Original Article

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Dentistry Section

Efficacy of Simvastatin versus Hydroxyapatite in the Regeneration of Periapical Bone Defects When used in Conjunction with PRF: A Prospective Interventional Study

KAVYA PINNAMANENI[1], ANITA D PARUSHETTI[2], CN SRINIVAS[3], AISHWARYA VENKAT[4], SUNNY PRIYATHAM TIRUPATHI[5], SNEHA M NAIR[6]

ABSTRACT

Introduction: The complete healing process for periapical bone defects involves a focused regenerative approach. Simvastatin (SIM), and Hydroxyapatite (HA) saturated PRF scaffold provides osteopromotive and anti-inflammatory properties, creating a predictable osteoconductive environment. Platelet-Rich Fibrin (PRF) also aids in regeneration through the sustained release of growth factors.

Aim: To evaluate and compare SIM and HA efficacy in bone regeneration of periapical defects when used in conjunction with PRF.

Materials and Methods: This 18-month prospective interventional study was conducted on 20 patients requiring apicoectomy (15-50 years of age) who reported to the Outpatient Department of Oral and Maxillofacial Surgery, Malla Reddy Institute of Dental Sciences, Hyderabad Telangana, India, from June 2022 to February 2024. Eligible subjects were randomised to Group-I (SIM+PRF; n=10) or Group-II (HA+PRF; n=10). The graft materials were placed into the defects after apicoectomy prior to suturing. The clinical parameters (pain, extraoral swelling, and signs of infection) were assessed on postoperative days 1, 3, 7, 15, and 30. Radiographic healing was monitored with Cone Beam Computed Tomography (CBCT) Periapical Index (PAI) scores at baseline, six months, and 12 months. Statistical analysis was performed using Analysis of Variance (ANOVA) ($p<0.05$).

Results: The study group comprised 10 males and 10 females, with an average age of 33.6 years in Group-I and 29.2 years in Group-II. No statistically significant differences were noted for any interval as measured by inter-group clinical parameters for pain, extraoral swelling, or evidence of infection such as pus discharge and sinus opening where, $p>0.05$. The average Visual Analogue Scale (VAS) scores on the 7th postoperative day were 0.6±0.69 for Group-I, and 0.8±0.78 for Group-II. Although Group-I showed more diminished infection markers and swelling, the differences were not statistically significant. Conversely, the findings of a radiographic analysis showed that for the 12-month CBCT-PAI, Group-I had a significantly better score than Group-II ($p=0.005$). There were seven cases classified as "healed" during final evaluations compared with six in Group-II.

Conclusion: The findings of the present study demonstrated that when compared to HA-augmented PRF, SIM-augmented PRF achieves significantly better and faster bone formation. SIM appears a novel and advantageous potential medicine for restoring bone healing within periapical defects.

Keywords: Apicoectomy, Bone substitutes, Cone beam computed tomography, Growth substances, Periapical diseases, Platelet-rich fibrin, Wound healing

INTRODUCTION

The periapical lesion results from a chronic inflammatory response to microorganisms around the tooth root and its apex. Periapical radiolucency is the most frequent radiologic sign of these lesions. Most periapical lesions heal after non surgical endodontic therapy. Endodontic failure means the recurrence of clinical symptoms along with the persistence of a periapical radiolucency. Mostly these lesions heal after simple endodontic therapy but sometimes they may require surgery along with regenerative therapy [1-5]. The success of traditional non surgical treatment with the standard technique reaches 91%, this rate ranges from 53% to 98% in cases, when it is carried out during the initial stage of pulpitis and the absence of periapical lesions [1]. In re-treatment cases with an apical lesion, this percentage decreases to 72% [2]. The literature data and histopathology show that only 10-15% of all apical lesions need surgical therapy in addition to non surgical [3].

Periapical surgery is aimed at the excision of periapical pathologies along with a with resection of a portion a root with anatomical complexities having undebrided canals and incomplete seal. However, it leaves a residual bone defect. This space must be grafted to maintain the hard and soft-tissue architecture and regenerate the lost bone. The rate of successful healing of periapical surgery has been reported to range from 60% to 91% [4-6]. Various materials used to fill the defect for better healing following surgery include autografts, xenografts, alloplasts and bioactive materials. Autografts have been considered the gold standard. However donor site morbidity and inadequate bone at the donor site have limited their use, this prompted the development and use of various alloplastic and regenerative materials [7]. In regenerative medicine, various anabolic drugs and platelet concentrates are being used for the repair of bony defects [7-9].

Statins {3-Hydroxy-3-Methylglutaryl coenzyme A (HMG CoA) reductase inhibitors} have been used in medicine as cholesterol-lowering agents to reduce cardiovascular disease and mortality. Oral administration of low-dose statin enhances the rate of bone formation by increasing the expression of the Bone Morphogenic Proteins-2 (BMP-2) gene and by reducing bone resorption markers. Its pleiotropic actions like vasodilative, antithrombotic, antioxidant, anti-inflammatory, and immune-modulatory effects have proven to be beneficial in other bone metabolic diseases [10]. SIM promotes

osteoblastic activity and inhibits osteoclastic activity and suggested to support BMP-induced osteoblast differentiation through antagonising TNF-α-to-Ras/Rho/mitogen-activated protein kinase and augmenting BMP-SMAD signalling. The mevalonate pathway plays a crucial role in bone metabolism. Bone regeneration following periapical surgery is an important event for long-term success [11-14].

Recent advances in regenerative endodontic surgery have focused on the use of bioactive materials and pharmacological agents to enhance bone healing following periapical surgery [2,6].

Platelet concentrates such as PRF have been extensively studied for their ability to release growth factors that enhance angiogenesis and accelerate osseous healing. HA remains one of the most widely used osteoconductive graft materials for managing periapical bone defects. SIM has demonstrated osteogenic potential through stimulation of osteoblastic differentiation and enhancement of bone formation. Although SIM, HA, and platelet concentrates have been evaluated individually for bone regeneration [8], there is a paucity of randomised clinical trials directly comparing the regenerative efficacy of SIM and HA when used in combination with PRF in periapical defects.

Based on these existing gaps in comparative clinical evidence, the present prospective interventional study was aimed to evaluate and compare the clinical and radiographic outcomes of SIM and HA used in conjunction with PRF for the management of periapical bone defects.

MATERIALS AND METHODS

A prospective interventional study was conducted from June 2022 to February 2024 on 20 patients indicated for apicoectomy who reported to the Outpatient Department of Oral and Maxillofacial Surgery, Malla Reddy Institute of Dental Sciences, Hyderabad, Telangana, India. The study protocol for the present study was approved by the Institutional Ethics Committee (IEC) (Approval number - IEC/MRIDS/3/2022).

Sample size calculation: The sample size was determined based on a power analysis conducted using G*Power software (version 3.1.9.7). Based on similar previous clinical trials evaluating the efficacy of SIM in periapical bone regeneration, an effect size (d) of 0.8 was anticipated for the primary outcome measure, the CBCT-PAI score. With the alpha level set at 0.05 and a desired statistical power of 80%, a minimum of 9 participants per group was required to detect a significant difference. To account for a potential 10% attrition rate or loss to follow-up, the final sample size was established at 20 patients (n=10 per group) [7,8].

Inclusion criteria: Systemically healthy patients aged 15-50 years of age of either gender, anterior teeth indicated for periapical surgery in the maxilla and mandible, failed Re-RCT cases with recurrent sinus tract and pus discharge, periapical radiolucency of diameter >5 mm and PAI scores of 4 and 5 on CBCT [9].

Exclusion criteria: Patients requiring re-apicoectomy, palatal perforations, pregnant and lactating females and patients having allergies or hypersensitivity to drugs specifically statins or HA, or on any systemic medication like bisphosphonates, chronic corticosteroid therapy, immunosuppressants, and Non Steroidal Anti-Inflammatory Drugs (NSAIDs) taken on a chronic basis that can affect the periapical healing.

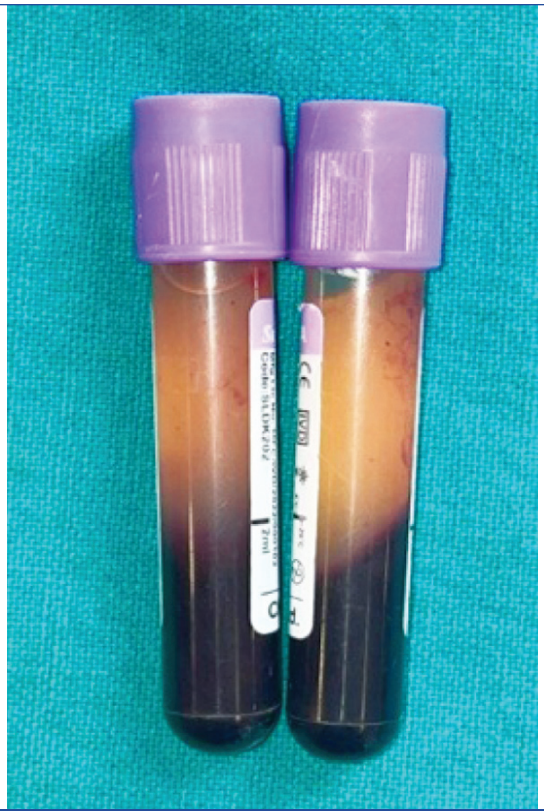
Participants were randomly allocated into two treatment groups using a simple randomisation method based on a lottery system. Due to the nature of the surgical procedures, operator blinding was not feasible and blinding was not performed. The sealed opaque chits indicating the treatment group were drawn for each participant prior to surgery.

- Group-I: SIM with PRF
- Group-II: HA with PRF.

Study Procedure

A CBCT-PAI scoring was performed according to the criteria described by Estrela C et al., [9]. Lesions were assessed using the CBCT measurement tools in three orthogonal dimensions - buccopalatal, mesiodistal, and diagonal planes. The largest linear measurement observed in any of the planes was used to determine the final CBCT-PAI score. All scans were evaluated using standardised viewing settings by a single calibrated examiner. The CBCT-PAI scoring system consisted of six scores (0-5): Score 0=intact periapical structures; Score 1=radiolucency 0.5-1.0 mm; Score 2=1-2 mm; Score 3=2-4 mm; Score 4=4-8 mm; Score 5=>8 mm. Additional parameters included, E – cortical bone expansion and D – cortical bone destruction.

Preparation of Platelet-Rich Fibrin (PRF): Before starting the surgical procedure, PRF was prepared 30 minutes before surgery by drawing 10 mL of venous blood collected from the patient's cubital fossa and was immediately transferred to test tubes without adding an anticoagulant and centrifuged at 3000 rpm for 10 min. At the end of the centrifugation, three layers were formed in the tube: Platelet-Poor Plasma (PPP) on the top, PRF clot in the middle, and RBCs at the bottom as shown in [Table/Fig-1].

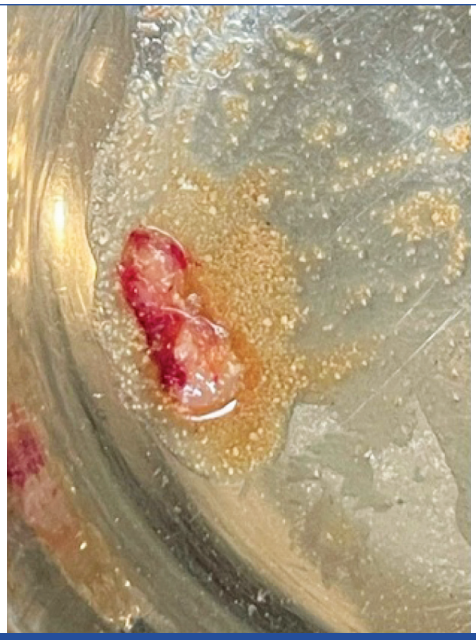


[Table/Fig-1]: PRF prepared in tubes.

The PRF layer was taken and mixed with SIM/HA to prepare a graft. The second PRF layer was then compressed to form a membrane which was used to cover the surgical site post-graft placement in both groups. The surgical technique was carried out using the conventional apicoectomy procedure with apical 3 mm root resection and retrograde filling. The periapical defect was filled with the graft.

Preparation of the Simvastatin (SIM) graft: SIM 10 mg (SIMVOTIN® 10, Sun Pharmaceutical Industries Ltd.) tablets were used. The outer coating was scraped off, and the tablets were then crushed into powder form. The SIM powder along with PRF as the carrier was moistened with normal saline was prepared and carefully packed in the bone defect taking care not to disturb the retro-filling [Table/Fig-2].

Preparation of Hydroxyapatite (HA) graft: Nano-crystalline HA bone graft (SYBOGRAF®) granules of 600-700 micrometres in size



[Table/Fig-2]: Simvastatin (SIM) graft.

were mixed with the PRF and placed into the bone cavity without disturbing the root-end filling [Table/Fig-3].

[Table/Fig-3]: Hydroxyapatite graft.

After placement of the respective bone graft material into the periapical defect, a PRF membrane was positioned over the surgical site. The mucoperiosteal flap was then repositioned and secured with sutures. Standard postoperative instructions were given to all patients. Sutures were removed on the seventh postoperative day. A therapeutic regimen consisting of amoxicillin 500 mg with clavulanic acid 125 mg three times daily for five days and a combination of aceclofenac 100 mg, paracetamol 325 mg, and serratiopeptidase 15 mg twice daily for five days was prescribed. Patients were also instructed to maintain oral hygiene using 0.2% chlorhexidine gluconate mouthwash twice daily for seven days.

Outcomes: Postoperative clinical assessment was performed at standardised follow-up intervals of 24 hours (Day 1), 72 hours (Day 3), 1 week (Day 7), 2 weeks (Day 15), and one month (Day 30).

- **Pain:** Postoperative pain was assessed at 24 hours, 72 hours, and one week using a 10 point Visual Analogue Scale (VAS), where 0 indicated no pain and 10 represented the worst imaginable pain. Patients were instructed to mark their perceived pain intensity at each follow-up visit.
- **Swelling:** Postoperative swelling was evaluated at 24 hours, 72 hours, and one week through both intraoral and extraoral clinical examination. Swelling was recorded as a binary variable (present/absent). Extraoral swelling was assessed by comparing the surgical side with the contralateral side to identify visible facial asymmetry, while intraoral swelling was determined based on clinical inspection of the surgical site.
- **Signs of Infection:** The surgical site was evaluated for the presence of pus discharge and sinus tract formation at one week, two weeks, and one month postoperatively. Findings were recorded as present or absent. Infection-related outcomes were not assessed separately at 72 hours, as early postoperative inflammatory changes may mimic infection and reliable clinical differentiation is typically established at later follow-up visits.

Evaluation of radiographic outcomes: CBCT scans were obtained at six and 12 months to evaluate periapical healing and bone regeneration. Radiographic findings were compared with preoperative scans to assess changes in lesion size and CBCT-PAI score. Treatment outcomes were categorised as healed, healing, or diseased based on the combined clinical and radiographic criteria described by Rud J and Molven JO and adapted for CBCT assessment by Estrela C et al., [9-11].

At the 6- and 12-month follow-up visits, teeth were classified as:

- **Healed:** Absence of clinical signs and symptoms with CBCT-PAI scores of 0-2 indicating normal or near-normal periapical structures.
- **Healing:** Absence of clinical symptoms with a reduction in lesion size and a decrease in CBCT-PAI score compared with baseline.
- **Diseased:** Presence of clinical signs/symptoms and/or CBCT-PAI score ≥3 with unchanged or increased lesion size.

The overall outcome was further evaluated, teeth classified as healed or healing at the 12th month were considered successful, and diseased teeth were considered unsuccessful.

STATISTICAL ANALYSIS

Data were collected according to the standard proforma and entered in MS Excel then was analysed using Statistical Package for the Social Sciences (SPSS) software version 25.0, with appropriate statistical tests: ANOVA test, Chi-square test. The $p<0.05$ was considered statistically significant.

RESULTS

A total of 20 patients (10 males and 10 females) in the age range of 15-50 years participated in the study. The mean age distribution was 33.6±7.14 years in Group-I and 29.2±8.44 years in Group-II, indicating comparable baseline age characteristics between the groups.

Gender distribution was 80% females and 20% males in Group-I and 80% males and 20% females in Group-II. All the patients underwent the periapical surgery of the anterior teeth in either of the arches. Over the healing period, all the graft materials were successfully incorporated into the bone without any complications and the periapical defects were successfully filled with the bone.

Clinical Assessment

Pain (VAS): In Group-I, the mean VAS score was 0.6±0.69 and in Group-II, the mean VAS score was 0.8±0.78 by 7th day. VAS score on the 7th postoperative day in both groups was less than 1 [Table/Fig-4].

Swelling: The presence of extraoral swelling in Group-I was less when compared to Group-II and was not statistically significant by 24 hour and 3rd day. It was absent by the 7th day in both groups [Table/Fig-5]. There was no presence of intraoral swelling in either of the groups.

Signs of infection: The presence of signs of infection was less in Group-I when compared to Group-II and was not statistically significant by the 7th and 15th days. By the end of the one month, there was a complete absence in both groups [Table/Fig-6].

VAS score	Groups	N	Mean	Std. Deviation	Z value	p-value
24 hr	I	10	8.0000	0.94281	-0.72	0.52
	II	10	8.3000	0.67495		
3rd day	I	10	4.6000	0.96609	-0.27	0.78
	II	10	4.7000	0.94868		
7th day	I	10	0.6000	0.69921	-0.57	0.56
	II	10	0.8000	0.78881		

[Table/Fig-4]: Mean comparison of VAS.
Mann-Whitney U test: p≤0.05 was considered statistically significant

Extraoral swelling			Groups I	Groups II	Chi-square	p-value
24 hr	Absent	n (%) within Group	5 (50)	7 (70)	0.83	0.36
	Present	n (%) within Group	5 (50)	3 (30)		
3rd day	Absent	n (%) within Group	7 (70)	8 (80)	0.26	0.60
	Present	n (%) within Group	3 (30)	2 (20)		
7th day	Absent	n (%) within Group	10 (100)	10 (100)	-	-
	Present	n (%) within Group	0	0		

[Table/Fig-5]: Extraoral swelling comparison.
Chi-square test: p≤0.05 was considered statistically significant

Signs of infection				Group I	Group II	Chi-square	p-value
Pus discharge	1 week	Absent	Count	7	6	0.22	0.63
			% within Group	70.0%	60.0%		
		Present	Count	3	4		
			% within Group	30.0%	40.0%		
	2 weeks	Absent	Count	10	8	2.22	0.13
			% within Group	100.0%	80.0%		
		Present	Count	0	2		
			% within Group	0.0%	20.0%		
	1 month	Absent	Count	10	10	-	-
			% within Group	100.0%	100.0%		
Sinus opening	1 week	Absent	Count	7	6	0.22	0.63
			% within Group	70.0%	60.0%		
		Present	Count	3	4		
			% within Group	30.0%	40.0%		
	2 weeks	Absent	Count	9	8	0.39	0.53
			% within Group	90.0%	80.0%		
		Present	Count	1	2		
			% within Group	10.0%	20.0%		
	1 month	Absent	Count	10	10	-	-
			% within Group	100.0%	100.0%		

[Table/Fig-6]: Signs of infection comparison.
Chi-square test: p≤0.05 was considered statistically significant

CBCT-PAI scoring: The CBCT scoring was significant in Group-I when compared to Group-II at preoperative and was highly significant at the end of the 12th month [Table/Fig-7].

CBCT-PAI scoring			Groups I	Groups II	Chi-square	p-value
Preoperative	4	n (%) within Group	5 (50)	0	8.44	0.03
	5	n (%) within Group	1 (10)	2 (20)		
	5+D	n (%) within Group	4 (40)	5 (50)		
	5+E	n (%) within Group	0	3 (30)		
6th month	1	n (%) within Group	3 (30)	1 (10)	2.00	0.36
	2	Count % within Group	6 (60)	6 (60)		
	3	n (%) within Group	1 (10)	3 (30)		
12th month	0	n (%) within Group	9 (90)	2 (20)	10.45	0.005
	1	n (%) within Group	0	5 (50)		
	2	n (%) within Group	1 (10)	3 (30)		

[Table/Fig-7]: Mean comparison of CBCT-PAI scoring.
Chi-square test; Significant at p<0.05; Highly significant at p<0.01

Radiographic outcomes: The final radiographic outcomes by the end of the 12th month show more healed outcomes in Group-I than in Group-II, and healing more in Group-II than in Group-I were insignificant [Table/Fig-8].

Final outcome		Groups I	Groups II	Chi-square	p-value
Healed	n (%) within Group	7 (70)	6 (60)	1.97	0.16
Healing	n (%) within Group	3 (30)	4 (40)		

[Table/Fig-8]: Radiographic outcomes.
Chi-square test: p≤0.05 was considered statistically significant

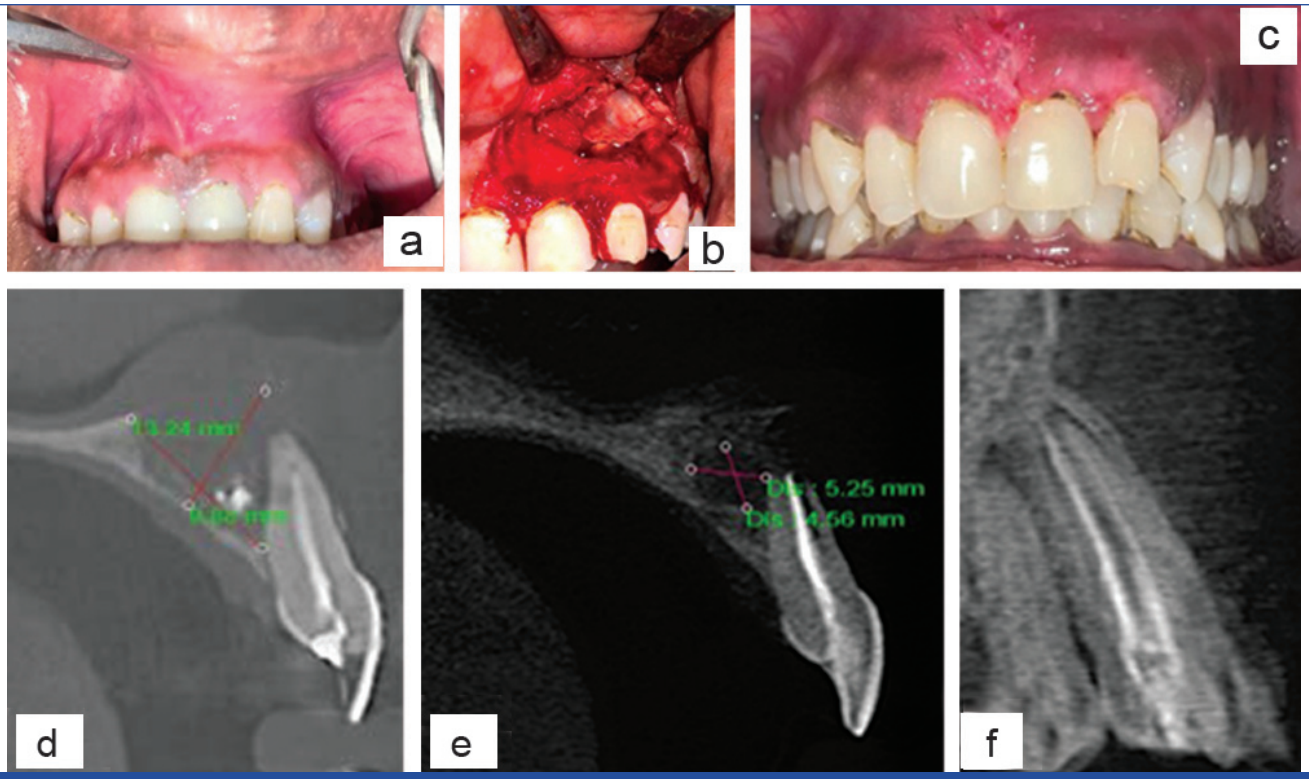
Representative clinical and radiographical images of Group-I and Group-II were shown in [Table/Fig-9a-f,10a-f], respectively.

DISCUSSION

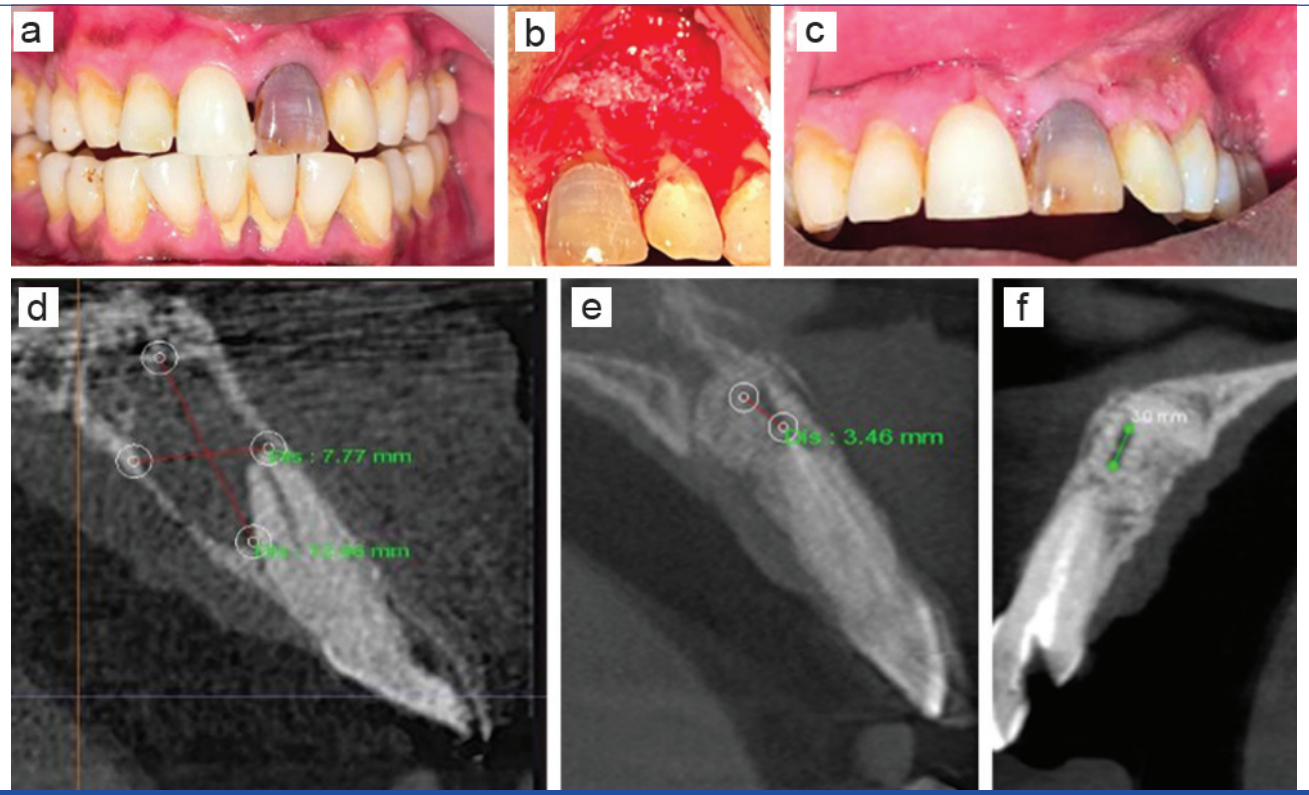
The present study demonstrates that while both SIM-saturated PRF and HA-PRF are clinically effective, the SIM-PRF combination yields a significantly accelerated rate of radiographic bone healing. The present findings show that Group-I (SIM+PRF) achieved a superior reduction in CBCT-PAI scores by the 12-month follow-up (p=0.005) compared to Group-II (HA+PRF). Clinically, both modalities proved successful with a 0% failure rate at one year; seven cases in Group-I and six cases in Group-II showed significant radiographic improvement. Although transient signs of infection (minor pus discharge) were noted at the 15-day postoperative interval with a lower incidence observed in the SIM group, these symptoms resolved completely by the end of the first month (p>0.05). This suggests that while early inflammatory responses are comparable, the osteogenic stimulus provided by SIM leads to more rapid and substantial defect resolution over time.

The present study findings regarding enhanced bone fill are strongly corroborated by the existing literature. Degala S and Bathija NA utilised CBCT imaging to demonstrate significantly higher bone density in SIM-treated sockets, with mean gray-scale values of 179.0 compared to 125.67 in controls (p<0.001) [12]. This mirrors the present observed CBCT-PAI score reductions and suggests a consistent pattern of increased mineralisation. Similarly, Saifi AM et al., reported a significantly higher percent increase in bone density at 16 weeks for the SIM group (p<0.001) [13].

The results of the present study are also consistent with Gupta S et al., who noted superior CBCT-PAI score reductions in SIM-treated groups compared to PRF or HA alone [8]. While Chauhan AS et al., evaluated extraction sockets rather than periapical defects, their report of significant improvements in bone density (p<0.001) reinforces the universal osteogenic potential of local SIM application across various oral osseous defects [14]. The accelerated radiographic healing observed in this study is strongly supported by Harsha G et al., who demonstrated that mean gray-level histogram values (bone density) were statistically highly significant



[Table/Fig-9]: a) Preoperative image (Group-I); b) Operative image (Group-I); c) Follow-up image (Group-I); d) Preoperative CBCT (Group-I); e) 6th month CBCT (Group-I); f) 12th month CBCT (Group-I).



[Table/Fig-10]: a) Preoperative image (Group-II); b) Operative image (Group-II); c) Follow-up image (Group-II); d) Preoperative CBCT (Group-II); e) 6th month CBCT (Group-II); f) 12th month CBCT (Group-II).

in SIM-treated third molar sockets compared to controls across all follow-up intervals ($p<0.05$), mirror the accelerated mineralisation pattern that was observed in periapical defects [15]. Sezavar M et al., stated that SIM improves the osteogenesis quality by increasing the percentages of vital bone than dead and nonosteoblastic bone [16]. In the present study, HA and SIM were combined with PRF which improved graft handling properties and stabilisation and its anti- inflammatory action.

A critical point of contrast in the present study is the carrier system. Degala S and Bathija NA and Saifi AM et al., utilised a gelatin sponge as a carrier [12,13]. While effective, local drug delivery via sponges can occasionally lead to variable infection rates. In contrast, the present protocol utilised PRF, which provides a more stable, biologically active scaffold. To address the requirement for contemporary evidence, the present results strongly align with Mahendra J et al., who demonstrated that PRF serves as an ideal biological reservoir for SIM, ensuring sustained release while maintaining cell viability [17]. Furthermore, Aminov A et al., confirms that local SIM application yields higher CBCT-PAI score reductions compared to traditional scaffolds, mirroring the 12-month data [18]. Although Chmielewski M et al., emphasised the role of PRF primarily in soft-tissue healing, the present data demonstrates a clear hard-

tissue regenerative advantage when SIM is integrated into the fibrin matrix (p=0.005) [19]. This synergy is likely due to the simultaneous induction of BMP-2 expression by SIM and the sustained release of autologous growth factors from the PRF matrix, which together enhance angiogenesis and rapid mineralisation [20-22].

Limitation(s)

To the best of the authors' knowledge, the present study represents the first investigation into the clinical and radiographic outcomes of local SIM application combined with PRF for managing endodontically-associated osseous defects post-periapical surgery. However, several limitations must be acknowledged. The relatively small sample size may limit the generalisability of the findings to a broader population. While 12 months provided significant data, physiological bone regeneration is a protracted process that can extend beyond four years. Consequently, the long-term stability and complete remodelling of the regenerated bone could not be assessed within this timeframe. As a single-centre study, the results may be influenced by specific Institutional protocols. The absence of histological correlation further limits the ability to assess the qualitative nature of the newly formed bone.

Future multicentric Randomised Controlled Trials (RCTs) with larger cohorts and extended longitudinal follow-ups (3-5 years) are essential to establish definitive protocols for both hard and soft-tissue regeneration and to validate these results on a larger scale.

CONCLUSION(S)

Within the limits of the study, SIM with PRF is a superior therapeutic option for enhancing periapical bone regeneration and soft-tissue healing compared to HA-PRF. It achieved significantly better radiographic "healed-than-healing" outcomes and reduced postoperative discomfort. While promising, long-term longitudinal studies are essential to establish this biologically active protocol as a standard of care for complex periapical defects.

Authors' contributions: All authors have made a substantial contribution to the present study and/or manuscript, and all have reviewed the final paper prior to its submission.

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PARTICULARS OF CONTRIBUTORS:

1. Postgraduate Student, Department of Oral and Maxillofacial Surgery, Malla Reddy Institute of Dental Sciences, Malla Reddy Vishwavidyapeeth (Deemed to be University), Suraram, Hyderabad, Telangana, India.
2. Professor, Department of Oral and Maxillofacial Surgery, Malla Reddy Institute of Dental Sciences, Malla Reddy Vishwavidyapeeth (Deemed to be University), Suraram, Hyderabad, Telangana, India.
3. Professor and Head, Department of Oral and Maxillofacial Surgery, Malla Reddy Institute of Dental Sciences, Malla Reddy Vishwavidyapeeth (Deemed to be University), Suraram, Hyderabad, Telangana, India.
4. Postgraduate Student, Department of Oral and Maxillofacial Surgery, Malla Reddy Institute of Dental Sciences, Malla Reddy Vishwavidyapeeth (Deemed to be University), Suraram, Hyderabad, Telangana, India.
5. Associate Professor, Department of Pedodontics and Preventive Dentistry, Saveetha Dental College and Hospital, Saveetha Institute of Medical Sciences (SIMATS), Chennai, Tamil Nadu, India.
6. Paediatric Dentist, Private Practice, Pune, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sunny Priyatham Tirupathi,
Associate Professor, Department of Pedodontics and Preventive Dentistry, Saveetha Dental College and Hospital, Saveetha Institute of Medical Sciences (SIMATS), Saveetha University, Chennai-600077, Tamil Nadu, India.
E-mail: dr.priyatham@gmail.com

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