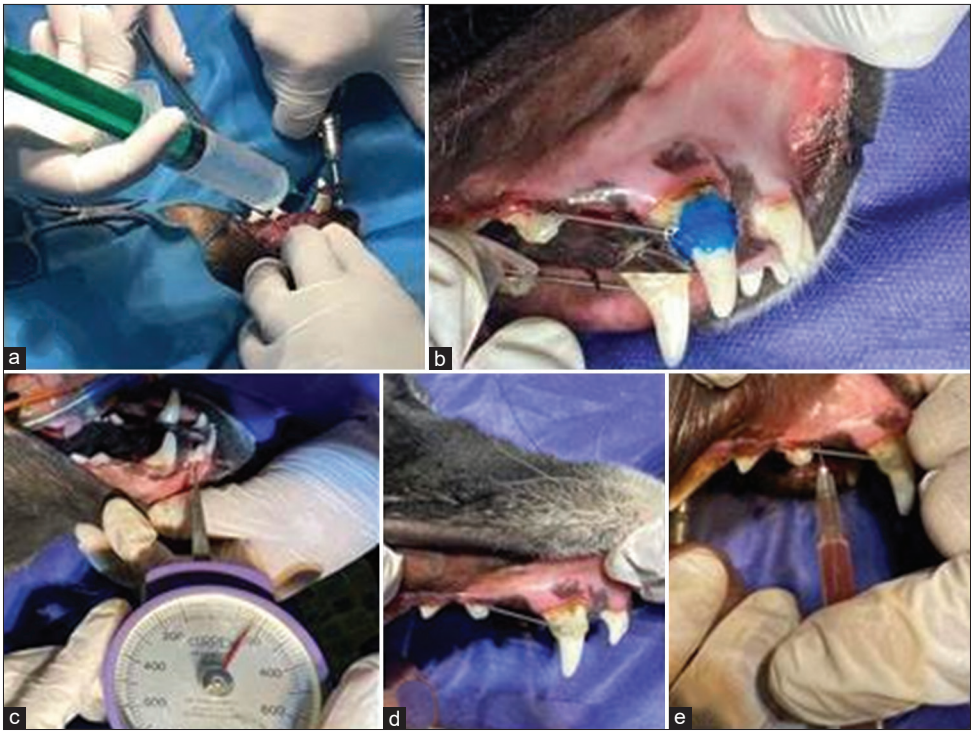

Figure 1: (a) Creating a groove on the canine tooth by a diamond disc and high-speed hand-piece; (b) fixing the closed coil spring attached to the tooth by composite resin; (c) measuring the orthodontic force by a force-meter; (d) the placed coil spring; (e) injectable platelet-rich fibrin was injected into the periodontal ligament around the second premolar.

light microscope (Olympus BX) at ×100 and ×400 magnifications.

The percentage of cementum resorption (the ratio of resorbed surfaces to the entire root surface area), the percentage of secondary cementum, number of osteoblasts, and number of osteoclasts were measured on the five slides of each premolar tooth using Adobe Photoshop 7 software (San Jose, CA, USA), and the mean values were calculated and reported.

Statistical analysis

Data were analyzed by SPSS version 22 (SPSS Inc., Chicago, IL, USA). Due to the small sample size, skewness and kurtosis were calculated and since kurtosis was >2 for all variables, data were found to have nonnormal distribution. Thus, the nonparametric Friedman test, Wilcoxon test, and Mann–Whitney test were used to compare the variables between the two groups at 0.05 level of significance.

RESULTS

Qualitative findings

Figure 2a shows the normal structure of cementum, PDL, and alveolar bone in the control group. Figure 2b shows the initiation of cementum resorption and cementoblastic activity in the control group. Figure 2c shows compact PDL and the presence of cementoblasts along with resorptive activity in the test group. Figure 2d indicates less osteoclastic activity and more prominent osteoblastic activity in the test group. PDL had a rather irregular orientation with fewer and smaller blood vessels. Figure 2e shows several multinucleated mature osteoclasts, indicating high resorptive activity which can accelerate OTM. PDL had an irregular orientation and some dilated blood vessels could be seen. Figure 2f shows the enhancement of osteoblastic and osteoclastic activities due to the presence of several growth factors.

Quantitative findings

Table 1 shows the measures of central dispersion for cementum resorption and secondary cementum formation in the two groups. As shown, the mean percentage of root resorption was 17.75% ± 5.56% in the i-PRF and 13.75% ± 4.34% in the control group. As shown, the two groups had no significant difference in cementum resorption (P = 0.285).

The mean secondary cementum formation was 14.50% ± 6.65% in the i-PRF and 8.50% ± 2.88% in the control group. The two groups had no significant difference in secondary cementum formation (P = 0.144).Table 2 presents the measures of central dispersion for the number of cementoblasts and cementoclasts. As shown, the mean number of cementoblasts was 25.36 ± 10.2 in the i-PRF and 7.75 ± 1.25 in the control group, and this difference

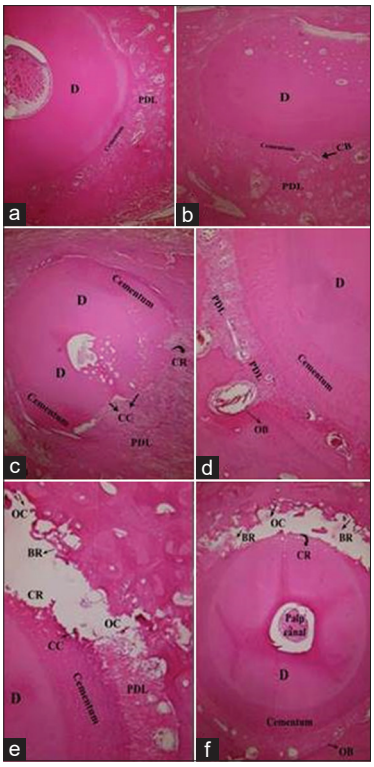

Figure 2: (a) Photomicrograph of a transverse tooth section indicating normal cementum, dentin (d), periodontal ligament (PDL) and alveolar bone in the control group; (b) cementum resorption, PDL, and cementoblasts in the control group; (c) cementum resorption, cementoclasts and alveolar bone in the test group; (d) cementum resorption, PDL and osteoblasts in the test group; (e) PDL, cementum loss, osteoclasts, cementoclasts and bone resorption in the test group; (f) cementum resorption, osteoblasts, osteoclasts, and bone loss in the test group (H and E, ×100 magnification). PDL: Periodontal ligament, CB: Cementoblasts, CR: Cementum resorption, CC: Cementoclasts, AB: Alveolar bone, OC: Osteoclasts, BR: Bone resorption.

Table 1: Measures of central dispersion for cementum resorption and secondary cementum formation in the two groups

Variable	Group	Mean percentage±SD	Minimum	Maximum	*P*
Cementum resorption	i-PRF	17.75±5.56	10	23	0.285
	Control	13.75±4.34	10	20	
Secondary cementum formation	i-PRF	14.50±6.65	5	20	0.144
	Control	8.50±2.88	5	12	

SD: Standard deviation; i-PRF: Injectable platelet-rich fibrin

Table 2: Measures of central dispersion for the number of cementoblasts and cementoclasts

Variable	Group	Mean±SD	Minimum	Maximum	*P*
Number cementoblasts	i-PRF	10.25±2.36	7	12	0.063
	Control	7.75±1.25	6	9	
Number of cementoclasts	i-PRF	9.75±4.71	3	14	0.273
	Control	6.50±3.10	3	10	

SD: Standard deviation; i-PRF: Injectable platelet-rich fibrin

was not significant (P = 0.063). The mean number of cementoclasts was 9.75 ± 4.71 in the i-PRF and 6.50 ± 3.10 in the control group. The two groups had no significant difference in this regard either (P = 0.273).

DISCUSSION

This study assessed the effect of local administration of i-PRF on root resorption during OTM in dogs. The results showed that administration of i-PRF insignificantly increased the percentage of cementum resorption, formation of secondary cementum, number of cementoblasts, and number of cementoclasts.

Due to the novelty of this topic, search of the literature for relevant articles yielded only one similar study; thus, studies on cementum resorption, secondary cementum formation, cementoblasts, and cementoclasts are discussed as possible factors effective on the speed of remodeling and OTM.

Tehranchi *et al*.[16] applied leukocyte -PRF in first premolar socket in one quadrant of 8 patients and retracted the canine tooth. They measured OTM bilaterally on dental casts of patients at 2-week intervals for 3 months and found that the PRF membrane enhanced OTM. Histological analyses in the present study revealed an increase in all tested parameters in the i-PRF group; however, this increase did not reach statistical significance, which may be due to small sample size.

Akbulut *et al*.[17] reported no significant effect of PRP on OTM in rats. Clinically, OTM in the PRP group was even smaller than that in the control group, but this difference was not statistically significant. Their results were in line with the present findings. Amiri *et al*.,[18] in their systematic review showed that i-PRF had no significant effect on OTM in the first month; however, it significantly enhanced OTM in the 2nd month. They stated that application of i-PRF appeared to be effective for enhancement of OTM in canine teeth; although a definite conclusion could not be reached. They called for further high-quality studies with a larger sample size. Difference between their results and the present findings may be due to different assessment times (1 month in their study vs. 63 days in the present study). Erdur *et al*.[19] reported that i-PRF significantly increased OTM. They showed that the level of cytokines and pro-inflammatory markers significantly changed 1 week after the first injection of i-PRF, and 2 weeks after the second injection. They demonstrated an increase in interleukin-1b, matrix metaloprotenase-8, and RANKL in i-PRF group compared with the control group, while OPG significantly decreased in the i-PRF group. They stated that the positive effects of i-PRF on OTM started from the 1st week and continued during the follow-up. Their results were different from the present findings, which may be due to different times of assessments.

In the process of orthodontic treatment, some changes occur in the cementum similar to bone. The thickness of the cementoid decreases at the resorption site, and if pressure continues for long, root resorption occurs. The resorbed lacunae in secondary cementum layers are often covered by a fibrous layer.[20]

Zeitounlouian *et al*.[1] evaluated the efficacy of i-PRF for preservation of bone and prevention of root resorption, and found no significant difference in bone height and thickness between the two groups before or after retraction. Root length decreased after retraction but the difference was not significant between the two groups. Their results were in agreement with the present findings although the variables were assessed by cone-beam computed tomography in their study.

The present study was conducted on four dogs of the same breed and age to eliminate the effect of confounders such as age and bone density on the response to i-PRF. However, it should be noted that tooth extraction increases the activity of pro-inflammatory markers, which can mask the effects of i-PRF. To control for this effect, tooth extraction was performed at the same time in the test and control quadrants, and also saline was injected into the control quadrant to control for the effect of injection trauma.

OPG binds to RANKL and prevents the differentiation of osteoclasts. Such cytokines play an important role in the reinforcement and activation of preosteoclasts. Increased release of cytokines is associated with greater activity of osteoclasts and subsequently higher speed of OTM.[21,22]

Some other studies reported increased OTM both clinically and histologically following the application of PRP, probably due to the presence of a high number of growth factors in PRP that stimulate osteoblastic and osteoclastic activities.[23,24] Moreover, the cytokine-rich content of PRP[25] plays an important role in OTM and activation and viability of all bone cells.[26]

The present results showed an insignificantly higher number of multi-nucleated mature osteoclasts on the i-PRF side, indicating high resorptive activity and higher OTM in this group. The PDL fibers of second premolars had an irregular orientation in both groups, mainly due to compaction and degradation of fibers, and may be considered as an initiator of the cascade of complex cellular and molecular events that finally lead to OTM. Moreover, dilated blood vessels were more commonly seen in the i-PRF group than the control group, which can probably be due to the effect of pro-inflammatory mediators such as prostaglandins, cytokines, leukotrienes, and VEGF released from the PDL following mechanical loading in addition to those already present in PRF.[24,25,27] Similarly, some other studies reported dilated blood vessels at the resorption site only after surgical interventions conducted for acceleration of OTM.[28-30] Rashid *et al*.[31] indicated higher rate of new bone formation in the PRP group compared with the control group, which was in the form of thick newly formed bone trabeculae along with several large and irregular osteocytes. In contrast, new bone trabeculae were thinner in the control group and were associated with smaller number of irregular osteocytes.[31] Active osteogenesis is probably due to greater tension of periodontium and subsequently faster OTM in the PRP group along with the healing capacity of PRP as the result of presence of PDGF, which increases the proliferation and mitogenesis of bone cells.[32] Their results were histologically similar and statistically different from the present findings, which may be due to small sample size of the present study and use of PRP in their study versus PRF in the present investigation.

Histological findings of another study revealed numerous osteoclasts on the socket surface at the resorption side, indicating high resorptive activity in the PRP group.[31] In addition, PDL had an irregular arrangement, and a high number of dilated blood vessels were reported in the abovementioned study. Their results were in agreement with the present findings showing cementoblastic activity with root surface preservation. In fact, cementum and normal PDL cells that cover the root surface contain a possible preventive factor, which prevents root resorption. By breaching this barrier, root resorption may occur. In the process of remodeling, hyalinized area, necrotic tissue, and alveolar bone are removed by macrophages and osteoclasts. As a side effect, the cementoid layer of the root surface may also be removed, which leads to the subsequent initiation of root resorption.[33]

Although statistically adequate, the small sample size was a limitation of this study. Future studies with a larger sample size are required on the effects of i-PRF on OTM, duration of treatment, and level of inflammatory markers. Moreover, clinical trials are required to obtain more reliable results generalizable to the clinical setting.

CONCLUSION

The administration of i-PRF insignificantly increased the percentage of cementum resorption, formation of secondary cementum, number of cementoblasts, and number of cementoclasts. Thus, injection of i-PRF is probably not effective for the prevention of root resorption in the clinical setting.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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