Original Article

Clinical efficacy of subgingivally delivered simvastatin gel in chronic periodontitis patients

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Abstract:

Background: Simvastatin (SMV), a new locally delivered drug of class statins, is a specific competitive inhibitor of 3-hydroxy-2-methyl-glutaryl coenzyme A reductase. Statins, besides having lipid-lowering abilities, also have pleiotropic effects like host modulation and bone regeneration. The present study was designed to investigate the effectiveness of SMV, 1.2 mg, in an indigenously prepared biodegradable controlled-release gel as an adjunct to scaling and root planing (SRP). **Materials and Methods:** A total of 60 sites, with pocket depth ≥5 mm, two from each of 30 patients after SRP, were categorized into two treatment groups, for subgingival placement of placebo (Gp 1) or SMV (Gp 2). Clinical parameters were recorded at baseline and at 1, 3 and 6 months comprising plaque index, gingival index, probing pocket depth (PPD) and clinical attachment level (CAL). The osseous changes were evaluated radiographically by measuring vertical gain, INFRA 1 and angle of the defect, INFRA 2 from baseline to 6 months. **Results:** All subjects tolerated the drug, without any post-application complication. The treatment improved the periodontal condition in both the groups but significant reductions in PPD (p= 0.04), and INFRA 1 (p= 0.000), along with gain in CAL (p= 0.02) and INFRA 2 (p= 0.000) were observed in Gp 2. In one site, an unexpected 5 mm decrease in INFRA 1 was found. **Conclusion:** Local drug delivery of SMV enhanced the beneficial effect of SRP, in pocket reduction, gain in CAL and bone fill.

Key words:

Chronic periodontitis, INFRA 2, INFRA 1, periodontal regeneration, simvastatin, subgingival drug delivery

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INTRODUCTION

Scaling and root planing (SRP) is the gold standard, but this mechanical debridement alone may fail to eliminate the putative pathogens from the pockets completely because of the invasion of these organisms within the gingival tissue or in deeper areas inaccessible to periodontal instrumentations and thus, results in recurrence of periodontal disease. Therefore, the selective removal or inhibition of pathogenic microbes with systemic or locally delivered antimicrobial and host modulating agents, in combination with SRP, is often considered as an effective approach at specific disease active sites.[1,2]

Various local delivery methods for administering chemotherapeutic agents, directly into the periodontal pockets, have been tested. These methods minimize the total dosage and resulting side effects and also maintain therapeutic drug levels in the gingival crevicular fluid over an extended period securing their therapeutic effects for a prolonged period of time.[3-8]

The use of inexpensive pharmacologic compounds to stimulate the host to produce autogenous bone growth factors such as BMP-2 could be a cost-effective, nonsurgical alternative to treat osseous defects. Statins such as simvastatin (SMV), lovastatin, and pravastatin are specific competitive inhibitors of 3-hydroxy-2-methyl-glutaryl coenzyme A reductase[9] and are widely used to lower cholesterol in the treatment of hyperlipidemia and arteriosclerosis.[10] SMV, an off-patent drug, used traditionally as a cholesterol-lowering medication and has recently been used as a craniofacial bone anabolic agent. It blocks the production of mevalonate, and its downstream products inhibit protein prenylation of geranylgeranyl-PP and farnesyl-PP. It seems to decrease osteoclast numbers, enhance alkaline phosphatase activity, and mineralization; increase sialoprotein, osteocalcin, type I collagen, and vascular endothelial growth factor; and decrease the production of interleukin-6 showing

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anti-inflammatory effect.[11-13] It also exhibits a positive effect on osteoblastic proliferation and differentiation of human periodontal ligament cells. These effects may be caused by the inhibition of the mevalonate pathway.[12,14] Pradeep and Thorat have analyzed the bioavailability and degradability of 1.2 mg of SMV gel in detail.[14] Hence, the subgingival drug delivery of SMV can produce advantages of achieving high intrasulcular drug concentrations, simultaneously avoiding its systemic side effects.

In this background, the present study was designed to evaluate the effectiveness of SMV, 1.2 mg, in an indigenously prepared biodegradable controlled-release gel, as an adjunct to SRP, comparing it with a placebo gel.

MATERIALS AND METHODS

A prospective, interventional, and randomized controlled trial with split-mouth design was planned. Approval was obtained from the Ethical Committee of the institute (reference number - KDCRC/ETH/Perio/2011/01). The cases were selected from the outpatient Department of Periodontology of the institute. After a detailed explanation of the procedures, written consents were obtained from the participants. The sample size was calculated with the help of a statistician. A total of sixty sites, two from each of thirty patients comprising both sexes, aged between 25 and 50 years completed the study. There was 11 drop-out of cases in the study.

Patients with definite clinical evidence of periodontitis, according to American Dental Association classification criteria 1999,[15] having at least two periodontal pockets of ≥5 mm on contralateral sides irrespective of single or multirooted teeth, having a minimum of twenty natural teeth, and normal lipid profile level were included in the study. Patients on systemic lipid lowering medication, smokers, pregnant women or lactating mothers, medically compromised patients, and mentally challenged, and physically challenged cases were excluded from the study.

Sites with periodontal pocket measuring ≥5 mm and vertical bone loss ≥2 mm between the base of defect and adjacent alveolar crest on intraoral periapical radiograph in different quadrants of the mouth were selected in cases for the two different treatment modalities by one examiner (KK). Each site was randomly assigned to either test group or the control group. Randomization was done by folded paper bits method and recorded secretly and coded by the second examiner (AC). The third examiner (EM), who was calibrated for intra- and inter-examiner variability and blinded for the study, recorded the clinical parameters-plaque index (PI), gingival index (GI), probing pocket depth (PPD), and clinical attachment level (CAL) at baseline and later on 1, 3, and 6 months. Radiologic assessment of interdental alveolar bone height using grid and Extended Cone Projection technique was recorded at baseline and 6 months. The fourth examiner (SA) performed SRP and delivery of SMV or the placebo gels according to the coded instructions. All the records were maintained by the second examiner who randomized the selection of the sites. At the end of the study, decoding was done. The data were compiled by the fifth examiner (MCA), and the statistical analysis and interpretation were done by the sixth examiner (VA).

Baseline values were recorded before providing any sort of treatment to the either sites. For the measurement of PPD and CAL, occlusal stents were prepared. For radiographic interpretation of the vertical depth of the defect, the contact point was taken as the reference point, and the distance from the contact point to the most apical extension of the defect was measured in mm, first at baseline and finally at 6 months.[16] The difference between the two readings gave the gain in vertical defect of the bone. The parameter was termed as INFRA 1, following the technique as used by Eickholz *et al*.[17]

The pattern, direction, and amount of bone regeneration in an infrabony defect also needed attention. To study this, the measurement of angulation of the bony defect was also taken into consideration.[17,18] Following the method applied by Tsitoura *et al*.,[18] the radiographic angle of the infrabony component of the defect was measured. As presented diagrammatically in Figure 1, the following anatomical landmarks of the infrabony defect were identified on the radiograph:

- A: The contact point between the two teeth to avoid any confusion in the location of the cementoenamel junction
- B: The most coronal position of the alveolar crest of the infrabony defect where it touched the root surface of the adjacent tooth before treatment (the top of the crest)
- C: The most apical extension of the infrabony destruction where the periodontal ligament space still retained its normal width before treatment (the bottom of the defect).

The radiographic defect angle was then defined by the two lines that represented the root surface of the involved tooth and the bone defect surface. These lines were expressed linearly as AC and BC, and the angular parameter between them was termed as preoperative INFRA 2.[17] Postoperatively, any change in the bone defect surface was represented by B_1C_1 and the angle was measured between B_1C1 and AC_1.

The measurement of INFRA 2 is shown diagrammatically in Figure 1.

Thus, the following two groups were formed:

1. Group I, control group (SRP + placebo gel) = In which a placebo gel was placed after SRP

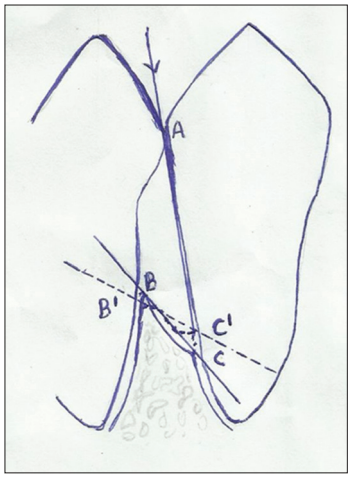


Figure 1: Measurement of angle of the defect (INFRA 2), i.e. angle between AC and CB

2. Group II, test group (SRP + SMV gel) = In which SMV gel was locally delivered after SRP.

Preparation of simvastatin gel

SMV and placebo gel were prepared in the Department of Pharmacology, Institute of Foreign Trade and Management, Moradabad - 244 001. SMV gel was prepared 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 SMV was added slowly with continuous stirring to get the preparation. The placebo gel was also prepared by the same technique except that SMV was not added.

The gel, thus prepared, was subjected for laboratory analysis to confirm the percentage of SMV at Arbro Pharmaceuticals Limited (Analytical Division), ISO 9001:2000 Certified, Government Approved, Test House, 4/9, Kirti Nagar Industrial Area, New Delhi - 110 015.

Periodontal therapy

Scaling and root planing

After recording the PI (Silness and Loe 1964) and the GI (Loe and Silness 1963), full-mouth SRP was performed in both the groups with the help of ultrasonic scaler (Satelac P5 Acteon, North America) and Gracey curettes (Hu-friedy Mfg. Co., LLC, 3232 N. Rockwell St. Chicago, IL 60618-5935, USA). PPD, CAL, and radiographic findings were then recorded. The local delivery of SMV was done with the insulin syringe whose needle was made blunt by cutting its tip. The gel was loaded and delivered into the pocket with gentle force, and the needle was slowly taken out of the periodontal pocket so that the material filled the depths and curves of the pocket site. The gingiva was subsequently, carefully adapted to close the entrance of the gingival margin and Coe-Pak (Coe-Pak™, GC America Inc., ALSIP, IL 60803, USA) was placed. The periodontal dressing of Coe-pak was removed after 2 days. Patients were expedited with postoperative compliance to report at 1, 3, and 6 months, during which their oral hygiene practices and status were evaluated and recordings of the postprocedural clinical parameters were done. The achieved data were statistically analyzed.

Table 1a: Age and gender wise distribution of cases

Total number of subjects	Sex	Number of subjects	Age; Mean Score	SD	%	*P*
30	M	14	30.461	9.786	46.6	0.65
	F	16	32.058	8.996	53.3	

M – Male F – Female '*P*'>0.05 Non-significant

RESULTS

The statistical analysis was done using the Statistical Package or Social Sciences analysis software version 17 produced by SPSS Inc., IBM. Paired and independent Student's *t*-test, Pearson's correlation coefficient, and test of significance for correlation coefficient were used to derive the result. Demographic characterizations are depicted in Table 1a.

Significant reduction in PI ($P = 0.000$) and GI ($P = 0.000$) from baseline to 6 months was observed in both the groups [Table 1b]. Reduction in PPD was also observed in both the groups from baseline to 6 months ($P < 0.5$). But, a noticeable reduction in PPD was observed in Group II between 3 and 6 months ($P = 0.04$), whereas it was insignificant in Group I during this period ($P = 0.32$) [Table 2 and Graphs 1, 2]. Similarly, a tendency to gain in CAL was observed in both the groups between baseline and 6 months (Group I, $P < 0.001$; Group II, $P = 0.001$). In Group I, although there was slight gain in CAL between 3 and 6 months, which was insignificant statistically ($P = 0.326$), the gain in CAL in Group II continued during this period of 3–6 months, and it was significant also ($P = 0.023$) [Table 3 and Graphs 3, 4].

Radiographic measurement of osseous defects was compared, and no significant differences were observed at baseline between Group I and II ($P = 0.655$); however, the INFRA 1 values were found to be significant at 6 months in Group I and II ($P = 0.007$) [Table 4 and Graph 5]. When the baseline values of INFRA 1 were compared with that of 6 months within groups, no significant differences were found between the values in Group I ($P = 0.161$) [Figures 2 and 3], while significant differences were found between the values in Group II ($P = 0.000$) [Figures 4, 5, Table 5 and Graph 5].

No significant differences were observed between the values of INFRA 2, angle of defect, at baseline between Groups I and II ($P = 0.736$). They were nonsignificant at 6 months as well in Group I and II ($P = 0.074$) [Table 6 and Graph 6], but an inclination toward an increase in angulation was clearly observed in Group II. When the baseline values of INFRA 2 were compared with that at 6 months within groups, the values in Group I were identical, hence could not be calculated statistically, while significant differences were found between the values in Group II ($P = 0.000$) [Table 7 and Graph 6].

DISCUSSION

The ideal objective for using local drug delivery[19,20] adjunct could be not only to arrest the disease but also to

Table 1b: Analysis of plaque index and gingival index in test and control groups at baseline and at six months

		Mean values±standard deviation Baseline	Mean values±standard deviation 6 Months	Paired differences Difference of mean±standard deviation	'*P*' value Sig. (2-tailed)
Group 1	PI	1.991±0.379	0.006±0.130	1.925±0.416	0.000
	GI	1.825±0.247	0.375±0.268	1.450±0.355	0.000
Group 2	PI	1.966±0.358	0.025±0.076	1.941±0.345	0.000
	GI	1.841±0.258	0.141±0.142	1.450±0.355	0.000

Group 1 – Control group; Group 2 – Test group; PI – Plaque Index; GI – Gingival Index '*P*'<0.05=Significant

Table 2: Evaluation of probing pocket depth in Groups I and II at baseline, 1, 3, and 6 months

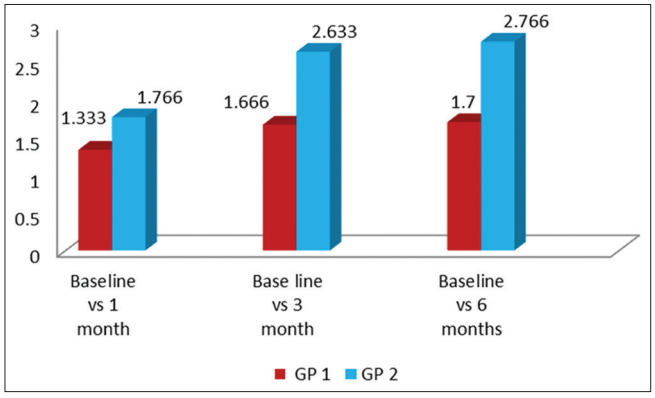
Duration	PPD		Paired differences		*P* value significant (two-tailed)	
	Parameter					
	Mean±SD		Difference of mean±SD			
	Group I	Group II	Group I	Group II	Group I	Group II
Baseline	6.000±0.694	6.400±0.894	1.333±0.479	1.766±0.568	0.000*	0.000*
1 month	4.666±0.711	4.633±0.764				
Baseline	6.000±0.694	6.400±0.894	1.666±0.479	2.633±0.614	0.000*	0.000*
3 months	4.333±0.479	3.766±0.626				
Baseline	6.000±0.694	6.400±0.894	1.700±0.466	2.766±0.678	0.000*	0.000*
6 months	4.300±0.466	3.633±0.614				
1 month	4.666±0.711	4.633±0.764	0.333±0.479	0.866±0.434	0.001*	0.000*
3 months	4.333±0.479	3.766±0.626				
1 month	4.666±0.711	4.633±0.764	0.366±0.490	1.000±0.525	0.000*	0.000*
6 months	4.300±0.466	3.633±0.614				
3 months	4.333±0.479	3.766±0.626	0.033±0.182	0.133±0.345	0.326**	0.043*
6 months	4.300±0.466	3.633±0.614				

*P<0.05 significant; **P>0.05 nonsignificant. PPD – Probing pocket depth; Group I – Control group; Group II – Test group; SD – Standard deviation

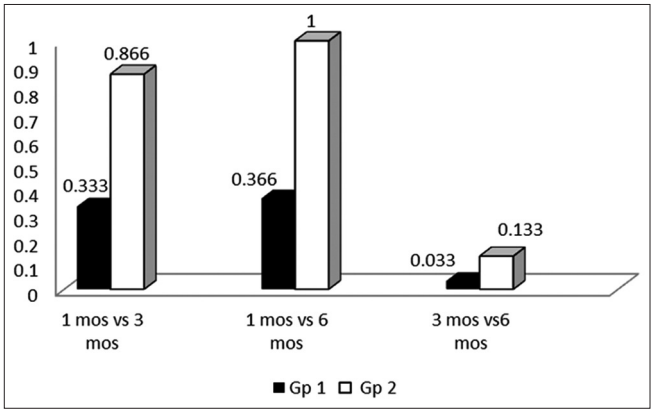
Table 3: Evaluation of clinical attachment level in Groups I and II at baseline, 1, 3, and 6 months

Parameter	CAL		Paired differences		*P* value significant (two-tailed)	
	Mean±SD		Difference of mean±SD			
	Group I	Group II	Group I	Group II	Group I	Group II
Baseline	7.966±0.764	8.500±0.900	1.266±0.520	1.533±0.571	0.000*	0.000*
1 month	6.700±0.836	6.966±0.964				
Baseline	7.966±0.764	8.500±0.900	1.533±0.507	2.233±0.568	0.000*	0.000*
3 months	6.433±0.727	6.266±0.868				
Baseline	7.966±0.764	8.500±0.900	1.500±0.508	2.400±0.563	0.000*	0.000*
6 months	6.466±0.730	6.100±0.803				
1 month	6.700±0.836	6.966±0.964	0.266±0.520	0.700±0.466	0.009*	0.000*
3 months	6.433±0.727	6.266±0.868				
1 month	6.700±0.836	6.966±0.964	0.233±0.568	0.866±0.628	0.032*	0.000*
6 months	6.466±0.730	6.100±0.803				
3 months	6.433±0.727	6.266±0.868	0.033±0.182	0.166±0.379	0.326**	0.023*
6 months	6.466±0.730	6.100±0.803				

*P<0.05 significant; **P>0.05 nonsignificant. CAL – Clinical attachment level; Group I – Control group; Group II – Test group; SD – Standard deviation



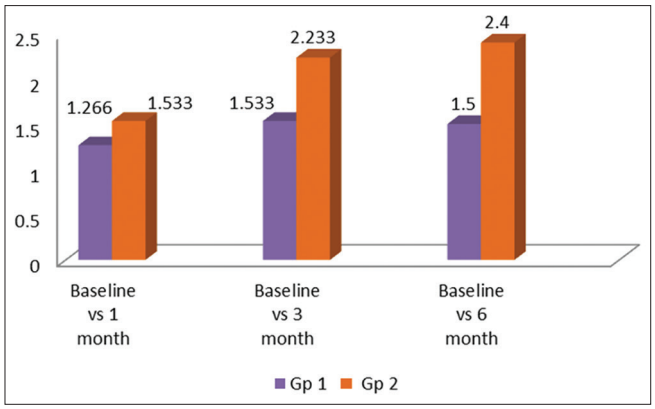
Graph 1: Evaluation of decrease in probing pocket depth in Groups I and II at baseline and 1, 3, and 6 months



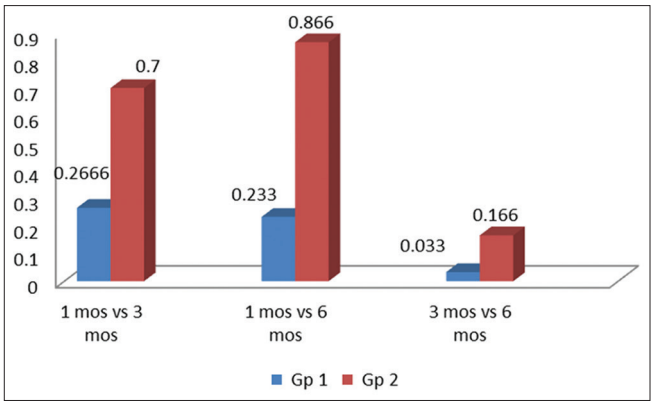
Graph 2: Evaluation of decrease in probing pocket depth in Groups I and II at 1, 3, and 6 months

achieve the regeneration of the lost periodontium. Since the first and foremost task is to control the host-mediated tissue destruction, various means have been employed for modulating this response. These include inhibition of MMPs with antiproteinases, blocking the proinflammatory cytokines and prostaglandins by use of anti-inflammatory drugs, and by inhibiting the osteoclasts activity by use of bone-sparing agents.[21] Simultaneously, the second and equally important task is to regain the lost periodontium. Some newer drugs have been found to have such effects, out of them statins are opening a new era of interest.

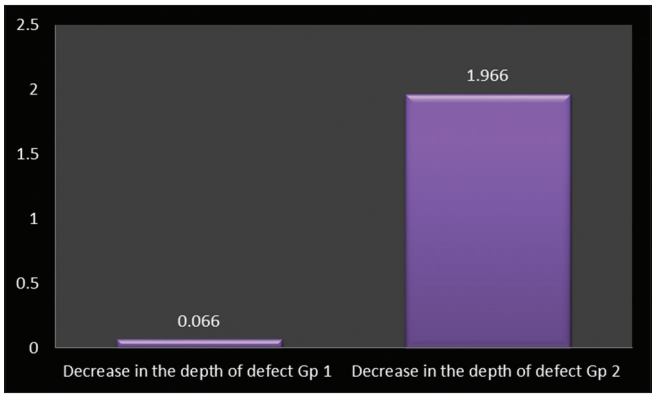
Statins were primarily approved as lipid lowering agent to prevent cardiovascular events. They lower the low-density lipoprotein-C, but recent studies provide compelling evidence that statins, in addition to their lipid-lowering capacity, also possess potential pleiotropic effects which seem to be beneficial in periodontics. These beneficial effects, which are independent



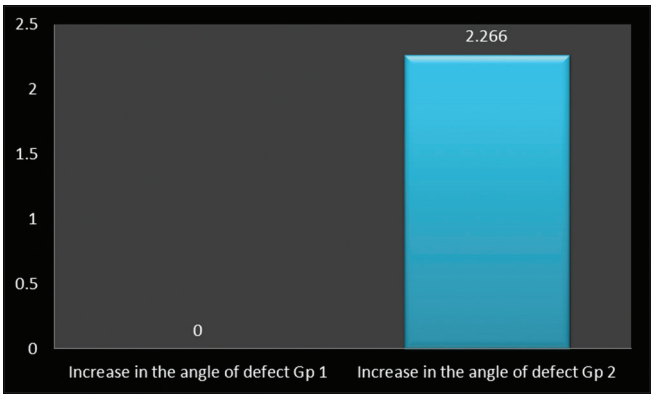
Graph 3: Evaluation of gain in clinical attachment level in Groups I and II at baseline and 1, 3, and 6 months



Graph 4: Evaluation of gain in clinical attachment level in Groups I and II at 1, 3, and 6 months



Graph 5: Comparison of decrease in infrabony defect fill (INFRA 1 in Groups I and II at baseline and 6 months)



Graph 6: Comparison of increase in INFRA 2 in Groups I and II at baseline and 6 months

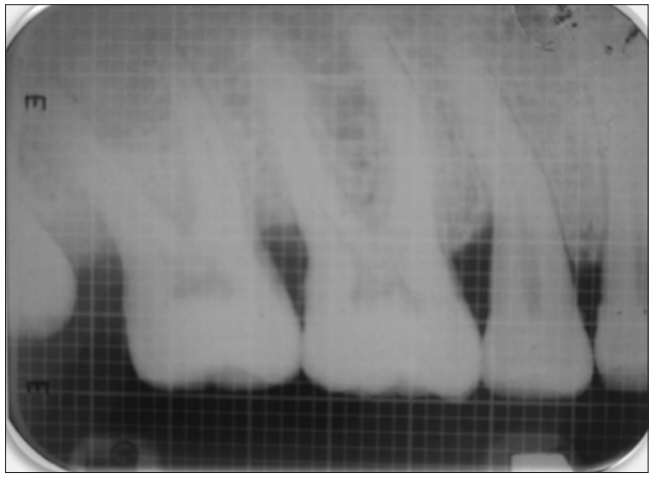


Figure 2: Preoperative radiograph (Group I)

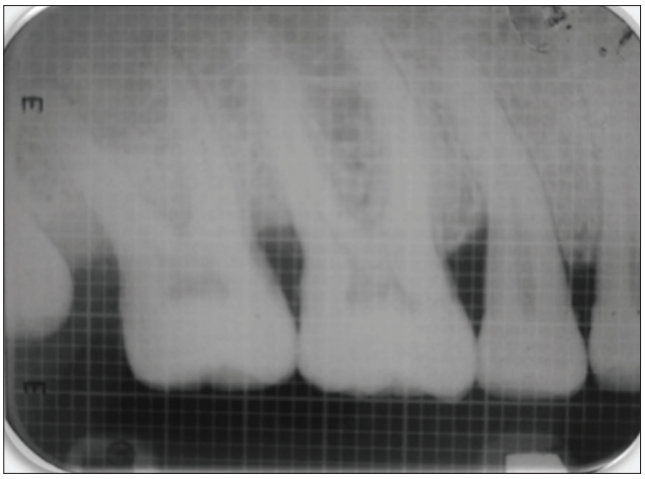


Figure 3: Postoperative radiograph (Group I)

of their lipid-lowering effects, include anti-inflammatory,[22] immune-modulatory,[23,24] antioxidant,[25-28] antithrombotic, and endothelium stabilization actions.[29] They also cause the inhibition of MHC-II expression, and inhibition of release of pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-1 β, and IL-6 from various cell types, thereby, providing immunomodulatory effects as well.[23] Statins also cause inhibition of NADPH, a major source of oxidant production, thereby providing antioxidant effect,[25] as well as angiogenesis promotion and increase of osteoblastic differentiation, inducing bone formation. In addition, statins can inhibit tumor cells growth and enhance intracellular calcium mobilization.[11]

Hence, the present study was designed to evaluate the effectiveness of SMV, 1.2 mg, in an indigenously prepared

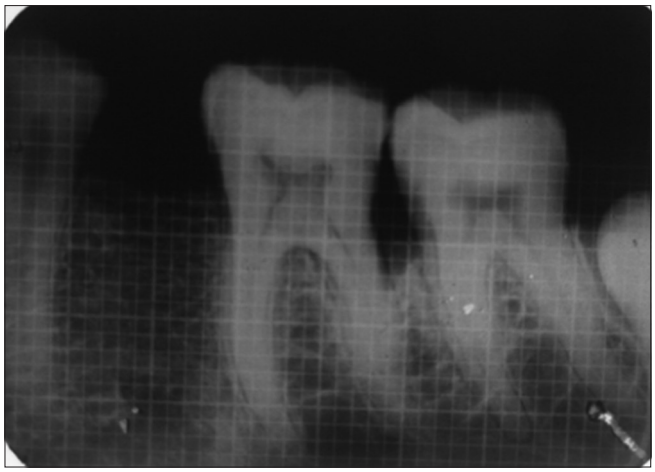


Figure 4: Preoperative radiograph (Group II)

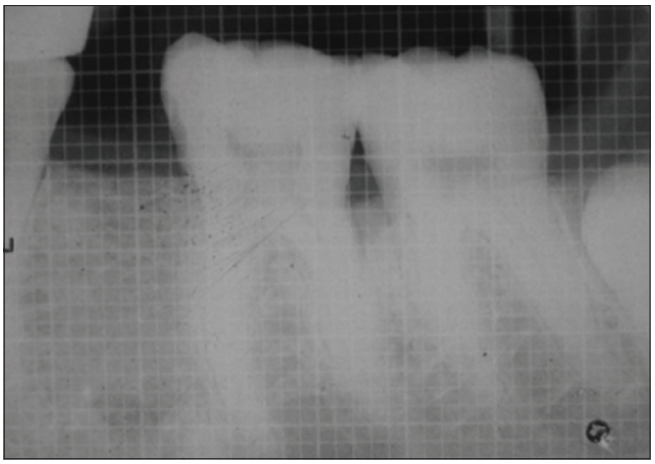


Figure 5: Postoperative radiograph (Group II)

Table 4: Comparison of radiographic infrabony defect fill (INFRA 1) between groups at baseline and 6 months

	t-test for equality of means (INFRA 1), mean±SD	*P* value significant (two-tailed)
Baseline Group I	11.233±2.207	0.655*
Baseline Group II	11.500±2.388	
6 months Group I	11.166±2.245	0.007**
6 months Group II	9.533±2.300	

*P<0.05 significant; **P>0.05 nonsignificant. Group I – Control group; Group II – Test Group; INFRA 1 – Vertical depth of the defect; SD – Standard deviation

biodegradable controlled-release gel as an adjunct to SRP comparing with a placebo gel.

Clinical observations

The placebo and SMV gels were well tolerated in all the cases, and no untoward reaction was observed. Both the PI and GI revealed a significant progressive regression during the entire study period at 1, 3, and 6 months ($P < 0.05$). There was a significant reduction in the values of PPD and gain in CAL in both the groups at 6 months from baseline. This substantiates the different studies which also advocate that SRP is an initial gold standard treatment strategy for periodontal diseases.[30-32] A striking observation was a significant reduction in PPD between 3 and 6 months in Group II ($P = 0.043$), whereas in Group I, it was nonsignificant ($P = 0.326$). Similarly, there was a slight gain in CAL between 3 and 6 months, which was insignificant statistically ($P = 0.326$) in Group I, but in Group II, a significant gain in CAL continued during this period of 3–6 months ($P = 0.023$). These observations may suggest the immunomodulatory effect of SMV as observed in various other studies also.[23,24,29] In addition, it may be interpreted that the significant reduction in PPD is not only due to the shrinkage of the soft tissue but also in response to SMV. This was further substantiated by getting a significant correlation between reduction in PPD and gain in CAL signifying the gain in attachment was taking place along with shrinkage of soft tissue, side by side [Table 6]. Radiographic evaluation further justifies these results. It was done by measuring the vertical depth of defect, INFRA 1 at baseline and at 6 months in both the groups. At baseline, between the groups, there was no significant difference which became significant at 6 months ($P = 0.007$). The decrease in INFRA 1 is more in Group II ($P = 0.000$) which concludes, relatively, more bone gain in Group II than in Group I. In one case, an unexpected INFRA 1 of 5 mm was also found at an SMV applied site.

The pattern, direction, and amount of bone regeneration in an intrabony defect also need attention. To study this, angulations of defects were calculated between root surface and defect surface and categorized as INFRA 2 [Figure 1]. In Group I, the values were compared between baseline and 6 months and was found to be identical so could not be calculated statistically, whereas in Group II, it was significant ($P = 0.000$) [Table 7]. No significant differences were seen between the groups, when the values of INFRA 2 were subjected for statistical analyses at baseline ($P = 0.736$) and at 6 months ($P = 0.074$) [Table 6]. This might reflect that bone gain is parallel, i.e. from the lateral aspect also. Thus, the potential role of SMV as bone-sparing agent, and in the regeneration of lost periodontium could be justified along with other effects.[33]

Although the present study is of short-term, the adjunctive use of subgingivally delivered biodegradable 1.2% SMV gel as evaluated in this study is safe and provides statistically significant results. Thus, on the basis of this study, it can be said that local SMV therapy markedly improves the benefits of SRP, both clinically and radiographically. By the use of these classes of drugs, the threshold for surgical periodontal therapy might move toward deeper pockets where better and additional effects might be expected with their use as local delivery drugs.

Future trends

A point to be questioned is that why the deeper pockets are not always accompanied by bone gain with any of the nonsurgical procedures including local drug delivery. The answer could be that any of the above-mentioned techniques are blind techniques, and some amount of residual plaque and calculus could be left unnoticed. Hence, to achieve the osteogenic (modulatory) effect, placement of SMV mixed

Table 5: Evaluation of radiographic infrabony defect fill (INFRA 1) between groups at baseline and 6 months

	Mean±SD			*t*	*P* value significant (two-tailed)
	Baseline	6 months	Difference		
Group I	11.233±2.208	11.167±2.245	0.066±0.253	1.44	0.161*
Group II	11.500±2.389	9.533±2.300	1.967±0.556	19.37	0.000**

SD – Standard deviation, **P*<0.05 Significant; ***P*>0.05 Non- significant

Table 6: Comparison of radiographic (INFRA 2) between groups at baseline and 6 months

	t-test for equality of means (INFRA 2), mean±SD	*P* value significant (two-tailed)
Baseline Group I	39±5.825	0.736
Baseline Group II	39.533±6.251	
6 months Group I	39±5.825	0.074
6 months Group II	41.8±6.093	

SD - Standard deviation, **P*<0.05 Significant; ***P*>0.05 Non- significant

Table 7: Comparison of increase in INFRA 2 between groups at baseline and 6 months

	Mean±SD			*t*	*P* value significant (two-tailed)
	Baseline	6 months	Difference		
Group I	39.000±5.83	39.000±5.83	0.000±0.000	*	*
Group II	39.53±6.25	41.80±6.09	2.267±1.530	8.12	0.000**

SD - Standard deviation, ***P*< 0.05 Significant;*All values in column are identical

with bone graft after open flap debridement can give more challenging outcomes, and this has been proved clinically more effective in one of the studies.[16] The slow bio-absorption of this variant of SMV may be advantageous in patients in whom bone healing is slow. However, further research is demanded in this direction with long follow-ups.

CONCLUSION

SMV gel in the treatment of infrabony defects has shown favorable results clinically as evident by reduction in PPD and gain in CAL. Regarding radiographic changes as well, significant bone fill could be appreciated in the test group.

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Conflicts of interest
There are no conflicts of interest.

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