ORIGINAL RESEARCH

Comparison between Different Combinations of Alendronate, Platelet-rich Fibrin, Hydroxyapatite in Bone Regeneration in Endodontic Surgeries Using Cone-beam Computed Tomography

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Abstract

Aim: To compare different combinations of alendronate, platelet-rich fibrin (PRF), and hydroxyapatite in bone regeneration in endodontic surgeries using cone-beam computed tomography (CBCT).

Methods and subjects: During this study, 28 patients were selected who were found to have pathology in the periapical area in the anterior region. The study subjects were categorized into four categories, each consisting of seven subjects. Category one—there was no placement of any material; category two—PRF; category three—hydroxyapatite along with PRF; category four—alendronate along with PRF. Root canal treatment followed by endodontic surgery in each patient was carried out. Volumetric analysis of the lesions was carried out before surgery and 12 months after surgery using CBCT. Analysis of variance (ANOVA) test and Tukey *post-hoc* test were used for statistical analysis.

Results: There was a maximum change in the volume of lesions in the study subjects in which PRF was used along with hydroxyapatite in comparison to other combination of materials. There was no significant difference when PRF was placed along with alendronate in comparison to study subjects when PRF was placed alone. The difference was not significant when PRF was placed in defects of bone in comparison to study subjects when no materials were placed in the defects of bone.

Conclusion: It can be concluded from the current research that PRF along with hydroxyapatite is a better option for the healing of defects of bone in surgeries performed in the area around the root apex in endodontic patients. But further studies should be carried out with a large sample size and for a longer duration.

Clinical significance: It is a very important consideration that there should be healing of the lesion after surgery around the root apex by actual bone regeneration. The healing of the larger lesions does not take place easily as compared with the lesions having a small size. This is because there is healing by secondary intention where there is formation of scar instead of actual healing by formation of bone. There are several methods by which proper bone regeneration can be obtained.

Keywords: Alendronate, Bone regeneration, Cone-beam computed tomography, Endodontic surgeries, Hydroxyapatite, Platelet-rich fibrin.

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Introduction

Apicoectomies are the surgeries carried out in endodontic patients to manage those cases where nonsurgical means of endodontic treatment and retreatment get failed. It has been observed that 89% of endodontic patients managed by surgeries around the root apex with the help of recent advancements have shown a good prognosis. A lot of research has been carried out to evaluate the factors which affect the prognosis of the surgeries carried out in endodontic patients.[1,2] One of the most important factors affecting the prognosis of surgery around the root apex is the size of the pathology around the root apex. The healing of the larger lesions does not take place easily as compared with the lesions having a small size. This is because there is healing by secondary intention where there is formation of scar instead of actual healing by formation of bone. In the case of lesions of small size, few studies demonstrated that the prognosis of surgeries carried out by modern techniques as well as conventional techniques is better.[3,4]

It is a very important consideration that there should be healing of the lesion after surgery around the root apex by actual bone regeneration. There are several methods by which proper bone regeneration can be obtained. These methods are the utilization of autologous and allogenous bone grafts, use of barrier membranes, use of medical substances which causes modulation of the host

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environment like platelet-rich with fibrin. Among these agents, bone grafts are most usually used for bone regeneration.[5,6] These bone grafts are believed to have osteoconductive, osteoinductive, and osteogenic properties. The properties of bone grafts are mainly dependent on the method of their processing and the location from where they have been obtained. Hydroxyapatite is one of the allogeneous bone grafts which are usually very effectively used for the regeneration and repair of the defects of bones in various oral and dental surgical procedures.[7]

In recent times several hormones, derivatives from platelet and several growth factors, have been also used for regeneration of the bone in the surgeries performed around root apex in endodontic patients. But there is still a debate going out to confirm their effectiveness in the regeneration of defects of bone. As far as grafts obtained from bone are concerned they need the synergic effect from the host blood components like PRF and blood clots for proper healing of wounds after the surgeries around the root apex.[8]

It has been advocated that a combination of grafts prepared from bone and host blood agents like fibrin rich in platelets can be quite effective in the regeneration of bone in the area around the root apex after surgery. The advantages of utilizing this combination of bone grafts with PRF are improvement in the properties of handling, and stabilization of bone grafts, improvement in hemostasis, growth of bone, healing of wounds, and maturation of the new bone. In recent studies, a new substance called alendronate has also been advocated to be useful in the reduction of resorption of alveolar bone after conduction of flap surgery involving mucoperiosteal surgical flaps. But there is a need for evaluation of evidence to show its effectiveness in the healing of wounds after surgery in the area around the root apex.[9]

Several studies have been conducted that have evaluated the individual role of the bone grafts like hydroxyapatite, platelet-rich in fibrin, and alendronate in the regeneration of the bone in the surgeries conducted in the area around the root apex but very few studies have been conducted to evaluate the effect of various combinations of these agents in the regeneration of the bone in surgeries in the area around root apex. In earlier studies, the technique used was the conventional two-dimensional radiographic techniques which have several limitations.[10]

In recent times there has been the use of three-dimensional radiographic technology like cone-beam computed technology, popularly called as CBCT, to analyze the pathologies related to defects of the bone around the root apex in endodontics patients for carrying out surgeries in this region. The advantage of using this three-dimensional technique in endodontics is that there can be the identification of the lesions around the root apex even before the appearance of demineralization occurring in alveolar cortical plates appears. There is added advantage of minimum superimposition of images of anatomical structures in this technique as compared with two-dimensional imaging techniques like intraoral periapical radiographs and orthopantomography. Besides, there can be proper visualization of different changes taking place in the cancellous bone.[11]

Therefore, the present research was performed with following aims:

- To compare different combinations of alendronate, PRF, hydroxyapatite in bone regeneration in endodontic surgeries
- Comparison of the healing of surgical wounds volumetrically after surgery in the area around the root apex in different combinations of various agents used in the healing of bone with the help of CBCT

Methods and Subjects

The study was conducted as a multidisciplinary approach involving the department of conservative and endodontics and the department of oral and maxillofacial surgery. The study was started after obtaining approval from the committee of the institute for ethical clearance. The reference number of the ethical clearance was SDC/2021/A-137. It was a prospective study conducted over a duration of 1 year (12 months) starting from March 2020 and extending to March 2021 at Dehradun, Uttarakhand, India.

Sample Size

A sample size of twenty eight was required to achieve 80% power and 5% significance. During this study, 28 patients reporting to the outpatient department were selected who were found to have pathology in the area around the root apex in the anterior region. The study subjects were categorized into four categories each consisting of seven subjects.

The sample calculation was:

$$n = \frac{Z_\alpha{}^2 \sigma^2}{d^2}$$

where

Z_α = standard table value for 95% CI
σ = standard deviation
d = precision
= 10% of mean

Selection Criteria

Study subjects of age 25–35 years were selected. The size of the pathology in the area around the root apex in the maxillary anterior region as observed in IOPAR was more than 5 mm in the study participants. Study subjects were included in the study only after obtaining their informed content.

Patients having other systemic diseases including bone diseases like osteoporosis, rickets, etc., and those subjects not willing to report for follow-up were excluded from the study.

Preliminary Investigations

There was conduction of preliminary blood examinations of all the subjects which included complete blood count, hemoglobin, important markers for viral infections like HIV and Hepatitis B, prothrombin time, and INR examination, bleeding time examination, and clotting time examination.

Methods

A radiographic image of the affected tooth using CBCT was taken before carrying out any clinical procedure. The voxel size used for this analysis was 0.125 mm by 0.125 mm by 0.125 mm.

Scaling and root planning followed by root canal treatment were carried out in all the affected teeth using standard protocol by the same clinician. Once the obturation of teeth was completed, study subjects were recalled after 24–48 hours.

Surgical Procedure

Anesthesia of the area isolated for the surgical procedure was provided with the help of an adequate nerve block. The

anesthetic agent used for nerve block was 2% lignocaine with adrenalin having a concentration of 1:80,000. The surgical procedure started with the placement of a crevicular incision which was followed by two releasing vertical incisions. A periosteal elevator was used for reflection of the full thickness flap in such a way that there was easy access to the area around the root apex after the removal of sufficient bone of the cortical plates. While there was the removal of bone from cortical plates, care was taken that the area of bone removal was irrigated with normal saline constantly. There was proper curettage of the area around the root apex to remove the pathology along with epithelial lining if present. After that, there was resection of the end of the root up to 3 mm. There was the preparation of cavity at the end of the root and MTA was used for filling of this cavity at the end of the root.

Randomization and Blinding

All the clinical procedures were carried out by the same clinician who was kept unaware of the study protocol in order to reduce the bias. The patients were distributed into four categories and each category included seven patients. This division was carried out based on materials/combination of materials kept in the bone defect in the area around the root apex.

Category one—there was no placement of any material
Category two—platelet-rich fibrin (PRF)
Category three—hydroxyapatite along with PRF
Category four—alendronate along with PRF.

Around 5 mL of whole venous blood was collected from the patients in each of the two sterile vacutainer tubes of 6 mL capacity without anticoagulant. The vacutainer tubes were placed in a centrifugal machine at 3,000 revolutions per minute (rpm) for 10 minutes, and the middle fraction containing the fibrin clot was collected 2 mm below lower dividing line, to obtain the PRF.

Commercially available hydroxyapatite bone graft crystals (Biograft HA, IFGL Bioceramics Ltd., India) were used. They were sprinkled over the PRF gel and together the mixture was placed into defect site. Platelet-rich fibrin membrane was prepared with compresses and placed as two layers covering the edge of the defect.

The 1% alendronate gel was formulated as proposed by Reddy et al.[12] Alendronate sodium (mol wt 325.12) (Sun Pharmaceuticals, Baroda, India) was dispersed in the solvent to achieve 1% w/v concentration of alendronate sodium. Platelet-rich fibrin and ALN were mixed in equal ratio (1:1) and were filled into the bony defect.

Repositioning of the full thickness flap followed by suturing was carried out and medicines for pain control and infection controls were prescribed. Antibiotics (500 mg amoxicillin capsules thrice daily for 7 days; 500 mg metronidazole tablets thrice daily for 7 days) and analgesics (800 mg ibuprofen tablets thrice daily) were advised. Chlorhexidine mouthwash rinses (0.12%) two times daily was also prescribed for 2 weeks.

Study subjects were given proper postoperative instructions. They were recalled for removal of the suture after 1 week. For the next 12 months, there was regular follow-up. Weekly examination of patients for 1 month after surgery was carried out and follow-up was done again at 3, 9, and 12 months. Once there was the completion of follow-up duration there was obtainment of a radiographic image using CBCT of each study participant.

Measurement of the Dimensions of Periapical Lesion in CBCT

Evaluation of CBCT radiographic images obtained before the surgery and 12 months after the surgery was carried. Measurements of the dimensions of the periapical lesion were carried out in all three directions, namely, mesiodistal, labiolingual, and the apicocoronal direction (Figs 1 to 3). In order to carry out these measurements, specific anatomical landmarks were considered as the reference points and distance between these reference points was calculated. All the measurements in CBCT examination were carried out by same oral and maxillofacial radiologist who was completely unaware of the study protocol.

Calculation of Volume of Periapical Lesion

The volume of the lesion was calculated with the following formula:

$$\text{Volume} = \frac{4}{3}\pi.x.y.z$$

where

x = maximum diameter in the mesiodistal direction divided by 2
y = maximum diameter in the labiolingual/labiopalatal direction divided by 2
z = maximum diameter in the apicocoronal direction divided by 2.11

Statistical Analysis

Analysis of variance (ANOVA) test and Tukey *post-hoc* test were used for statistical analysis. SPSS 20 (IBM, USA) was the software used for the statistical analysis. p-value ≤ 0.05 was taken as statistically significant.

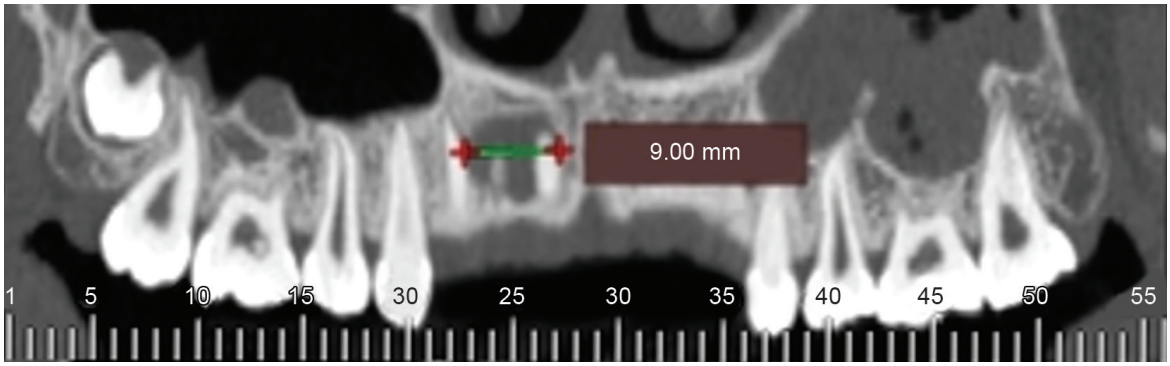

Fig. 1: CBCT scan image showing maximum diameter in the mesiodistal direction

Fig. 2: CBCT scan image showing maximum diameter in the labiolingual/labiopalatal direction

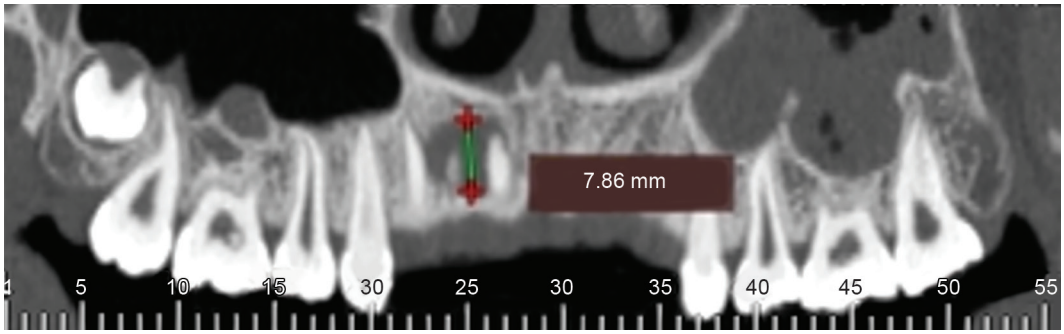

Fig. 3: CBCT scan image showing maximum diameter in the apicocoronal direction

Results

In our research, it was found that only two lesions out of 30 lesions showed complete healing after 12 months of the start of treatment. The volume of the lesions was calculated by obtaining the values of *x*, *y*, *z* from the analysis of images of CBCT both before the surgery and after the 12 months of surgery. The mean values of volumes of different categories before surgery were nonsignificant statistically (Table 1).

The volume change was evaluated for each category after 12 months of surgery. It was found that maximum reduction in volume was observed in category three (458.57 ± 44.98 mm^3). The mean value of change in volume of bony defects after surgery was 99.64 ± 38.39 mm^3, 102.32 ± 22.41 mm^3, 458.57 ± 44.98 mm^3, and 97.89 ± 51.55 mm^3 in category one, two, three, and four, respectively (Table 2).

The mean value of difference in change in volumes in category one and two was 13.79 mm^3. There was no statistically significant difference observed on comparing category one with category two ($p = 0.985$). It meant that volume change was not significant on the addition of PRF in bony defects as compared to the condition when no materials were placed in the bony defects. The mean value of difference in change in volumes in category three and one was 358.93 mm^3. The difference was statistically significant ($p = 0.03$). It can be inferred that volume change was significant when PRF was used with hydroxyapatite as compared to bony defects without any materials. The mean value of difference in change in volumes in category four and one was 1.75 mm^3. The difference was not statistically significant ($p = 0.907$). It reflected that there was no significant change in volume when PRF was placed along with alendronate as compared to bony defects without any materials. The mean values of difference in change in volumes in category three and two was 356.25 mm^3. The difference was statistically significant ($p = 0.02$). This was inferred that volume change was greater when PRF was used along with hydroxyapatite as compared to PRF used alone. The mean value of difference in change in volumes in category two and four was 4.43 mm^3. The difference was not statistically significant ($p = 2.00$). It showed that when PRF was used along with alendronate then there was no significant difference in change in volume as compared to PRF used alone. The mean value of difference in change in volumes in category four and three was 361.66 mm^3. The difference observed was significant statistically ($p = 0.03$). It demonstrated that the reduction in the volume was significantly greater when PRF was used along with hydroxyapatite as compared with being used along with alendronate (Table 3).

Table 1: Preoperative values of volume of bony defects in different categories

	Mean values ± S.D (mm^3)	*p value*
Category one	659.24 ± 23.47	0.16
Category two	687.41 ± 41.36	
Category three	701.59 ± 12.21	
Category four	686.11 ± 19.39	

Table 2: Data showing the change of the volume in different categories after 12 months of surgery

	Preoperative mean volume values	*Values of mean change of volume (mm^3)*	*p value*
Category one	659.24 ± 23.47	99.64 ± 38.39	0.01*
Category two	687.41 ± 41.36	102.32 ± 22.41	
Category three	701.59 ± 12.21	458.57 ± 44.98	
Category four	686.11 ± 19.39	97.89 ± 51.55	

*Statistically significant

Table 3: Data showing a comparison of volume in different categories after 12 months follow-up

	Mean difference values	*p value*
Category two vs category one	13.79	0.985
Category three vs category one	358.93*	0.03*
Category four vs category one	1.75	0.907
Category three vs category two	356.25	0.02*
Category two vs category four	4.43	2.000
Category three vs category four	361.66	0.030*

*Statistically significant

Discussion

Alendronate is a bone regenerating material that is found to be actively used in periodontal surgeries for healing the defects of bone. But there are no studies mentioned earlier in the literature regarding its application in surgeries in endodontic patients.[13] Since the results regarding alendronate obtained from studies on periodontal surgeries have been very encouraging, we decided to use it in our study.

The present study demonstrated that there is no significant effect in the change of the volume in the defects of bone in surgeries conducted in the area around the root apex on the addition of PRF as compared with the condition when no PRF was placed. The outcomes of our study are not similar to the results obtained from the study conducted by Angeramea et al. because they observed that there was statistically significant change of the volume in the bone defects in periapical endodontic surgeries on the addition of PRF as compared with the condition when no PRF was placed.[14] Monga et al. conducted a study and found that PRF is more effective in the healing of bone after surgery in the area around the root apex when used along with hydroxyapatite.[15] Similarly in our study it was observed that PRF used along with hydroxyapatite showed better results as compared with the PRF used alone in the healing of bone after surgery in the area around the root apex.

The reason for this finding can be because PRF behaves as a medium that promotes the development of new blood cells, holding of the stem cells which can differentiate into new blood and bone cells, and movement of precursor cells of bone toward the bone graft.[16] It was observed that in the category of patients where PRF was used along with hydroxyapatite, healing was much better. Gupta et al. and Reddy et al. conducted a study and found that alendronate acts as an inhibitor of the osteoblast and can be used actively in the healing of the bone defects in periodontal defects.[17,18] They found that alendronate used in the form of gel gave better results than other materials for bone regeneration. In our study, we used alendronate along with PRF because PRF has established itself as a bone regenerating material in periapical surgeries.[19]

However, results in our study were against our expectations. It was found that there was no significant difference in the volume of the lesions after 12 months of follow-up on using alendronate along with PRF as compared to lesions when PRF was used alone. There was no improvement in healing observed when alendronate was used along with PRF. It meant there is no added effect of alendronate in this study as reported in the studies on periodontal surgeries.

In our research, it was found that only two lesions out of 30 lesions showed complete healing after 12 months of the start of treatment. This finding of our study is similar to the findings of the studies carried out by Liang et al. and Van der Borden et al.[20] This can be due to the reason that CBCT were taken postoperatively at 12 months or less which is a relatively shorter duration for study.

In our study, CBCT was used which has some added advantages.[21] It does not have limitations present in the intraoral periapical radiographs. The lesions which are small and restricted within the cancellous bone cannot be detected easily by periapical radiographs.[22] Cone-beam computed tomography does not have this limitation. It can diagnose such lesions. Cone-beam computed tomography has been conferred the most standard radiographic technique for the analysis of the teeth and periapical areas.[23] It has added advantage that there is no distortion and elongation of images. It provides details in three dimensions. The measurements

provided by this technique are very accurate as compared with other radiographic techniques.[24]

In a study conducted by Patel et al., it was suggested that it is better to utilize CBCT scans having a small field of view (FOV) for the clinical trials of teeth in near future. Besides they also suggested that there should be the use of smaller FOVs in a manner so that healing of lesions as smaller as apical periodontitis can be analyzed. In our study, these suggestions were followed and there was the use of FOVS which were small.[25]

There have been various methods by which analysis of the change in the volume of the radiolucencies at the area around the root apex can be performed by utilizing the CBCT.[26] But the method described by Fike et al. is being considered standard. In this study also the method suggested by Fike has been used.[27]

The clinical implication from the current study can be summarized as the use of PRF along with hydroxyapatite is the better option for healing defects of bone in surgeries performed in the area around the root apex in endodontic patients.

As far as limitations of the study are concerned, the sample size of the study was small in every group. It was due to the high cost of the CBCT examination. Besides healing of wounds after surgery is a dynamic procedure that is influenced by several factors associated with the general health of patients.[28] The results of this study can be applied with certain limitations in patients suffering systemic diseases because this factor was not taken into consideration during the inclusion of study subjects.

Conclusion

It can be concluded from the current research that PRF along with hydroxyapatite is the better option for the healing of defects of bone in surgeries performed in the area around the root apex in endodontic patients. More studies should be carried out in future with larger sample size.

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