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Evaluation of Healing of Periodontal Tissues with and Without Simvastatin 1.2% Gel as a Local Drug Delivery in Adjunct to Scaling and Root Planing in Chronic Periodontitis Patients - A Clinical Study

Dr. Devishree CP[1], Dr. Manjushree Kadam[2]

[1]MDS. Periodontics & Oral Implantology

[2]MDS, Professor, Department of Periodontology, AJ Institute of Dental Sciences, Mangalore

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. These agents are widely used to lower cholesterol and also they seem to modulate bone formation by increasing the expression of bone morphogenetic protein-2, inflammation, and angiogenesis, thus providing a new direction in the field of periodontal therapy. Aims & Objective: The present study was designed to investigate healing of periodontal tissues with and without simvastatin 1.2% gel as a local drug delivery in adjunct to scaling and root planing in chronic periodontitis patients. Materials and Methods: A total of 60 sites of patients aged between 25-50 years of age with chronic moderate periodontitis with localized probing pocket depth of ≥4≤ 6mm, clinical attachment loss of ≥ 4 mm & vertical bone loss of ≤3mm (intrabony defects) were categorized into two treatment groups, for SRP (Gp 1) & 1.2 % SMV gel (Gp 2). Clinical Parameters were recorded at baseline and at 3,6 and 9 months comprising of oral hygiene index simplified, modified plaque index, modified sulcular bleeding index index, probing pocket Depth (PPD) and clinical attachment level (CAL). The osseous changes were evaluated radiographically by measuring vertical bone fill, using grid IOPA from baseline to 6 & 9months. Results: All subjects tolerated the drug, without any post-application complication. The treatment improved the periodontal healing in both the groups. There was a greater decrease in OHIs, mPI, mSBI and PD and more CAL gain with significant IBD fill at sites treated with SRP plus locally delivered SMV gel. Conclusion: Local Drug delivery of 1.2% SMV gel enhanced the beneficial effect of SRP in pocket reduction, gain in CAL and bone fill suggestive of better periodontal tissue healing***

Keywords: Simvastatin gel, SRP, periodontitis, local drug delivery, CAL, PD, vertical bone fill

1. Introduction

Periodontitis is a chronic infectious disease of the supporting tissues of the teeth. Due to bacterial infection, periodontal tissues become inflamed and are slowly destroyed by the action of the inflammatory process. If the disease is left untreated, teeth lose their ligamentous support to the alveolar bone, alveolar bone itself is resorbed, and the teeth become mobile and are finally lost[1]. The inflammation in the periodontal tissue is initiated by microbial plaque and bacterial infection. In the periodontal pocket the bacteria form a highly structured and complex biofilm. As this continues, the biofilm reach far subgingivally and it becomes difficult for the patient to reach it during oral hygiene practices. Traditional treatment options for such conditions includes mechanical debridement aimed at removing the subgingival flora providing a clean, smooth and compatible root surfaces. But, in several instances, the complex anatomy of the root and the location of the lesion may hamper the treatment and prevent sufficient reduction of the bacterial load[2] .Certain organisms within the microbial flora of dental plaque are the major etiologic agents of periodontitis which produce endotoxins in the form of lipopolysaccharides (LPS) that are instrumental in generating a host-mediated tissue destructive immune response by mobilizing their defensive cells and releasing cytokines like Interleukin-1β (IL-1β), Tumor Necrosis Factor-α (TNF-α), and Interleukin-6 (IL-6), which lead to tissue destruction by stimulating the production of the collagenolytic enzymes: Matrix metalloproteinases (MMPs).

Statins like simvastatin (SMV), lovastatin, and pravastatin are specific competitive inhibitors of 3-hydroxy-2-methyl-glutaryl coenzyme A (HMG CoA) reductase. These agents are widely used to lower cholesterol, and they provide an important and effective approach for the treatment of hyperlipidemia and arteriosclerosis. Statins also seem to modulate bone formation by increasing the expression of bone morphogenetic protein-2, inflammation, and angiogenesis, thus providing a new direction in the field of periodontal therapy. Various animal studies showed that SMV assists in bone regeneration as well as the anti-inflammatory effect when delivered or applied locally[3]. Elimination or adequate suppression of putative periodontopathic microorganisms in the subgingival microbiota is essential for periodontal healing. For the effective treatment, the antibiotic must reach the depth of the pocket and produce gingival fluid concentrations higher than the minimum inhibitory concentrations (MIC) of the suspected pathogens.

Systemic administration has been useful in treating periodontal pockets, but repeated and long-term use of systemic antibiotics possess potential danger including resistant strains and superimposed infections. Local administration, therefore provide a useful answer to these problems. The principle requirement for effectiveness of this form of therapy is that the agent reaches the base of the pocket and is maintained there by means like reservoir for an adequate time for the antimicrobial effect to occur[4]. The use of controlled-release locally delivered antimicrobial agents in adjunct to mechanical treatments, especially when placed subgingivally targeting specific microorganisms, offers

favorable results in the treatment of localized periodontally destructed areas. According to the American Academy of Periodontology's (AAP's) 2006 statement, the results achieved according to recent systematic reviews ranged between 0.25-0.5 mm^3.

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 anti-inflammatory effect [1,16]. 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 [1,17]. Pradeep and Thorat have analyzed the bioavailability and degradability of 1.2 mg of SMV gel in detail[1]. Hence, the subgingival drug delivery of SMV can produce advantages of achieving high intrasulcular drug concentrations, simultaneously avoiding its systemic side effects.

2. Materials and Methods

Source of data- Patients aged 25-50 years were selected from Outpatient Department of Periodontics, A.J. Institute of Dental Sciences, Mangalore. The study sample consisted of patients (both male and female) who were diagnosed to have chronic periodontitis with age ranging from 25-50 years. Before the study, the health of the patients was assessed by using detailed medical history and clinical examination following the inclusion and exclusion criteria mentioned above. Subjects were informed about the treatment and an informed consent was obtained from all the patients prior to the clinical examination. All the clinical measurements was performed in 4 quadrants using a Williams' graduated periodontal probe.
The following criteria were considered for selection of patients-

Inclusion Criteria
1) Patients willing to participate in the study.
2) Patients aged between 25-50 years.
3) Systemically healthy patients with chronic moderate periodontitis.
4) Patients with localized probing pocket depth of ≥4≤ 6mm.
5) Patients with clinical attachment loss of ≥ 4 mm.
6) Patients with vertical bone loss of ≤3mm (intrabony defects)
7) Patients not being subjected to/willing for periodontal surgery for the same as above mentioned criteria

Exclusion Criteria
1) Patients who are unable to provide information or to co-operate with the dental examination.
2) Patients who have undergone any periodontal, surgical or non-surgical therapy for past 6 months.
3) Patients who have received any chemotherapeutic mouth rinse or oral irrigation during the past 6 months.
4) Patients who have received antibiotics and anti-inflammatory drugs in the past 4-6 weeks and during the study.
5) Patients with a history of underlying systemic diseases and condition.
6) Patients diagnosed with trauma from occlusion
7) Patients with a habit of smoking, tobacco chewing, and alcohol consumption.
8) Pregnant and lactating women and those using hormonal contraceptives.

Ethical Consent
Permission for this study was obtained from the Ethical Committee of A.J. Institute of medical Sciences and Research Centre.

Clinical Trail Resistration
Clinical trail registration was done under Clinical Trials Registry- India (CTRI) CTRI NUMBER: CTRI/2021/02/031513

Examiner Calibration
Study was carried out by a single examiner throughout the study period

Power and Sample Size Calculations:
Based on the study conducted by the author NS Rao, AR Pradeep et al (2012)25 In order to expect a difference of 1.07 (in the probing depth (mm) at / between the groups ,assuming 95% confidence interval & 90 % power and a pooled standard deviation of 1.1,the sample size estimated for the study is 23 sites in each group .Further assuming 10% lost of follow up the final sample size estimated for the study is 30 in each group

Formula: $n=([z1-\alpha 2/+z1-\beta]^2\times 2SD^2)/(Mean\ difference)^2$

The selected patients were randomly allotted by lottery method into 2 groups (n=30 sites)4 in each group
1.Group A (n=30 sites) - Scaling and root planing(SRP)
2.Group B (n=30 sites)- Use of Simvastatin 1.2% as a local drug delivery after SRP.

Formulation of 1.2% SMV Gel
Simvastatin powder was obtained. Methyl cellulose in situ gel was prepared by adding the required amount of biocompatible solvent to an accurately weighed amount of methyl cellulose. The vial was heated to 50-600 C and agitated using a mechanical shaker to obtain a clear solution. A weighed amount of Simvastatin was added to the above solution and dissolved completely to obtain a homogenous phase of polymer, solvent, drug. Thus, Simvastatin in situ gel was prepared with a concentration ~1.2%.
Simvastatin in powder form was obtained from Microlabs Pharmaceutical Company, Bangalore.
Simvastatin 1.2% gel was formulated in Srinivas College of Pharmacy, Mangalore

Local Drug Delivery
10 µL prepared SMV gel (1.2 mg /0.1 ml) was injected into the periodontal pockets using a syringe. Patients were instructed to refrain from chewing hard or sticky foods,

brushing near the treated areas, or using any interdental aids for 1 week.

Radiographic assessment of intrabony defects was done using grid IOPA. The depth of intrabony defects (IBD) was evaluated at baseline, 6 and 9 months

Primary and Secondary Outcome Measures:
The primary outcome of the study was intrabony defect fill. The secondary outcomes included PD, CAL, OHI-S,and mSBI.

Statistical Analysis
Statistical Package for Social Sciences [SPSS] for Windows Version 22.0 Released 2013. Armonk, NY: IBM Corp., was used to perform statistical analyses. Descriptive analysis of all the explanatory and outcome parameters was done using frequency and proportions for categorical variables, whereas in Mean & SD for continuous variables. Independent Student t Test was used to compare the mean values of study parameters between 2 groups at different time intervals. Repeated Measures of ANOVA test followed by Bonferroni's post hoc test was used to compare the mean values of study parameters between different time intervals in each group. Mann Whitney test was used to compare the Infra bony defect depth (in mm) & Vertical bone fill between 2 groups. Wilcoxon Signed Rank test was used to compare the mean Vertical bone fill between 6 & 9 months in each group. The level of significance was set at P<0.05

3. Results

A total of 60 sites were selected for the study in the patients with chronic periodontitis, divided into two groups and was assigned for scaling and root planning in group 1(n=30) and scaling and root planning with subgingivally delivered 1.2% simvastatin gel in group 2(n=30).

The mean OHIs, mPI, mSBI scores in Group 1 & Group 2 did not show significant difference at baseline period. At 3 months' post treatment period, Group 2 showed significantly lesser OHIs, mPI, mSBI scores as compared to Group 1 and the difference was statistically significant at p=0.02, p=0.006, p=0.003 respectively. At 6 months' post treatment period, Group 2 showed a relatively lesser OHIs, mPI, mSBI scores as compared to Group 1 and the difference showed a borderline significance at p=0.07, p=0.001 respectively. At 9 months' period, there was no significant difference observed in the mean OHIs, mPI, mSBI scores between 2 groups.

The mean PD &Clinical Attachment Level gain value in Group 1 & Group 2 did not show significant difference at baseline period. At 3 months' post treatment period, Group 2 showed significantly lesser PD value and significantly greater clinical attachment level gain as compared to Group 1 and the difference showed a borderline significance at p =0.74& p=0.06 respectively. At 6 months' post treatment period, Group 2 showed a relatively lesser PD value and greater clinical attachment level gain as compared to Group 1 and the difference was statistically significant at p=0.04 & p=0.006 respectively.

The mean IBD fill value in Group 1 & Group 2 did not show significant difference at baseline period. At 6 months' post treatment period, Group 2 showed a relatively greater IBD fill as compared to Group 1 and the difference was statistically significant at p=0.001. At 9 months' post treatment period, Group 2 showed a relatively greater IBD fill value as compared to Group 1 and the difference was statistically significant at p=<0.001.

Table 1: Comparison of mean OHIs scores b/w 2 groups at different time intervals

Independent Student t test							Repeated Measures of ANOVA Test		
Time	Groups	N	Mean	SD	Mean Diff	p-value	Min	Max	p-value
Baseline	Group 1	30	2.944	0.434	-0.051	0.67	1.99	3.43	<0.001*
	Group 2	30	2.995	0.485			2.16	3.83	
3 Months	Group 1	30	1.093	0.319	0.170	0.02*	0.76	1.99	
	Group 2	30	0.924	0.201			0.66	1.32	
6 Months	Group 1	30	0.600	0.220	0.090	0.07	0.32	0.99	
	Group 2	30	0.511	0.149			0.32	0.83	
9 Months	Group 1	30	0.380	0.143	0.011	0.73	0.16	0.60	
	Group 2	30	0.369	0.085			0.16	0.50	

Table 2: Comparison of mean Modified PI scores b/w 2 groups at different time intervals

Independent Student t test							Repeated Measures of ANOVA Test		
Time	Groups	N	Mean	SD	Mean Diff	p-value	Min	Max	p-value
Baseline	Group 1	30	1.764	0.286	-0.074	0.24	1.28	2.1	<0.001*
	Group 2	30	1.838	0.185			0.185	1.17	
3 Months	Group 1	30	0.398	0.097	0.073	0.006*	0.21	0.532	
	Group 2	30	0.325	0.103			0.21	0.5	
6 Months	Group 1	30	0.337	0.095	0.072	0.001*	0.23	0.5	
	Group 2	30	0.266	0.057			0.21	0.39	
9 Months	Group 1	30	0.191	0.073	0.029	0.07	0.12	0.32	
	Group 2	30	0.161	0.047			0.12	0.30	

Table 3: Comparison of mean Modified SBI scores b/w 2 groups at different time intervals

Independent Student t test							Repeated Measures of ANOVA Test		
Time	Groups	N	Mean	SD	Mean Diff	p-value	Min	Max	p-value
Baseline	Group 1	30	2.40	0.56	0.133	0.41	1.0	3.0	<0.001*
	Group 2	30	2.27	0.69			0.185	1.17	
3 Months	Group 1	30	0.60	0.67	0.433	0.003*	0.0	2.0	
	Group 2	30	0.17	0.38			0.0	1.0	
6 Months	Group 1	30	0.00	0.00	0.000	..	0.0	0.0	
	Group 2	30	0.00	0.00			0.0	0.0	
9 Months	Group 1	30	0.00	0.00	-0.033	0.32	0.0	0.0	
	Group 2	30	0.03	0.18			0.0	1.0	

Table 4: Comparison of mean Pocket Depth (in mm) b/w 2 groups at different time intervals

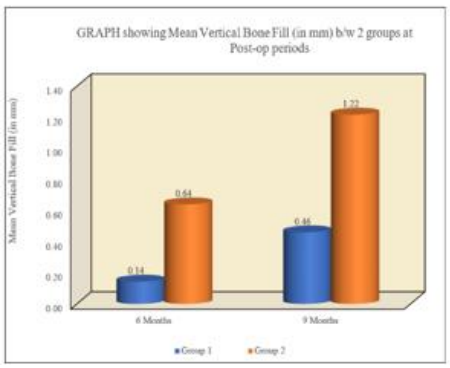
Independent Student t test							Repeated Measures of ANOVA Test		
Time	Groups	N	Mean	SD	Mean Diff	p-value	Min	Max	p-value
Baseline	Group 1	30	5.53	0.68	0.00	1.00	4	6	<0.001*
	Group 2	30	5.53	0.57			4	6	
3 Months	Group 1	30	2.97	0.81	0.07	0.74	2	5	
	Group 2	30	2.90	0.71			2	5	
6 Months	Group 1	30	3.10	0.48	0.70	<0.001*	2	4	
	Group 2	30	2.40	0.72			1	4	
9 Months	Group 1	30	2.67	0.48	0.33	0.04*	2	3.00	
	Group 2	30	2.33	0.71			1	4.0	

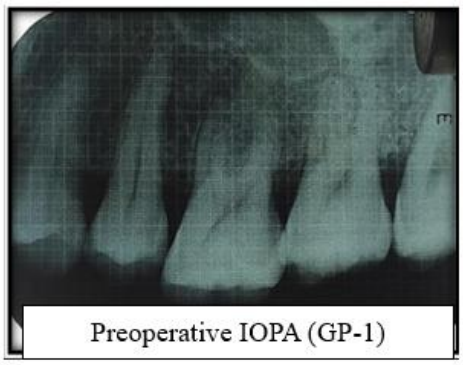
Table 5: Comparison of mean Clinical Attachment Gain (in mm) b/w groups using Repeated Measures of ANOVA Test followed by Bonferroni's post hoc Test

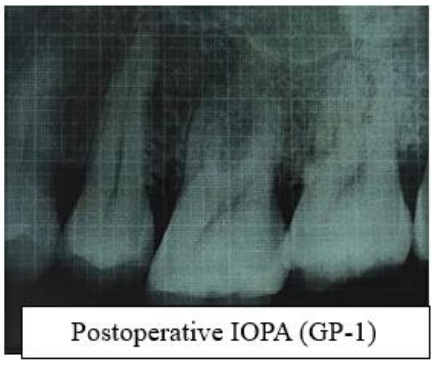
Groups	Time	N	Mean	SD	p-value [a]	Sig. Diff	p-value [b]
Group 1	3 Months	30	2.27	0.69	0.005*	3m vs 6m	1.00
	6 Months	30	2.13	0.78		3m vs 9m	0.32
	9 Months	30	2.57	0.82		6m vs 9m	0.005*
Group 2	3 Months	30	2.63	0.76	0.002*	3m vs 6m	0.02*
	6 Months	30	3.13	0.82		3m vs 9m	0.007*
	9 Months	30	3.20	0.89		6m vs 9m	1.00

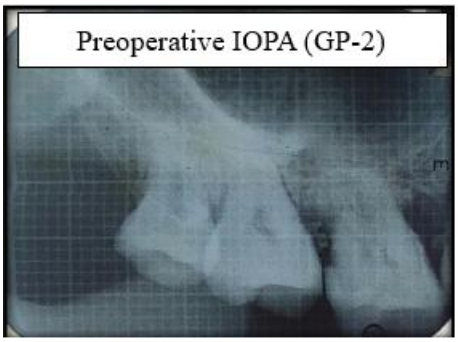
Table 6: Comparison of mean Vertical Bone Fill (in mm) b/w 6 & 9 months period in each group using Wilcoxon Signed Rank Test

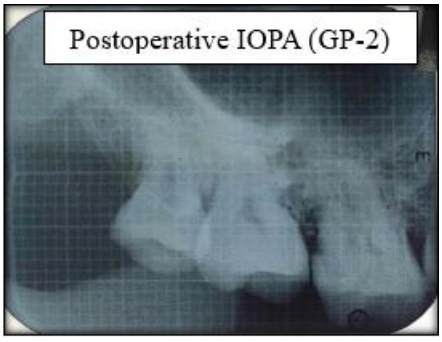
Groups	Time	N	Mean	SD	Mean Diff	p-value
Group 1	6 months	30	0.143	0.359	-0.317	0.001*
	9 months	30	0.460	0.621		
Group 2	6 months	30	0.640	0.683	-0.577	<0.001*
	9 months	30	1.217	0.924		











4. Discussion

Over the years, various treatment modalities have been tried with varying success to correct periodontal attachment and alveolar bone loss resulting from this disease. Periodontal therapy is aimed at the restoration of tissues destroyed by disease. However, achieving greater predictability with regenerative therapy requires the introduction of an agent which not only hampers tissue destruction but also enhances the regenerative capabilities of the periodontal tissues. The periodontal treatment to eradicate gingival inflammation, bleeding, periodontal pocket depth and arrest destruction of soft tissue and bone by removal of the bacterial deposits from the tooth surface and to shift the pathogenic microbiota to one compatible with periodontal health. Therapeutic approach includes mechanical scaling and root planning (SRP)[10]. The effectiveness of this method is limited due to the lack of accessibility in deep periodontal pocket[11].Putative pathogens associated with periodontal diseases are susceptible to a variety of antiseptics and antibiotics[12,13].

The ideal objective for using local drug delivery [18,19] adjunct could be not only to arrest the disease but also to 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[20]. 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[5].

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 their lipid-lowering effects, include- anti- inflammatory, immune- modulatory, antioxidant, antithrombotic, and endothelium stabilization actions. 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[8]. Statins also cause inhibition of NADPH, a major source of oxidant production, thereby providing antioxidant effect[9], 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[5]

Hence the present study was designed to investigate healing of periodontal tissues with and without simvastatin 1.2% gel as a local drug delivery in adjunct to scaling and root planning in chronic periodontitis patients .It was observed that in both the group of patients the scaling and root planning was effective and statistically significant results were seen in the clinical parameters such as probing depth, clinical attachment level gain ,OHI-s, mSBI & PI scores whereas in terms of radiographic intrabony defect fill it was seen that results were statistically significant in patients treated with 1.2% SMV gel as compared to patients treated with SRP alone.

5. Conclusions

This clinical trial thus demonstrates that local delivery of 1.2% SMV into periodontal pockets in chronic periodontitis stimulated a significant increase in the PD reduction, CAL gain and improved bone fill as compared to SRP. This can provide a new direction in the field of periodontal healing in this special group of patients who are at greater risk for periodontal destruction. However, long-term, multicentre randomized, controlled clinical trials are required to ascertain the clinical, histological and radiographical effect on bone regeneration in chronic periodontitis patients.

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