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Evaluation of healing of large periapical lesion by synergistic effect of Simvastatin and autologous PRF – A randomized controlled trial

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Abstract

Introduction: To the best of our knowledge, there are very few studies investigated the application of Simvastatin (SIM) loaded on autologous platelet-rich fibrin (PRF) in treatment of bone defects following surgical enucleation of large periapical lesions. Therefore, aim of this study was to evaluate the effects of SIM-PRF as filling material and to determine if there is synergistic effect of this combination.

Materials & Methods: 30 Patients, with periapical radiolucency in the anterior maxillary region, measuring more than 5 mm at its greatest diameter, were randomly allocated in 3 groups namely A, B and C (n=10 for each). Group A received alloplastic hydroxyapatite bone graft whereas group B received autologous PRF and Group C

received 1:6 SIM-PRF mixture for filling of cystic bony defects. Healing of the lesions was evaluated with CBCT imaging, preoperatively and on 1st, 3rd, 6th and 12th month postoperative follow-up days.

Result: In 1st month, the healing percentage was 36.24 ± 9.97 in Group A (Positive Control) whereas Group B (PRF) demonstrated a mean value of 32.00 ± 7.84 %; likewise, in 3rd and 6th month, Group A and Group B showed 63.85 ± 8.00% and 77.27 ± 11.43%, and 95.51 ± 1.13% and 94.49 ± 3.09% respectively. Group C (1:6 SIM-PRF group) demonstrated healing of 41.47 ± 4.44% in 1st month, 92.09 ± 0.53% and 99.31 ± 0.45% in 3rd and 6th months respectively; as compared with Group A, the results are consistently better and the data are statistically significant in 1st, 3rd and 6th months.

Conclusion: Overall results suggest that 1:6 SIM-PRF combination may be more effective in achieving complete healing of the bone defect. However, long term follow-up with histomorphologic analysis is required for better assessment of the efficacy of Simvastatin; also, to determine its optimal therapeutic threshold, mode of application etc

Keywords: Periapical Lesion, Bony defect, Autologous Platelet-rich Fibrin, Simvastatin, Endodontic Surgery, Cystic Enucleation

Introduction

Healing of periapical lesion is the key of success for root canal treatment (RCT). Endodontic surgery is the only way to cure the periapical lesions where orthograde treatment fails. Surgical Enucleation of the cystic lining and retrograde filling of the root tips do not always heal the bone defect. Tunnel defects (eroded buccal and palatal cortices) when left untreated, often lead to resorption of alveolar bone, causing bone deficiencies to be a major concern and severely affect the further oral rehabilitation of the patient. It was reported that each year a large number of apicectomies in the United States leave bone defects. (1) Bone formation following periapical surgery can be accelerated by placing synthetic bone graft into the bony defects, but that is also associated with minor to significant amount of graft resorption and often very expensive depending on the materials used. Over the time, efforts were made to look for agents that could provide the dual benefit of stimulating bone formation, in addition to, inhibiting bone resorption. (2) Platelet-rich fibrin (PRF) is a second-generation platelet concentrate that is prepared using simplified protocol, (4) and releases growth factors in about the same concentration approximately for a 7-day time duration. (3,4) Statins like simvastatin (SIM) are specific competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (5) and are widely used to lower cholesterol, and they provide an important and effective approach for the treatment of hyperlipidemia and arteriosclerosis. (6) Recent in vivo and in vitro studies found that statins reduce osteoclast activity and activate osteoblast differentiation and bone formation. Statins affects bone formation by direct increase in the bone morphogenetic protein-2 (BMP-2) expression. (2) Considering various regenerative materials available and the fact that combined properties of these materials could prove to be beneficial in regeneration of bony defects, this study aims to evaluate the synergistic action of SIM loaded on autologous PRF when applied in the cystic bony defects following surgical Enucleation.

Materials & Method

From March, 2017 to February, 2019; 30 patients (Age 18-45) undergoing endodontic therapy in the department of Conservative Dentistry & Endodontics, at Haldia Institute of Dental Sciences & Research were selected and randomly allocated in 3 different groups. Informed & written consent was obtained from all the patients &

Ethical approval was received from the Institutional ethical committee & review board.

Group A (N=10) received 'Alloplastic Hydroxyapatite bone graft' as filling material in the bony defect following surgical enucleation of periapical lesion. This group was considered as positive control group.

Group B (N=10) received 'autologous PRF' as filling material following enucleation, prepared fresh on the day of surgery.

Group C (N=10) received '1:6 SIM-PRF mixture' as filling material in the bony defect.

Inclusion Criteria

Patients, with periapical radiolucency in the anterior maxillary region, measuring more than 5 mm at its greatest diameter, and who are, therefore, undergoing endodontic treatment of the associated maxillary anterior teeth. Retreatment cases were also included in the study.

Exclusion Criteria

Patients with systemic diseases/conditions, deleterious oral habits (smoking, chewing tobacco abuse) that may alter the outcome of the study. Also, any evidence of subgingival carious extension, infrabony pocket, inadequate attached gingiva, bridge/faulty extracoronal restorations was chosen as exclusion criteria.

Radiographic Evaluation

Post-obturation intra-oral periapical (IOPA) & Maxillary Occlusal radiographs were taken to measure the size of the periapical radiolucency using grids. Radiolucency measuring > 5 mm at its greatest diameter was included in the study and CBCT of maxilla was advised to these patients preoperatively and postoperatively on 1st, 3rd, 6th and 12th month follow-up.

CBCT Measurement

CBCT Scan was acquired using the PLATINUM NEXT GENERATION SIRONA CBCT SCANNER using standard scanning protocols (Pulsed exposure, 120 kVp, 3-7 mA, 14.7 Sec exposure time, 0.25 X 0.25 X 0.25 mm isotropic voxel size, 14 bit, maxilla & mandible). Collimation was fully adjusted to include the maxilla & mandible only. The field of view (FOV) for maxilla was 16 cm (d) X 6 cm (h) and a limited FOV was used to scan the teeth involved. Obtained images were converted to Digital Imaging and Communications in Medicine (DICOM) format and were subsequently transferred into a medical image processing program (ITK- SNAP 2.4.1) to measure the volume of the bony defect using semi-automatic segmentation procedure (0.2 mm slice thickness).

Pre-Surgical Endodontic Therapy

Following mandatory oral prophylaxis, all the patients had undergone conventional Root Canal Treatment (RCT) of the associated teeth in the maxilla, using the step-back method (#80 2% Taper ISO Standard) under rubber dam isolation. Patients with endodontic flare-up were subjected to re-treatment. In retreatment cases, intracanal medication (Calcium hydroxide) was placed for 7 days prior to obturation by lateral condensation method using calcium hydroxide base sealer. In some cases, where the lesion extended upto pre-molar region, prophylactic RCT of the pre-molars were performed. Post-endodontic restoration was done with light cure composite resin. Surgical intervention was carried away after 7 days of obturation.

Autologous Prf Preparation & Formulation of 1:6 Sim-Prf Mixture

Autologous PRF was prepared following the classical technique demonstrated by Choukroun et al. (7)

Simvaststin tablets (10 mg by weight) were crushed, dispensed on a sterile dapendish and moistened with 2 ml of normal saline. The moistened SIM was then incorporated into 60 mg of autologous PRF in such a way that the SIM stays in the center of the PRF scaffold and have a slow sustained release as the PRF resorbs.

Surgical Procedure

All the surgical procedures were performed under local anesthesia, in aseptic condition. Proper care was taken to preserve the adequate amount of interdental & attached soft tissues during mucoperiosteal flap elevation and handling. Following enucleation of the lesion, retrograde cavity preparation was done using ultrasonic retrotips. Bony cavity was irrigated with normal saline to wash away blood clot, dentin mud etc. followed by retrograde filling with mineral trioxide aggregate (MTA).

In group A, the bony defect was filled with alloplastic Hydroxyapatine bone graft material.

In group B, the defect was filled with autologous PRF, and in group C, the bony defect was filled with 1:6 SIM-PRF mixture; followed by adaptation of the compressed PRF membranes over the defect, prior to secure the PRF (in group B) or 1:6 SIM-PRF mixture (in group C) in the bony defect. Wound closure was done with 3-0 non-absorbable silk.

Post-Surgical Care

Postoperatively, antibiotics and analgesics were prescribed (Tab. Amoxicillin 500 mg X 8 hourly and Tab. Metronidazole 400 mg X 8 hourly for 5 consecutive days; Ibuprofen 400 mg X 12 hourly for 3 days and thereafter, SOS in case of pain, taken with a PPI antacid).

Patients were advised mouth-rinsing with 0.2 % Chlorhexidine mouthwash twice daily for 2 weeks. Sutures were removed after 7 days.

Patients were followed up weekly in first month and then monthly on 3rd, 6th and 12th months postoperatively.

Data Collection

Healing of the bony defect in all the patients were evaluated using CBCT imaging in 1st, 3rd, 6th and 12th postoperative months.

Preoperatively, the volume of the periapical lesion was evaluated and measured after the completion of endodontic treatment. Postoperatively, in 1st, 3rd, 6th and 12th months follow-up the change in volume of the bony defect was measured and healing percentage of the bony defect was calculated for the entire patient using the following mathematical equation:

(Volume of the lesion pre-op – volume of lesion on post-op day) x 100 % volume of the lesion pre-op

Result and Analysis

Descriptive Statistics was performed for all the patient and the data are expressed as the Mean ± Standard deviation (SD). The results were analyzed using independent t-tests to compare between groups at different time periods. P values less than 0.05 was set to be considered statistically significant. IBM SPSS 24.0 software was used for statistical analysis.

The mean size of the lesion in Group A, B & C were found to be 128.92 ± 45.87 mm^3, 89.39 ± 38.59 mm^3 and 114.09 ± 34.95 mm^3 respectively. [Graph 1]

In 1st month, the healing percentage of lesion was found to be 36.24 ± 9.97 % in Group A (Positive Control) whereas Group B (PRF) demonstrated a mean value of 32.00 ± 7.84 %; likewise, in 3rd and 6th month follow-up, the mean values for Group A and Group B were recorded as 63.85 ± 8.00% & 77.27 ± 11.43%, and 95.51 ± 1.13% & 94.49 ± 3.09% respectively. So, Group B showed improved healing only in 3rd month follow-up when compared with Group A, and the data are statistically significant with a P value of 0.007 ($P < 0.05$).

The Group C (1:6 SIM-PRF group) demonstrated the score of healing percentage as 41.47 ± 4.44% in the 1st month, and 92.09 ± 0.53% & 99.31 ± 0.45% in the 3rd and 6th months respectively; as compared with Group A, the results are consistently better and the data are statistically significant in 1st, 3rd and 6th months follow-up. ($P < 0.05$).

Comparing the Group B with Group C, the later showed better healing as compared with Group B. The mean

scores of Group B were recorded 32.00 ± 2.48, 77.27 ± 3.61% and 94.49 ± 0.97% in 1st, 3rd and 6th month follow-up. The collected data are statistically significant in both 3rd and 6th month follow up. (Graph 2, Table 1, Table 2)

Discussion

Complete elimination of infectious processes is the main goal of endodontic treatment and regeneration of destroyed connective tissue and bone forms the fundamental basis of endodontic surgical procedures.

In our study, maxillary anterior teeth were selected because 'tunnel lesions' (through and through, involving both the buccal and palatal cortices) are majorly found in this region. [FIGURE: 1] The eroded buccal and palatal cortices allow granulation tissue proliferation inside the bony crypt, thereby preventing or retarding bone formation. Several clinical trials have demonstrated that cases with tunnel defects may benefit from the use of alloplastic bone grafting materials and/or membrane barriers, thereby reducing the amount of scar tissue formation (radiographically categorized as incomplete healing) (17). However, bone grafting methods have their own limitations that includes graft resorption; ultimately forcing the clinicians to look for alternative methods, (8) in terms of efficacy, expense etc., since bony defects are of important concern and if not treated optimally they pose problems in further rehabilitation of dentition, speech, swallowing etc.

The use of PRF as natural scaffolds for autologous tissue generation is more of a recent choice compared with the use of alloplastic graft materials. (9) Our study evaluated the efficacy of using autologous PRF alone and in combination with 10 mg of Simvastatin (1:6 SIM-PRF) to attain bone regeneration in cystic bony defects of anterior maxillary region. Furthermore, the efficacy has been compared with a positive control group who received alloplastic Hydroxyapatite bone grafting materials for cavity filling.

Simvastatin is a white to off-white, non-hygroscopic, crystalline powder that is practically insoluble in water, but freely soluble in chloroform, methanol and ethanol. Oral absorption of Statins varies from 40 to 75 % due to reductase inhibitors. Simvastatin is given orally in a dose of 20–40 mg daily. The toxic dose of simvastatin is 160 mg. Adverse effects are reported in less than 1 % of the patients, mostly as abdominal pain, feeling of weakness, very rarely joint pain and memory loss. Doses above 80 mg taken regularly on long term basis may cause liver damage, type II Diabetes or myopathy. (10)

Statins blocks the formation of mevalonate, the precursor not only of cholesterol but also of isoprenoid compounds that serve as lipid attachments required for proper localization and activation of a variety of proteins. (11) This includes monomeric GTPases such as Rho, Rac, and Ras. (12) The GTPases acts on a number of inflammatory reactions such as the activation of reactive oxygen species and nuclear factor kappa B (NF-kB) and the suppression of endothelial nitric oxide synthase. Statins can accelerate interleukin 6 production and NF-kB signalling in response to lipopolysaccharides (LPSs). Statins also have the ability to inhibit pro-inflammatory cytokine expression in monocytes. (13,14)

Simvastatin is reported to stimulate BMP-2 and nitric oxide formation and regional bone formation in rat mandible models. Simvastatin increases mRNA expression for BMP-2, vascular endothelial growth factor (VEGF), alkaline phosphatase, type 1 collagen, bone sialoprotien and osteocalcin in MC3T3-E1 cells. (11)

Simvastatin is a pro-drug and requires activation by lactonases, which usually occurs in liver by cytochrome P_{450}. (15)

Ayukawa et al. demonstrated the effect of the local administration of simvastatin in the healing of artificially created bone defects. In their histomorphological study, local application of simvastatin successfully increased the bone regeneration. (20)

Mouhamed et al. in their clinical trial confirmed that both digital radiological examination and histological analysis prove that adding simvastatin in tricalcium phosphate improves bone formation. (21)

Hassan et al. concluded that the use of simvastatin accelerates bone graft healing, maturation, maintains its volume to a great extent and decreases its resorption. It also increases the density of the graft compared to a native bone or autologous bone graft in human after ridge reconstruction. (22)

However, Statins are heavily metabolized during their first passage in the liver, and only very low concentrations of active metabolites are available after oral intake. (16) Therefore, an active form of SIM was administered locally inside the bony defect. 10 mg of SIM moistened with 2 ml of normal saline was incorporated inside a scaffold of freshly prepared autologous PRF as the powder cannot be directly administered over the raw tissue as that may lead to severe inflammation in the surrounding. The idea was to have the SIM protected by PRF and as the PRF resorbs slowly, the powder would have a slow sustained release. No adverse tissue reaction was noted in this way and rest of the gap in the bony cavity was left vacant to accommodate the bony bleeding induced blood clot.

In the current study, the choice of the 1:6 ratio of SIM and PRF to fill the bone defect was based on reports from earlier in vivo studies that demonstrated that SIM had a dose dependent effect on bone regeneration and that 1:6 SIM-PRF had a positive impact on bone defect repair. (17)

In the 1st month follow-up, Group A (positive control) showed better healing as compared with Group B (PRF), however, Group C (1:6 SIM-PRF) demonstrated marked healing as compared with both the other groups.

In the 3rd month follow-up, Group C (1:6 SIM-PRF) showed excellent result with a mean healing percentage of 92.03, as compared with Group B (PRF) (77.27%) and Group C (positive control) (66.85%), pertaining to the established fact that alloplastic bone graft has a tendency to resorb.

In the 6th month follow-up, Group C demonstrated a mean healing percentage of 99.31, [FIGURE: 2] whereas Group A showed 95.51% healing and Group B showed 94.49 % of healing.

Not to mention, healing was not evaluated histomorphologically to ascertain the quality of newly formed bone, rather CBCT being an accurate, non-invasive, practical way to reliably determine osseous lesion size and volume, the volume of periapical lesions was entirely measured with CBCT imaging and in 12th month follow-up all the patients showed 100% healing radiographically, despite the quality of newly formed bone. (18,19)

Conclusion

The limitation of the present study includes small sample size and cofounding biases like age of the patient, gender, unequal size of the lesions and individual patient biology. Nonetheless, it sets the stage for future research in the area using a larger sample size. However, overall results suggest that SIM and PRF may be more effective in achieving complete healing of the bone structure based on a 12 months follow-up. 12 months postoperative follow up period was short to comment on the effect of SIM in complete bone regeneration process, but adequate enough to evaluate the effects of SIM in initiating and enhancing hard tissue healing. Long term follow-up along with histological study of the bone is required for assessment of the efficacy of SIM and further research is needed to

determine the optimal therapeutic threshold, mode of application, etc.

	1st Month	3rd Month	6th Month	12th Month
Group A	36.24 ± 9.97 %	63.85 ± 8.00 %	95.51 ± 1.13 %	100 ± 00 %
Group B	32.00 ± 7.84 %	77.27 ± 11.43 %	94.49 ± 3.09 %	100 ± 00 %
Group C	41.47 ± 4.44 %	92.09 ± 0.53 %	99.31 ± 0.45 %	100 ± 00 %

Table 1 Mean ± SD of Healing %

Independent 't' test	1st month	3rd month	6th month
Group a (n=10) Group b (n=10)	Not significant	Significant (p – 0.345)	Not significant
Group b (n=10) Group c (n=10)	Not significant	Significant (p - 0.001)	Significant (p – 0.041)
Group a (n=10) Group c (n=10)	Significant (p- 0.047)	Significant (p – 0.003)	Significant (p – 0.004)

Table 2: P value of <0.05 was set to be considered statistically significant

References

1. Gökmenoğlu, M.C. Yavuz, E. Sadik, V. Çanakçi, and C. Kara, 'Treatment of Different Types of Bone Defects with Concentrated Growth Factor: Four Case Reports', Int J Oral Dent Health, 2 (2016).
2. R. Shah, C. A. Werlang, F. K. Kasper, and A. G. Mikos, 'Novel Applications of Statins for Bone Regeneration', Natl Sci Rev, 2 (2015), 85-99.
3. Kiritsy CP, Lynch AB, Lynch SE. Role of growth factors in cutaneous wound healing: A review. Crit Rev Oral Biol Med 1993;4:729-760
4. Dohan DM, Choukroun J, Diss A et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:37–4.
5. A. R. Pradeep, and M. S. Thorat, 'Clinical Effect of Subgingivally Delivered Simvastatin in, the Treatment of Patients with Chronic Periodontitis: A Randomized Clinical Trial', J Periodontol 81 (2010), 214-22.
6. A. Tawakol, Z. A. Fayad, R. Mogg, A. Alon, M. T. Klimas, H. Dansky, S. S. Subramanian, A. Abdelbaky, J. H. Rudd, M. E. Farkouh, I. O. Nunes, C. R. Beals, and S. S. Shankar, 'Intensification of Statin Therapy Results in a Rapid Reduction in Atherosclerotic Inflammation: Results of a Multicenter Fluorodeoxyglucose-Positron Emission Tomography/Computed TomographyFeasibility Study', J Am Coll Cardiol, 62 (2013), 909-17.
7. Dohan Choukroun J, Diss A et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:37–4. DM,
8. Q. Li, S. Pan, S. J. Dangaria, G. Gopinathan, A. Kolokythas, S. Chu, Y. Geng, Y. Zhou, and X. Luan, 'Platelet-Rich Fibrin Promotes Periodontal Regeneration and Enhances Alveolar Bone Augmentation', Biomed Res Int, 2013 (2013), ID 638043, 11 page
9. S. Prakash, and A. Thakur, 'Platelet Concentrates: Past, Present and Future', J Maxillofac Oral Surg, 10 (2011), 45-9.

10. Katzung BG (2007) Basic and clinical pharmacology, 9th Edn, Chapter 35, pp 796–99
11. Liao JK, Laufs U (2005) Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 45:89–118
12. Q. Li, S. Pan, S. J. Dangaria, G. Gopinathan, A. Kolokythas, S. Chu, Y. Geng, Y. Zhou, and X. Luan, 'Platelet-Rich Fibrin Promotes Periodontal Regeneration and Enhances Alveolar Bone Augmentation', Biomed Res Int, 2013 (2013), ID 638043, 11 page
13. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–7.]
14. Abeles AM, Pillinger MH. Statins as antiinflammatory and immunomodulatory agents: a future in rheumatologic therapy? Arthritis Rheum 2006;54:393–407.
15. Corsini A, Bellosta S, Baetta R, et al. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacol Ther 1999;84:413–28.
16. Gutierrez GE, Lalka D, Garrett IR, et al. Transdermal application of lovastatin to rats causes profound increases in bone formation and plasma concentrations. Osteoporos Int 2006;17:1033–42.
17. D. von Stechow, S. Fish, D. Yahalom, I. Bab, M. Chorev, R. Muller, and J. M. Alexander, 'Does Simvastatin Stimulate Bone Formation in Vivo?', BMC Musculoskelet Disord, 4 (2003), 8
18. Garcia de Paula-Silva FW, Hassan B, Bezerra da Silva LA, Leonardo MR, Wu M-K. Outcome of root canal treatment in dogs determined by periapical radiography and conebeam computed tomography scans. J Endod 2009;35: 723–726.
19. Ahlowalia MS, Patel S, Anwar HMS, et al. Accuracy of CBCT for volumetric measurement of simulated periapical lesions. Int Endod J 2013;46: 538–546
20. Ayukawa Y, Yasukawa E, Moriyama Y et al (2009) Local application of statin promotes bone repair through the suppression of osteoclasts and the enhancement of osteoblasts at bonehealing sites in rats. Oral Med Oral Pathol Oral Radiol Endod 107:336–342
21. Mouhamed ALM, Ismail Mouhamed A, Sadek H (2009) Evaluation of the outcome of adding biological modifier (simvastatin) to bone grafting material. Int J Oral Maxillofac Surg 38(5):455
22. Hassan S, Sadek H, Tantawi E (2011) Bone graft remodeling after ridge reconstruction with autogenous bone and statin. Int J Oral Maxillofac Surg 07(077):104.