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Original Research

Evaluating the therapeutic potential of atorvastatin and rosuvastatin gels in intrabony defects in chronic periodontitis: A comparative study

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ABSTRACT:
Background: Statins are the formidable inhibitor of 3-hydroxy-2-methyl-glutaryl coenzyme A reductase and known to inhibit osteoclastic resorption of bone. Present study was conducted with an aim to evaluate and compare the efficacy of two formulations: 1.2% ATV gel (Atorvastatin) and 1.2% RSV gel (Rosuvastatin) as a local drug-delivery system in conjunction with scaling and root planning (SRP) for the treatment of intrabony defects (IBD) in chronic periodontitis patients. **Methods**: A total of 92 individuals with periodontitis were screened, of which 11 patients with at least one pair of IBD were randomly selected as study subjects. These subjects were divided into two groups and assigned treatment with scaling and root planning (SRP) followed by subgingival local drug delivery (LDD). Group I received of 1.2% ATV gel whereas group II received 1.2% RSV gel. Clinical parameters evaluated were Plaque Index (PI), modified sulcular bleeding index (mSBI), Probing pocket depth (PPD) and relative clinical attachment level (RCAL) were evaluated at baseline, and at interval of 3 and 6 months. Radiographic parameter included filling of IBD evaluated at baseline and after 6 months using Cone-beam Computed Topography (CBCT). **Results:** Both the groups showed a significant improvement clinically and radiographically. A greater reduction in the mean PPD and gain in RCAL was observed in group II compared to group I at 3 months and 6 months. Furthermore, group II achieved a significantly greater bone fill (38.83%) compared to group I (19.53%) at 6 months. **Conclusion:** 1.2% RSV gel showed enhanced periodontal regeneration as compared to 1.2% ATV gel as an adjunct to SRP in treatment of IBD.
Keywords: Periodontal Disease(s)/Periodontitis, Regenerative medicine, Bone Remodeling/Regeneration, Drug Delivery, Bone Biology, Pharmacology

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INTRODUCTION

Periodontitis is a multifactorial disease of microbial origin, primarily affecting the supporting structures of teeth, accompanied by attachment loss and, lastly, alveolar bone destruction. Related to multiple complex microbial interactions, host response, genetic, and other modifying factors, it exhibits a wide range of pathological manifestations. [1] The progression of periodontitis is featured by increased pocket probing depth, increased RANKL activity leading to alveolar bone loss, and the formation of Intrabony defects (IBDs), which, if left untreated, may lead to tooth loss. [2]

The ultimate goal of periodontal therapy is periodontal regeneration, which necessitates the reconstruction of damaged elements in order to return the periodontium to its original anatomical and physiological state. The use of low-cost pharmacologic substances that induce the host to yield autogenous growth factors is a cost-effective approach for the treatment of osseous anomalies.[3] Various regenerative materials have been used including bone grafts, growth factors, statins, bisphosphonates, and platelet analogues like platelet rich fibrin (PRF) to achieve reduction in IBD depth.

Statins were first introduced as cholesterol-lowering drugs by inhibiting 3-hydroxy-3-methylglutaryl

coenzyme A reductase, interfering with the cholesterol synthesis process in the liver, which lowers cholesterol and further decreases the incidence of cardiovascular disease. In addition to their ability to decrease cholesterol, statins have also been linked to anti-inflammatory, antioxidative effects, antimicrobial activity, and pleiotropic traits, such as blocking the production of pro-inflammatory mediators and matrix metalloproteinases (MMP). [4] During the early and middle stages of osteoblast cell culture, statins enhance BMP-2 gene expression and encourage osteoblast development. This increases the synthesis and secretion of a wide spectrum of factors and matrix proteins related to osteoblast differentiation, ultimately stimulating mineralization via inhibition of the cholesterol synthesis pathway. [5]

Atorvastatin (ATV) and Rosuvastatin (RSV) have been found to stimulate improvements in periodontal clinical and radiographic parameters in patients with IBDs. [6] Cone Beam Computed Tomography (CBCT) is one of the more sophisticated and accurate methods for assessing periodontal regeneration; however, few studies have taken advantage of CBCT to measure regeneration. [7-9] The need to achieve and assess regeneration non-invasively and cost-effectively prompted us to design the current clinical study to evaluate and compare the efficacy of 1.2% ATV gel to 1.2% RSV gel as an adjunct to SRP in the treatment of periodontal IBDs clinically and radiographically, using CBCT.

MATERIALS AND METHODS

Study design and sample

To address the research purpose, the investigators designed and implemented a prospective split-mouth, single blinded clinical study. The study population consisted of all patients who sought treatment for periodontitis at the outpatient department of Periodontology at AMC Dental College and Hospital, Ahmedabad, India from December 2020 to June 2022.

To be included in the study, the following were the inclusion criteria:

1) Patient aged 30-55 years of either gender who fall into ASA I category as per the American Society of Anesthesiologist.
2) Patients with Pocket probing depth (PPD) between 5-8 mm and RCAL ≥ 4mm.
3) Intrabony Defect (IBD) ≥3 mm on CBCT radiographs.

The exclusion criteria included:

1) Patients with history of subgingival antimicrobial within 6 months prior to study.
2) Patients already receiving systemic statin therapy.
3) Endodontically treated teeth.
4) Patients who are smokers and tobacco or substance abusers.
5) Pregnant or lactating female patients.

Ethical approval was obtained priorly from the Institutional Ethics Committee (No. AMC/IEC/PERIO/PG65/21) and was conducted in accordance with guidelines provided by World Medical Association's Declaration of Helsinki(1964) and its seventh amendment (2013). Patients who voluntarily participated in the study and agreed to adhere the study protocols were selected and were informed about possible risks and benefits of the study, with duly signed informed consent forms.

Randomization, blinding, and study groups

Randomization was conducted to ensure unbiased allocation of participants to the study groups. The block randomization method was employed to create two study groups Group I and Group II, for this split-mouth study. Blinding was implemented to minimize the potential bias. The blinding was single blinded, where the administration of thegel for the Local Drug Delivery (LDD) was carried out by a third person not directly involved in the surgery or postoperative visits. This approach ensured that the assessors evaluating clinical parameters were unaware of which gel (1.2% ATV or 1.2% RSV) was used at each site. Out of 92 subjects screen initially, the final study sample consisted of 11 patients with total of 48 IBD sites. These 48 sites were divided into two groups. Group I received 1.2% ATV gel, whereas, group II received 1.2% RSV gel as part of this split mouth study.(Figure 1)

Surgical protocols

Preparation of LDD Gel: Statin gels were prepared at Department of Pharmaceutics and Pharm Technology, L.M. College of Pharmacy, Ahmedabad, India by adding 2.5 g of methylcellulose to 100 g of grade water slowly and stirring continuously to attain the gel consistency. Once this was prepared, 1.2 g of Atorvastatin/Rosuvastatin was added slowly with continuous stirring to get the preparation. 1.2% Atorvastatin Gel and 1.2% Rosuvastatin gel were packed in sterile tube container of 5 grams each.

Stent Fabrication: A sterile, perforated stock metal impression tray was selected for each patient. An irreversible hydrocolloid impression material (alginate) was utilized for to get maxillary and mandibular impressions from which study casts were prepared for each patient. A customized acrylic occlusal stent was fabricated from this cast to fit over the selected sites. A groove (guide plane) was made on the stent in relation to each involved tooth to guide the periodontal probe while taking measurements. This technique provided a fixed point and angulation for measurements with the probe at each site.

Surgical procedure: At BL visit, full mouth scaling and root planing (SRP) was performed using ultrasonic instruments followed by hand instruments until all supra and subgingival root surfaces felt hard and smooth. No time restriction was instituted for this treatment. The recording of all the parameters at the baseline were taken on the day of therapy. Local Drug Delivery of 0.1 ml of 1.2 % ATV gel/ 1.2% RSV gel

into periodontal pocket using blunt cannula syringe (26 gauge) was done after scaling and root planing. To ensure retention of the gel for long duration to be effective in the pocket, a periodontal dressing (Coe-Pak) was placed. All patients received same post-operative instructions and no mouthwashes were prescribed after treatment. Clinical parameters were evaluated at end of 3 months and end of 6 months whereas radiographic parameter was evaluated at the end of 6 months. At all follow-up visits, supragingival deposits were removed and adverse effects, if any were noted. (Figure2)

Data collection method

Clinical evaluation: Full mouth Plaque index [10], Modified Sulcus bleeding index [11], Pocket Probing Depth and Relative clinical attachment level scores were evaluated at baseline, 3 months and 6 months. Use of a University of North Carolina no.15 (UNC-15) color-coded periodontal probe and a custom-made acrylic stent was done for PPD and RCAL measurements standardization.

Radiographic Evaluation: CBCT (Newtom GiANO HR) was used to measure the intraosseous defect sites at baseline and after 6 months. This incorporated the measurement of the bone defect height [CEJ–BD (base of the defect)], the level of the alveolar crest [CEJ–AC (alveolar crest)], the bone defect depth (A line perpendicular was drawn from the AC to the root surface, and the intersection point across the root surface was considered as AC. The distance from the point AC to the base of the defect (AC–BD) was considered as the intraosseous defect depth. A Slice thickness of 0.2 mm was used for radiographic analysis.

Statistical Analysis

The sample size was estimated to be 24 per group in this prospective study to achieve statistical power of 80%, mean difference of 0.5 mm in clinical and radiographic parameters with pooled standard deviation (SD) = 0.6 and at significance level of 0.05. The collected data were entered into a Microsoft Excel spreadsheet and analyzed statistically using Statistical Package for Social Sciences (SPSS version 22.0, IBM Corporation, USA) for MS Windows. All the continuous variables were expressed as mean and standard deviation (SD). The Shapiro-Wilk test was used to check the normality of the continuous variables. All the categorical variables were expressed as numbers and percentages. Independent sample's t-test and paired sample t- test were used for both intergroup and intragroup comparison of clinical and radiographic parameters. To assess the level of significance between the groups, a p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Clinical Parameters

Out of 92 patients of chronic generalized periodontitis screen for IBD initially, the final study sample consisted of 11 patients with total of 48 IBD sites. Among them, 6 (54.54%) were male, and 5 (45.45%) were female. The mean age of the males was 39.83 ± 7.25 years and that of females was 32.6 ± 9.28 years. The male: female ratio was 6:5. Out of total 48 IBDs, 26 (54.16%) and 22 (45.83%) was present in male and female respectively. These 48 sites were divided into two groups of 24 each. (TableI)

In the present study, there was statistically significant reduction ($p \leq 0.05$) in Pl and mSBI scores from baseline to 3 months and 6 months in intragroup comparison. There was no statistically significant reduction ($p \geq 0.05$) in PI and mSBI scores in intergroup comparison between group I and Group II at BL, 3 months and 6 months. (TableII)

For PPD and RCAL values, there was statistically significant reduction from BL to 3 months and 6 months in both the groups on intragroup comparison. On intergroup comparison, PPD score reduction was statistically significant($p \leq 0.05$) in favor of RSV group. PPD values at baseline, 3 months and 6 months for ATV group were 6.7 ± 0.57 mm, 5.8 ± 0.55 mm and 5.08 ± 0.65 mm respectively. PPD values for RSV group at baseline, 3 months and 6 months were 6.69 ± 0.56 mm, 5.40 ± 0.60 mm and 4.40 ± 0.44 mm respectively. The mean reduction in RCAL in group I from BL to 3 months was 0.99 mm and at 6 months was 1.92 mm, whereas in group II mean reduction in RCAL from BL to 3 months was 1.30 mm and at 6 months was 2.29 mm showing statistically significant value in favor of group II. (TableII)

Radiographic Parameters

Defect depth reduction in ATV group from BL (4.91 ± 0.53) to 6 months (3.96 ± 0.54) was 0.95 mm, whereas for RSV group defect depth reduction from BL (5.05 ± 0.47) to 6 months (3.08 ± 0.48) was 1.97 mm, which was significantly greater in group II (TableIII). Means bone gain was significantly higher in RSV group (38.88%) as compared to ATV group (19.53%). (Figure3)

Table I: Distribution of study subjects based on age, gender and intra bony defects (IBDs).

Gender	N		%	Mean Age	IBD		Mean IBD	%
Male	11	6	54.54%	39.83 ± 7.25	48	26	4.33	54.16%
Female		5	45.45%	32.6 ± 9.28		22	4.4	45.83%

Descriptive statistics applied

Table II: Inter and intra group comparison of different clinical parameters at different time interval.

Variable	Groups	BL	3 Mo	6 Mo	*P* value‡
PI	**I (ATV)**	2.27 ± 0.26	1.79 ± 0.35	1.47 ± 0.27	0.001
	II (RSV)	2.35 ± 0.27	1.75 ± 0.35	1.46 ± 0.34	0.001
	***P* value†**	0.311	0.717	0.79	
mSBI	**I (ATV)**	2.29 ± 0.62	1.58 ± 0.58	1.00 ± 0.58	0.001
	II (RSV)	2.45 ± 0.58	1.62 ± 0.49	1.25 ± 0.60	0.001
	***P* value†**	0.346	0.791	0.155	
PPD	**I (ATV)**	6.70 ± 0.57	5.86 ± 0.55	5.08 ± 0.65	0.001
	II (RSV)	6.69 ± 0.56	5.40 ± 0.60	4.40 ± 0.44	0.001
	***P* value†**	0.96	0.001	0.001	
RCAL	**I (ATV)**	8.66 ± 0.39	7.67 ± 0.52	6.74± 0.56	0.001
	II (RSV)	8.60 ± 0.37	7.30 ± 0.32	6.31 ± 0.40	0.001
	***P* value†**	0.891	0.001	0.001	

†Independent sample t-test
‡Paired sample t-test
Level of Significance: $p \leq 0.05$, Statistically Significant
$p \geq 0.05$ Statistically Non -Significant

Table III: Inter and intra group comparison of radiographic parameter at different time interval

Variable	RBF		
Visits	**Groups**		***P* Value‡**
	I (ATV)	**II (RSV)**	
BL	4.91 ± 0.53	5.05 ± 0.47	0.38
6 Mo	3.96 ± 0.54	3.08 ± 0.48	0.002
Mean Difference	0.95	1.97	
***P* Value†**	0.001	0.001	

†Independent sample t-test
‡Paired sample t-test/ Repeated Measures ANOVA test
Level of Significance: $p \leq 0.05$, Statistically Significant
$p \geq 0.05$ Statistically Non –Significant

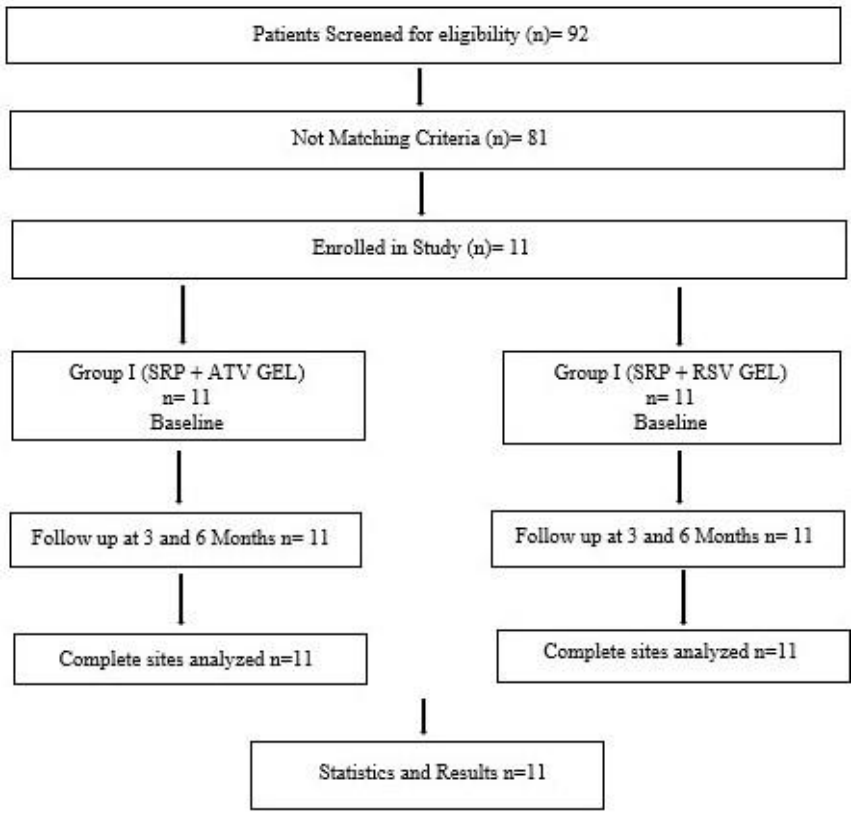

Figure 1: Flow chart demonstrating the randomization process adopted in the present study.

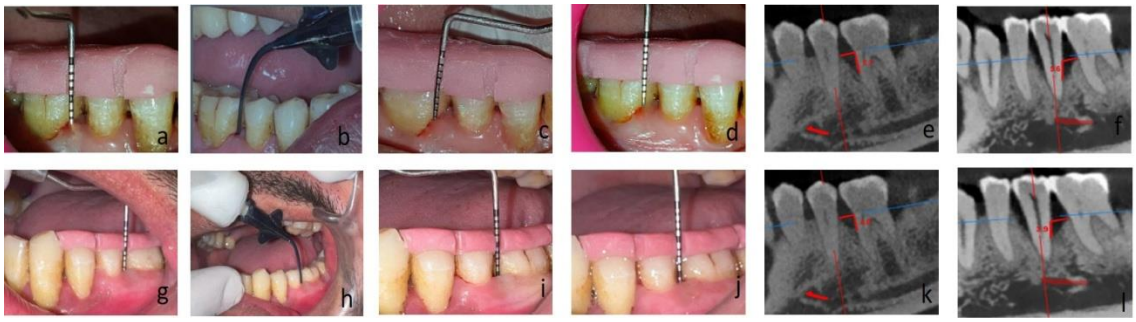

Figure 2: Comparison of PPD and RDD at baseline, 3 mo and 6 mo between group I and II. (a) PPD at baseline in group I (b) Subgingival delivery of ATV gel (c) PPD at 3 mo in group I (d) PPD at 6 mo in group I (e) RDD at baseline in group I (f) RDD at 6 mo in group I (g) PPD at baseline in group II (h) Subgingival delivery of RSV gel (i) PPD at 3 mo in group II (j) PPD at 6 mo in group II (k) RDD at baseline in group II (l) RDD at 6 mo in group II.

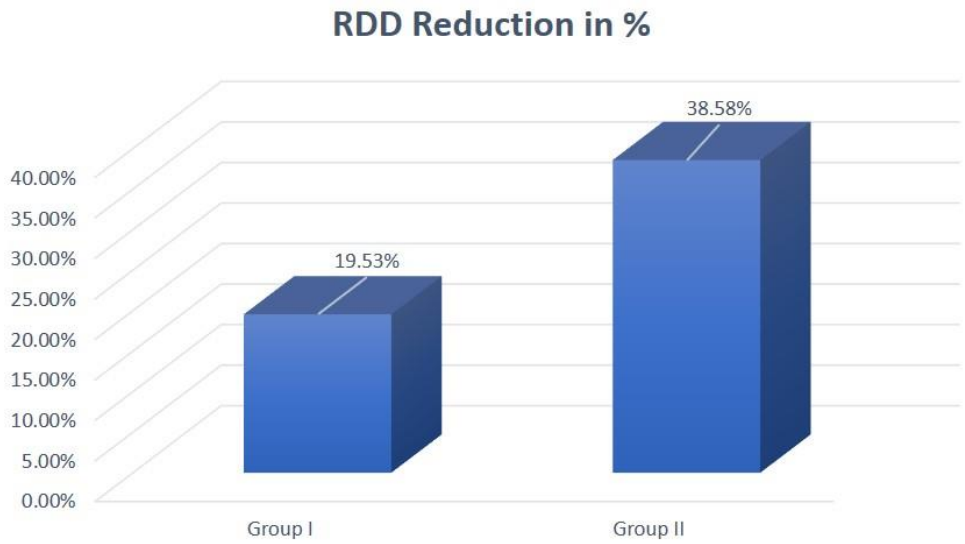

Figure 3: Intergroup comparison of RDD reduction in %.

DISCUSSION

Advances in periodontal healthcare encourage exploring methods beyond traditional surgery and non-surgical approaches. The contemporary therapeutic approach aims to resolve inflammation, infections, and restore lost anatomical structures for overall health. Some biological substances like Fibroblast Growth Factor (FGF) [12] and Bone Morphogenetic Protein-2 (BMP-2) [13] stimulate bone growth. However, their use has drawbacks like degradation and immune responses. Regenerative materials such as bone grafts, growth factors, statins, bisphosphonates, and platelet-rich fibrin (PRF) reduce intra-bony defect (IBD) depth.

"Statins" are medications that lower blood cholesterol by reducing liver production through HMG CoA reductase inhibition. Apart from lipid reduction, they offer anti-inflammatory, immune-modulatory, and antibacterial effects, potentially aiding bone healing-related infections. Statins also promote osteoblast differentiation, mineralization, and the expression of bone growth factors like vascular endothelial growth factor and BMP-2. Due to similarities with bisphosphonates in targeting the mevalonate pathway, statins could impact osteoclasts similarly. These versatile effects position statins as potential new agents in periodontics. [14]

No study to date has compared the effects of subgingivally delivered 1.2% ATV Gel and 1.2% RSV Gel using cone-beam computed tomography (CBCT). This study investigates these gels in intraosseous defects in chronic periodontitis patients.

Local delivery was, chosen over systemic administration for the following reasons: 1) Avoiding systemic adverse effects of statins such as diarrhea, dyspepsia, arthralgia, myalgia, nausea, rash, alopecia etc. [15] 2) To maintain the drug concentration higher than that achieved by systemic administration.[16] 3) Statin when administered in the prodrug form, is more lipophilic than the active beta-hydroxy acid form and can effectively cross cellular membrane barriers by passive diffusion. Clinical studies evaluating low-dose systemic statin administration as adjunct to SRP have failed to demonstrate any significant additional benefit for the statin groups, neither on clinical periodontal parameters nor on inflammatory and bone

metabolism markers,[17] while in a clinical study assessing the effect of daily systemic administration of 10 mg vs 80 mg of ATV, only the high-dose group showed a significant reduction in periodontal inflammation.[18] Furthermore, although several of the included studies have shown an improved effect on alveolar bone levels after administration of higher statin doses (i.e., mostly ≥10 mg/kg/d).

In both groups, there was a decline in PI scores at 3 and 6 months, indicating improved oral hygiene habits and reduced plaque accumulation. Additionally, statins exhibit antimicrobial effects [19], contributing to increased bacterial clearance from the infection site, consistent with previous studies by Pradeep et al. (2013) [20] and Garg et al. (2017) [21] on statin local delivery in periodontitis treatment.

The reduction in the bleeding index scores in both groups can be attributed to the anti-inflammatory effect of statins. Studies have shown that atorvastatin at doses higher than those required for cholesterol lowering, decrease basal and IL-1ß-induced plasma human C-Reactive Protein levels, a proinflammatory marker produced in liver inducing release of IL-1, IL-6, and tumor necrosis factor by macrophages.[22] Furthermore, statins affect the production of interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and chemotaxis in adherent human monocytes, signifying their anti-inflammatory action.

Periodontal pocket depth (PPD) is a critical indicator of periodontal disease progression and treatment success. The reduction in PPD depth after treatment is primarily due to inflammation reduction and pocket wall shrinkage. Intergroup comparison favored the RSV group, possibly due to RSV's hydrophilicity and longer elimination half-life. The majority of statins have shown to potently block the expression of MMP-1, MMP-8, and MMP-9 induced by LPS in mononuclear cells in vitro. Production of NADPH oxidase, which is a major source of oxidant production is inhibited by statins. [23] Reduction in PPD in our study can be corelated with the study done by Subramanian et al (2013) [24] and Ambrosio et al (2018) [25], showing a reduction of PPD at 6 months in healthy, smoking and diabetic patients.

An important clinical outcome of a periodontal treatment is gain of clinical attachment level, having the advantage of being a more realistic representation of attachment gain or loss than PPD, as they are not influenced by the gingival margin changes. Both ATV and RSV formulations significantly enhanced periodontal tissue repair and regeneration, evidenced by decreased RCAL values. Statins have shown to significantly increase Osteoblast differentiation factors such as alkaline phosphatase (ALP), osteocalcin (OCN), bone sialoprotein (BSP), BMP-2, osteopontin (OPN), and vascular endothelial growth factor (VEGF); all these factors help in regeneration which can be evaluated clinically by gain in attachment apparatus. [26]

Radiographic parameter evaluated by conventional IOPA (Intraoral periapical view) radiography technique has been used in most of the past studies. With the advent of technology today we have CBCT, which is easily available modality for accurate diagnosis and treatment planing for most of the periodontal defects. The difference in the mean RDD at 6 months from BL can be denoted as RDD gain. The percentage of RDD gain was the difference of the RDD at BL and at 6 months to the BL i.e. [(RDD 0-RDD 6) /RDD 0] %. The mean percentage RDD gain was 19.53% ± 0.10 for Group I and 37% ± 0.15. This can be attributed to the effects of statins on several pathways involved in bone metabolism. Statins decrease osteoclastogenesis via RANK/RANKL and NFkB signaling. Statins promote osteogenesis by increasing VEGF. BMP2 and TGF-β expression through the PI3-Akt pathway.

The significance of some clinical benefits with RSV over ATV can be attributed to higher anti-inflammatory action and greater reduction in CRP levels with RSV as compared to ATV. RSV has also been found to be superior to ATV in the reversion of coronary artery disease (CAD) and in reduction of small dense LDLs. [27] The overpowering effects of adjunctive RSV LDD over ATV LDD, as per our study, can be effectively utilized to influence statin selection for periodontal treatment. However, further multicentric interventional trials are needed to conclusively validate this superiority of RSV over ATV. In these studies, the defect fill was evaluated on digital radiographs by software using an image analyzer. On the contrary, our study used CBCT, which offers better visualization of the bone defect and has higher accuracy than any other radio-graphic image modality. Better defect visualization and preoperative treatment decision-making are made possible by the utilization of CBCT. In our study, the regeneration therapy of intraosseous defects was carried out non-surgically using LDD and evaluation of the regeneration was carried out after 6 months by the CBCT and, a surgical re-entry procedure was not made.

Within the confines of our study, it can be concluded that adjunctive subgingival administration of statins is superior to mechanical periodontal therapy alone in treatment of intrabony defects, with 1.2% RSV gel showing statistically superior clinical and radiographical results as compared to 1.2% ATV gel.

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Conflict of Interest: None

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