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Original Research Article **Periodontology**

Locally Delivered 1.2% Simvastatin Gel and 1% Metformin Gel in Chronic Periodontitis Patients

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Abstract

Background: This study was carried out to investigate the effectiveness of 1.2% Simvastatin gel and 1% Metformin gel in chronic periodontitis pockets. The rationale behind using Statins is that this class of drugs has a potential anti-inflammatory effect on oral epithelial cells, blocking the intermediate metabolites of the mevalonate pathway. Statins also modulate bone formation by increasing the expression of bone morphogenetic protein-2 providing a new direction in the field of periodontal therapy. Statin administration decreases GCF levels of pro-inflammatory mediators which are responsible for much of the host tissue destruction seen in periodontitis. Metformin acts at molecular level via both AMPK (5'adenosine monophosphate activated protein kinase) dependent & AMPK independent pathways. It shows effects on Nuclear Factor-κB (NF-κB), differentiation of monocytes into macrophages as well as suppressing IL-2, interferon (IFN)-γ and TNF-α from these macrophages which thereby improved the periodontal clinical parameters. There is no evidence of literature till now comparing the clinical efficacy of 1.2% Simvastatin gel with 1% Metformin gel in patients with chronic periodontitis. ***Method:*** The study population consisted of 48 sites from chronic periodontitis patients, divided into 3 groups which received sub gingival irrigation with Scaling and root planning alone, SRP with 1.2% Simvastatin gel and SRP with1% Metformin gel. ***Results:*** 1.2% Simvastatin gel and 1% Metformin gel improve the periodontal health with statistically significant improvement in the PPD, RAL, RGML values as compared to SRP alone. ***Conclusion****:* LDD systems using gel formulations are advantageous because of their sustainability, prolonged release, stability in the pockets, clinical effect of 1.2% Simvastatin gel and 1% Metformin gel improves the periodontal health compared to SRP alone.

Keywords: Simvastatin gel, mevalonate pathway, host tissue destruction, chronic periodontitis patients.

1. INTRODUCTION

Chronic Periodontitis (CP) is a disease which leads to the inflammation of the supporting structure of teeth, progressive attachment loss by pocket formation and subsequent bone loss due to host response [1]. It is a disease of multifactorial origin but there is considerable evidence implicating facultative and anaerobic bacteria as a primary cause that lead to exaggerated immune response and initiate production of pro-inflammatory cytokines eg. IL-1β linked to the production of collagenase, prostaglandin E and tissue degradative enzymes that result in periodontal tissue destruction and orchestrate bone resorption [2]. Due to their invasive potential into gingival epithelial cells and sub-epithelial connective tissue these bacteria are hard to eradicate from the periodontal pockets by means of mechanical scaling and root planning treatment [3]. The various limitations of systemic therapies including hypersensitivity, gastrointestinal intolerance, development of bacterial resistance, tooth staining, taste alteration and mostly lesser effect at the required site lead to development of local drug delivery (LDD) systems for direct administration of antibiotics into the periodontal pockets. LDD systems include gel delivery syringe, mucus adhesive gels, collagen fiber vehicle, films, synthetic polymer chips, strips and compacts [2]. Among which gel formulations have more advantages because of their sustainability, prolonged release, stability in the pockets [4].

Simvastatin (SMV) belongs to the family of statins. It is a specific competitive inhibitor of 3-hydroxy-2-methyl-glutaryl coenzyme A reductase and is widely used for lowering cholesterol and reducing the risk for heart attacks [4]. Statins have potential anti-inflammatory effect on oral epithelial cells blocking the

intermediate metabolites of the mevalonate pathway and also modulate bone formation by increasing the expression of bone morphogenetic protein-2 providing a new direction in the field of periodontal therapy [5, 6]. Statin administration decreases GCF levels of proinflammatory mediators which are responsible for much of the host tissue destruction seen in periodontitis [7, 8].

Metformin (1, 1-dimethylbiguanide) is a biguanide used in treatment of diabetes mellitus type II as an anti-hyperglycemic. It acts at molecular level via both AMPK (5'adenosine monophosphate activated protein kinase) dependent & AMPK independent pathways [9].

Metformin showed direct effects on inflammation, including effects on Nuclear Factor-κB (NF-κB) (which is a key regulator during inflammatory process), differentiation of monocytes into macrophages as well as suppressing pro-inflammatory cytokines like such as IL-2, interferon (IFN)-γ and TNF-α from these macrophages which thereby improved the periodontal clinical parameters [9].

There is no evidence of literature till now comparing the clinical efficacy of 1.2% Simvastatin gel with 1% Metformin gel in patients with chronic periodontitis.

Thus this study is designed to evaluate and compare the clinical efficacy of locally delivered 1.2% Simvastatin gel and 1% Metformin gel as an adjunct to scaling and root planning in chronic periodontitis patients.

2. MATERIAL AND METHODS

2.1. Sample Size: The study population consisted of 48 sites from chronic periodontitis patients, equal number of males and females in the age group of 25-55 years. The procedure was explained and a written informed consent was obtained from the participants prior to the study.

2.2. Patient Selection: The following inclusion and exclusion criteria were used for the selection of participants:

a. Inclusion Criteria:

1. Age group of 25 to 55 years both genders (equal sex predilection).
2. Chronic periodontitis patients with sites showing probing depth (PD) ≥5 mm.
3. Relative attachment level (RAL) ≥3 mm and radiographic evidence of bone loss on intraoral periapical radiographs.
4. Patients agreeing to sign informed consent and willing to return for follow up visits.

b. Exclusion Criteria:

1. Patients with known history of systemic diseases as hypertension, Human Immunodeficiency Virus (HIV), bone disorders, renal disorders, radiation therapy, cancer patients, infectious diseases and any other systemic disease that can alter the course of periodontal disease.
2. History of periodontal therapy or use of antibiotics in the preceding 6 months.
3. History of prolonged use of steroids/ immunosuppressive agents / anticoagulants.
4. Patients with aggressive periodontitis.
5. History of known allergy to Simvastatin.
6. Pregnant/Lactating women.
7. History of tobacco in any form.

c. Subject Stratification: A total of 48 sites with atleast 1 deep pocket with ≥ 5mm PPD ≥3 mm RAL in one quadrant were selected. Sample size was determined based on the power analysis at a confidence level of 95% ($p<0.05$). In each patient one pair of periodontal pocket was randomly divided into 3 groups (Figure 1):

Group A (n=16 sites): Scaling and root planing alone.
Group B (n=16 sites): Scaling and root planing + 1.2% Simvastatin gel.
Group C (n=16 sites): Scaling and root planing + 1% Metformin gel.

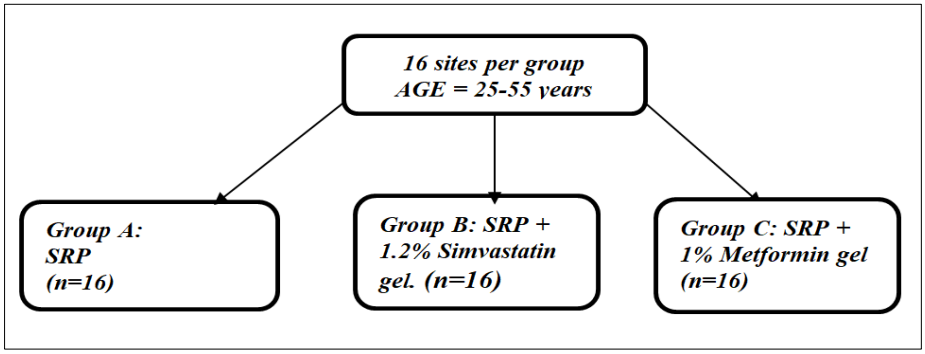


Figure 1

d. Clinical Parameters: Recorded at day 0 (baseline), 1 month, 3 months and 6 months post therapy:

1. **Plaque Index (PI)** – (Silness and Loë 1964) [10]
2. **Gingival Index (GI)** – (Loë and Sliness 1963) [11]
3. **Probing Pocket Depth (PPD):** from the crest of gingival margin to the base of gingival pocket
4. **Relative Attachment Level (RAL):** from the lower border of the acrylic stent to the base of pocket
5. **Relative Gingival Marginal Level (RGML):** from the lower border of the acrylic stent to the gingival crest

2.3. Preparation of Custom Made Acrylic Stent [12]:

For standardization of clinical measurements, occlusal acrylic stents were used. These stents were fabricated using cold cure acrylic resin on a cast model obtained from an alginate impression. Each stent was made to cover the tooth from the occlusal surface of the tooth being treated, the occlusal surfaces of at least 1 tooth in the mesial and distal directions and extended apically on the buccal and lingual surfaces to cover the middle third of the teeth involved. Grooves were placed so that measurements made post-treatment could be at the same position and angulation as those made prior to therapy. With the acrylic stent in position, the periodontal probe was inserted into the pocket at an angle necessary at an angle to reach the deepest portion of the pocket. A pencil mark was made where the probe made contact with the acrylic stent; and a groove was made on the pencil marked area with a cylindrical low speed bur. UNC-15 probe was used for measurements and all the measurements were rounded off to the nearest millimetre.

2.4. Preparation of Gel:

a. Metformin 1% Gel [7]: 20 mg of Metformin in required amount of distilled water, 75 mg of dry gellan gum powder dispersed in distilled water maintained at 95°C. The dispersion was stirred at 95°C for 20 minutes to facilitate hydration of gellan gum. The required amount of mannitol was added to the gellan gum solution with continuous stirring, the temperature was maintained above 80°C. A weighed amount of MF was added with stirring. Then glycerine, sucralose, citric acid, and preservatives (methylparaben) were added while stirring. Finally, the required amount of sodium citrate was dissolved in 10 mL distilled water and added to the mixture. The mixture was allowed to cool to room temperature to form gel.

b. Simvastatin 1.2 % Gel [13]: 2.5 g of methylcellulose was added to 100 g of water slowly and stirred continuously at 90°C for 20 minutes. Once this was prepared, 1.2 g of SMV was added slowly with continuous stirring to get the preparation. The mixture was allowed to cool at room temperature to form gel.

3. CLINICAL PROCEDURE

Patients with minimum 3 periodontal pockets ≥5 mm depth and ≥3 mm attachment loss were selected. (Minimum 1 deep periodontal pocket per quadrant). The selected sites were randomly divided into 3 groups (16 sites in each group) by SNOSE allocation and were treated with SRP alone (Group A), SRP plus 1.2% Simvastatin gel (Group B) and SRP plus 1% Metformin Gel (Group C).

Full mouth sub ragingival and sub gingival scaling and root planning were performed in single visit at baseline for all the 3 groups with the help of ultrasonic scalers and Gracey curettes until root surface appeared to be smooth and clean. No antibiotics, antiplaque and anti-inflammatory agents were prescribed after treatment.

Group A SRP Alone:

- SRP and saline irrigation were performed at the selected site and the entire quadrant, followed by the periodontal dressing at the entire quadrant.

Group B - SRP Followed by Application of 1.2% Simvastatin Gel:

- The entire quadrant including the selected treatment site was irrigated with normal saline and the treatment site was isolated with cotton roles.
- 1.2% Simvastatin gel was loaded in a syringe with a blunt needle and delivered into the pocket with gentle force.
- The needle was slowly withdrawn from the periodontal pocket so that the material filled the depths and curves of the pocket site.
- The gingiva was carefully adapted to close the entrance of the gingival margin of the periodontal pocket. Periodontal dressing was placed in the entire quadrant to ensure that the gel remained in place. The dressing was removed after 7 days.

Group C - SRP Followed by Application of 1% Metformin Gel

- The entire quadrant including the selected treatment site was irrigated with normal saline and the treatment site was isolated with cotton roles.
- 1% Metformin Gel was loaded in a syringe with a blunt needle and delivered into the pocket with gentle force.
- The needle was slowly withdrawn from the periodontal pocket so that the material filled the depths and curves of the pocket site.
- The gingiva was carefully adapted to close the entrance of the gingival margin of the periodontal pocket. Periodontal dressing was placed in the entire quadrant to ensure that the gel remained in place. The dressing was removed after 7 days.
- For Group B and Group C the entire quadrant including the selected treatment site was irrigated with normal saline and isolated with cotton roles.

4. POST THERAPY CARE AND FOLLOW UP

For the time the periodontal dressing was placed the patients were advised not to brush in the area. After which they were advised to use a soft bristled toothbrush with a fluoridated toothpaste and brush twice daily employing the modified Bass technique.

5. RESULTS

The present study was carried out to evaluate the clinical efficacy of locally delivered 1.2% Simvastatin gel and 1% Metformin gel as adjunct to scaling and root planning in Chronic Periodontitis patients.A total of 48 sites in chronic periodontitis patients satisfying the inclusion criteria and agreeing to participate voluntarily were included in the study.
At the selected sites, following clinical parameters were recorded at day 0 (baseline), 1 month, 3months and 6 months post therapy:

5.1. Clinical Parameters

A. Plaque Index (PI)

Group A: The mean plaque index score at baseline was 2.0750±.20817.
At 1 month it reduced to 1.8062±.32139 mm, at 3 months 1.600±.31411mm. At 6 months the PI reduced to 1.3438±.31405 mm which was not statistically not significant (p<0.01) at all time periods (Table1).

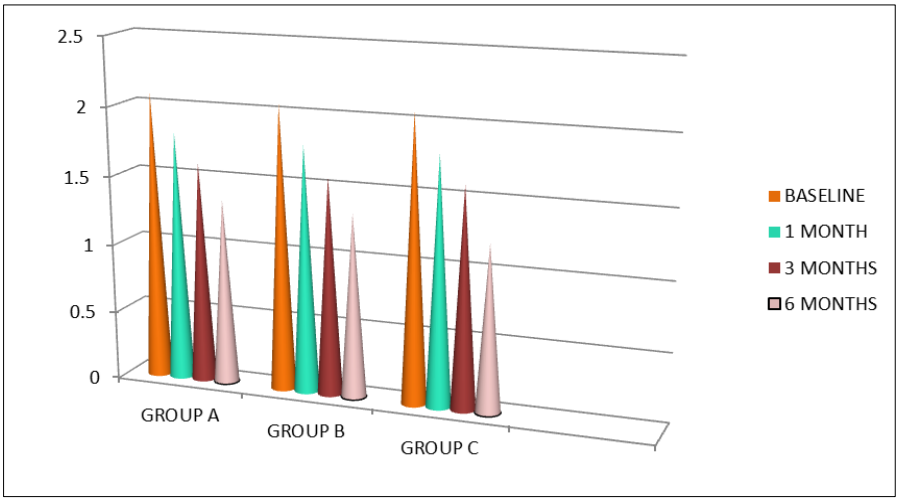
Group B: The mean plaque index score at baseline was 2.0563± .35957mm.
At 1 month it reduced to 1.7875± .36125mm, at 3 months1.5750±.339611mm, at 6 months the mean plaque index was 1.3313±.39110mm which was not statistically significant (p<0.01) (Table1)

Group C: The mean plaque index score at baseline was 2.0688 ±.21203mm.
At 1 month it reduced to 1.7938 ±.16112mm, at 3 months it reduced to 1.600±.24221mm. At 6 months it reduced to 1.2062± .37677 mm showing no statistical significant difference (p<0.01). (Table 1)

Intergroup Comparison: Comparison between PI scores of the three groups showed difference. At baseline p>0.980, 1 month p>0.983, 3 months p>0.964 and 6 months p>0.499 respectively but were not statistically significant. At 3 months the mean difference was 0.2500 and .0 respectively with p value of 1.00.At 6 months the mean difference was .01250 and .13750 with p value of 1.000 and .866 respectively which was not statistically different. (GRAPH 1)

Table 1

		GROUP A	GROUP B	GROUP C	P value
PLAQUE INDEX	**Baseline**	2.0750±.20817	2.0563±.35957	2.0688±.21203	.980
	1 month	1.8062±.32139	1.7875±.36125	1.7938±1.6112	.983
	3 months	1.6000±.31411	1.5750±.33961	1.6000±.24221	.964
	6 months	1.3438±.31405	1.3313±.39110	1.2062±.37677	.499



Graph 1: Intergroup Comparison of Plaque Index at Baseline, 1 Month 3 Months and 6 Months

B. Gingival Index (GI)

Group A: The mean gingival index score at baseline was 2.2875±.32634mm. At 1 month it was 1.963 ± .40161mm, at 3 months 1.6875 ±.46886mm. The gingival index score at 6 months was 1.3937±.46543mm. The difference was not statistically significant (Table 2).

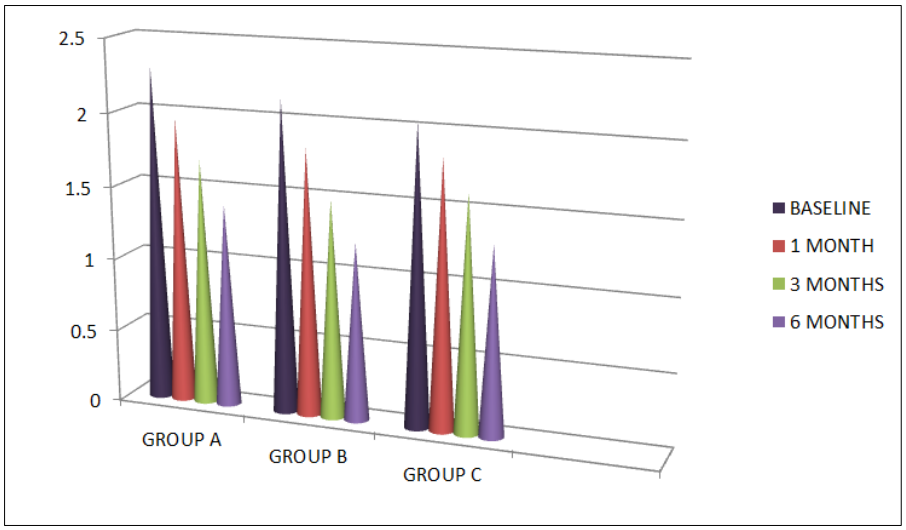
Group B: The mean gingival index score at baseline was 2.1375±.25788mm. At 1 month it was 1.8250 ± .40161mm, at 3 months 1.4938±.33160mm. The gingival index score at 6 months was 1.288±.35818 mm. The difference was not statistically significant (Table 2).

Group C: The mean gingival index score at baseline was 2.0500±.28284mm, at 1 month it was 1.8313± .28453mm, at 3 months the GI was 1.688± .31458mm. At 6 months it was 1.2938±.34150 mm. The difference was not statistically significant (Table 2).

Intergroup Comparison: Comparison between GI scores of group A, group B group **C** at baseline, 1 month 3 months and 6 months showed no statistical significant difference p>.076 , p>0.456 , p>0.348, p>0.455 respectively. (GRAPH 2)

Table 2

		GROUP A	GROUP B	GROUP C	p value
GINGIVAL INDEX	**Baseline**	2.2875±.32634	2.1375±.25788	2.0500±.28284	0.76
	1 month	1.9563±.40161	1.8250±.29552	1.8313±.28453	0.456
	3 months	1.6875±.46886	1.4938±.33160	1.6188±.31411	0.348
	6 months	1.3937±.46543	1.2188±.35818	1.2938±.34150	0.455



Graph 2: Intergroup Comparison of Gingival Index at Baseline, 1 Month 3 Months and 6 Months

C. Probing Pocket Depth (PPD)

Group A: The mean probing pocket depth at baseline was 8.6875±.94648 mm. At 1 month PD reduced to 7.5625±1.03078, and at 3 months PD reduced to 6.7500 ± 1.06458mm showing a reduction of 5.63mm. At 6 months the PPD was 5.7500±.68313mm. (Table 3).

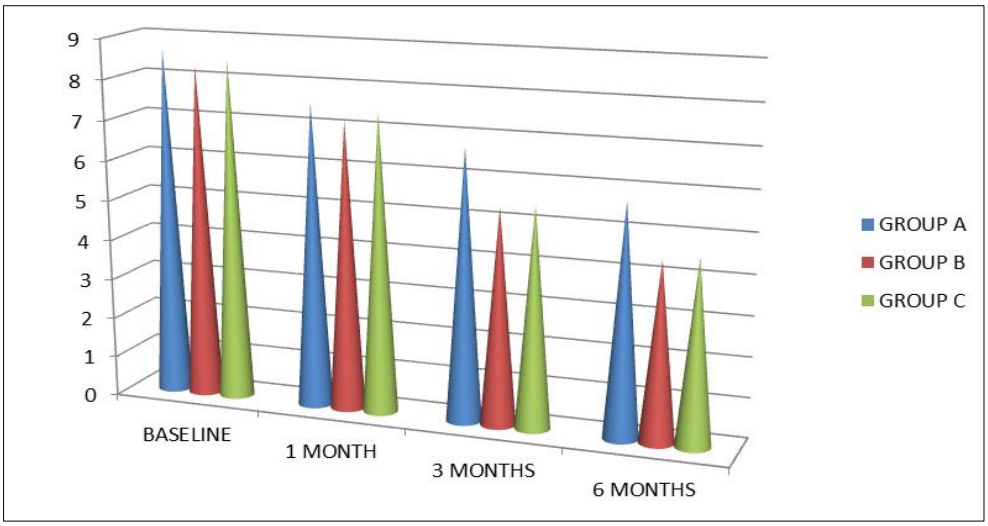
Group B: The mean probing pocket depth at baseline was 8.3125±1.07819mm**.** At 1 month PD reduced to 7.1875±.98107mm and at 3 months PD reduced to 5.3750±.80623. At 6 months PPD was 4.4375±.51235 mm. (Table 3).

Group C: The mean probing pocket depth at baseline was 8.500±.89443mm. At 1 month PD reduced to 7.4375± .81394mm and at 3 months PD reduced to 5.5000±1.03280 mm.At 6 months PPD was 4.5625±.62915 mm. (Table 3).

Intergroup Comparison: Comparison between PD of all groups at baseline and 1 month was not statistically significant p>0.558 and p>0.526, at 3 months and 6 months it was statistically significant, with p value p<0.001 respectively (GRAPH 3).

Table 3

		GROUP A	GROUP B	GROUP C	p value
PROBING POCKET DEPTH	**Baseline**	8.6875±.94648	8.3125±1.07819	8.5000±.89443	.558
	1 month	7.5625±1.03078	7.1875±.98107	7.4375±.81394	.526
	3 months	6.7500±1.06458	5.3750±.80623	5.5000±1.03280	**<.001***
	6 months	5.7500±.68313	4.4375±.51235	4.5625±.62915	**<.001***



Graph 3: Inter Group Comparison of Probing Pocket Depth of Group A, Group B, Group C at Baseline, 1 Month, 3 Months and 6 Months

D. Relative Attachment Level (RAL)

Group A: The mean relative attachment level at baseline was 10.8750 ± 1.31022mm.
At 1 month RAL reduced to 9.8750±1.14746 mm**,** at 3 months 8.3750±.80623mm and at 6 months RAL was 7.3125±.60208mm. (Table 4).

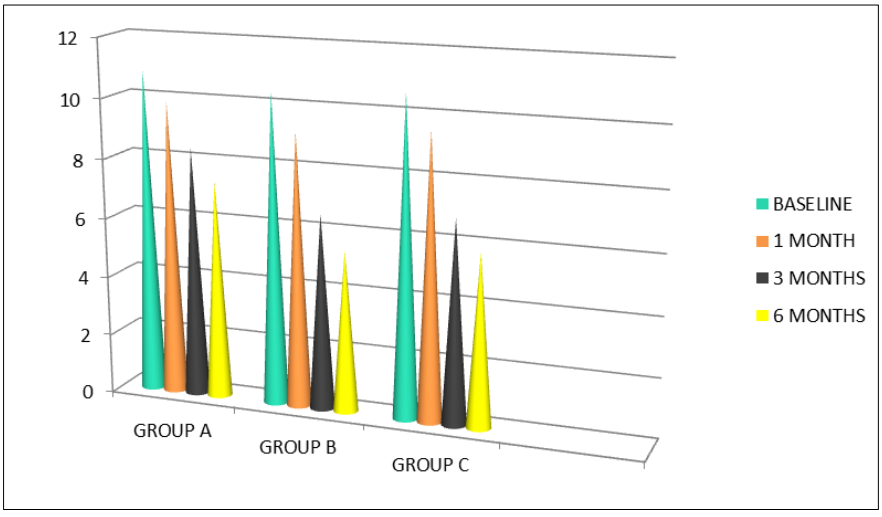
Group B: At baseline was 10.4375±1.09354mm, at 1 month RAL reduced to 9.1875±1.37689mm at 3 months RAL reduced to 6.5625±.96393 mm. At 6 months RAL was 5.4375±.51235mm. (Table 4).

Group C: The mean relative attachment level at baseline was 10.6875±1.07819 mm.
At 1 month RAL reduced to 9.5625±1.03078mm, at 3 months RAL reduced to 6.8125±1.16726mm.
At 6 months RAL was 5.8125±.75000mm. (Table 4).

Intergroup Comparison: Comparison between RAL of GROUP A, GROUP B, GROUP C baseline was not statistically significant p>0.571. At 3 months the RAL of GROUP A compared to GROUP B AND GROUP C was statistically significant**<0.001** At 6 months RAL was statistically significant compared to both GROUP B and GROUP C **<.001.** (GRAPH 4)

Table 4

		GROUPA	GROUPB	GROUP C	p value
RELATIVE ATTACHMENT LEVEL	**Baseline**	10.8750±1.31022	10.4375±1.09354	10.6875±1.07819	.571
	1 month	9.8750±1.14746	9.1875±1.37689	9.5625±1.03078	.275
	3 months	8.3750±.80623	6.5625±.96393	6.8125±1.16726	**<.001***
	6 months	7.3125±.60208	5.4375±.51235	5.8125±.75000	**<.001***



Graph 4: Inter Group Comparison Ral of Group A, Group B, Group C At Baseline, 1 Month, 3 Months and 6 Months

E. Relative Gingival Margin Level (RGML)

Group A: The mean RGML at baseline was 2.3750±.80623mm. At 1 month, this distance increased to 2.3125±.70415. At 3 months 1.6875± .60208 mm, 6 months 1.6250± .61914mm (Table 5).

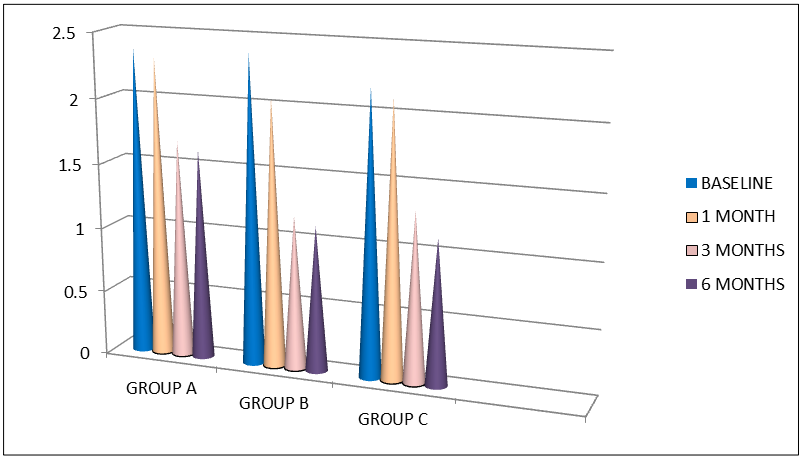
Group B: The mean Relative Gingival Margin level at baseline was 2.3750±.88506mm. At 1 month, this distance increased to 2.0625±.77190. At 3 months RGML was 1.1875±.40311. At 6 months 1.2500±.34157mm. (Table 5).

Group C: The mean Relative Gingival Margin level at baseline was 3.0±1.05mm. At 1 month, it was 2.1250±.71880mm. At 3 months RGML was 1.3125±.47871
At 6 months the RGML was 1.2500±.44721 (Table 5).

Intergroup Comparison: At baseline was statistically insignificant with a p value of 1.000. At 1 month it was statistically insignificant with a p value of 1.000. At 3 months it was p.021 statistically significant with respect to GROUP B, with GROUP C it was p.120 which was statistically insignificant.
At 6 months the RGML with respect to GROUP A was .016 which was statistically significant and GROUP C was 1.00 which was statistically insignificant (GRAPH 5).

Table 5

RELATIVE GINGIVAL MARGIN LEVEL		**GROUP A**	**GROUP B**	**GROUP C**	**P VALUE**
	Baseline	2.3750±.80623	2.3750±.88506	2.1875±.54391	.724
					H
	1 month	2.3125±.70415	2.0625±.7190	2.1250±.71880	.607
	3 months	1.6875±.60208	1.1875±.40311	1.3125±.47871	**.019***
	6 months	1.6250±.61914	1.1250±.34157	1.2500±.44721	**0.15***
		0.001*	0.001*	0.001*	



Graph 5: Inter Group Comparison of Relative Gingival Margin Level of Group A, Group B, Group C at Baseline, 1 Month, 3 Months and 6 Months

6. DISCUSSION

The current study has evaluated the clinical efficacy of two locally delivered drugs as an adjunct to scaling root planning (SRP) in Chronic Periodontitis (CP) patients.

Simvastatin (SMV) gel as an adjunct to SRP and Metformin (MF) gel as an adjunct to SRP for the treatment of patients with CP were evaluated in this split mouth study. The present study selected chronic periodontitis patients with a pocket probing depth (PPD) of ≥ 5mm, Relative Attachment Level (RAL) ≥3 mm. Patients from age group of 25 to 55 years from both genders were included in the study. This was done to comply with the indications for the use of Local drug delivery systems and avoid age and gender related bias in the final outcomes of the study [14].

The exclusion criteria for the study were patients with a known history of systemic antibiotics or other medications within the last 6 months as it could affect the outcome of the study. Those who smoked or consumed any form of tobacco were also excluded from the study as tobacco is known to impair periodontal healing and may also interfere with the therapeutic outcome of periodontal therapy [15]. Pregnant patients were not included as hormonal changes of pregnancy predispose to periodontal changes [16].

The present study was a randomized case controlled study with split mouth design so that the effect of a natural variation between different individuals can be avoided. In the present study, there was significant reduction in all the clinical parameters at 1 month, 3 months and 6 months compared to baseline in all the three groups, being most significant in group A (SRP+1.2% SMV) AND group B (SRP+1%MF) when compared to group A i.e SRP alone.

The Plaque index (PI) and Gingival Index (GI) values were significant between all groups at all-time intervals (baseline, 1 month, 3 months and 6 months) but the values were not statistically significant. This could be attributed to thorough Scaling and root planning at baseline and strict oral hygiene and home care maintenance advised to each patient. Moreover because it was a split mouth clinical trial, the PI and GI values were more or less similar at all-time intervals and were not statistically significant. Our study is in accordance with the study by Pradeep *et al*,[17].

The soft tissue evaluation parameters included our study were probing pocket depth (PPD), relative attachment level (RAL) and relative gingival margin level (RGML). All measurement were measured using UNC – 15 periodontal probe and an acrylic stent which served as a fixed reference point to standardize each measurement at recall visits as well. The RGML values were statistically significant in SMV group as well as MF group as compared to SRP alone attributing to greater tissue shrinkage followed by use of SMV and MF LDD systems.

Reduction in PPD is one of the most sought out outcomes of any periodontal therapy and is the most important factor in determining further treatment and maintenance there after by the patient.

Intra group comparison of PPD and RAL of group A(SRP) with group B(SRP +1.2% SMV) and group C(SRP+ 1% MF) was statistically significant at 3 months and 6 months, but there was no significant difference in PD and RAL of group B with group C.

Our study is in accordance with the studies by Pradeep *et al*, [7, 17] and Rao NS *et al*, [18] in which the clinical parameters PD and CAL also showed no difference between all groups at baseline. However, MF groups and SMV group showed significantly greater PD reduction and CAL gain at 3 and 6 months than the placebo group.

Scaling and root planing alone may not be capable of improving the clinical parameters in patients with CP as it may not eradicate the bacterial species colonizing the subgingival pockets due to their invasive potential into gingival epithelial cells and subepithelial connective tissues [19].

A reduction in the prevalence of these pathogens has been seen when SRP was used in combination with antimicrobials [20]. However antimicrobials have multiple systemic side effects unlike LDD which is highly site specific [21] and their local application into periodontal pockets may further suppress periodontal pathogens and thereby augment the effects of conventional mechanical periodontal therapy.

Simvastatin and Metformin have been used as adjuncts to scaling and root planning in treatment of chronic periodontitis patients showing clinically significant results.

Metformin (MF) (1, 1-dimethylbiguanide HCl), first developed in 1957, is one of the most commonly used oral anti-hyperglycemic agents for the treatment of type II diabetes mellitus [22].

Research has shed light on a therapeutic action of MF in stimulating osteoblastic differentiation and bone formation [23]. It is attributed to its effectiveness in increasing type I collagen production in cells and stimulating alkaline phosphatase activity in MC3T3E1 osteoblasts. Metformin has also shown to significantly suppressed the inflammatory responses induced by P. gingivalis LPS in hPDLCs characterized by reduced production and secretion of IL-1β and IL-18 [24] and its inhibitory effects on LPS-influenced inflammatory cytokine production in HGFs [25].

Simvastatin belongs to a 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 [26].

Statins also have potential anti-inflammatory effect owing to numerous reasons as proven by studies which state that Statins deplete the isoprenoids, which inhibit the signalling pathway for IL-1- and IL-6-mediated inflammation [27]. Studies have also shown that hyperlipidemic patients are more prone to periodontal disease and statins have positive impact on periodontal health [28] as a local drug delivery, both metformin and statins have shown to have several advantages in the treatment of periodontal diseases [29].

Hence, with the concluding results of the present study the clinical effect of 1.2% Simvastatin gel and 1% Metformin gel improve the periodontal health with statistically significant improvement in the PPD, RAL, RGML values compared to SRP alone.

6.1 Strength of the Present Study

- The present study was performed by the same operator; it was a randomized case controlled study with split mouth design in which the effect of a

natural variation between different individuals was avoided.

- Patients who met with all the inclusion criteria were included in the study.
- The follow up intervals and clinical parameters were uniform thus decreasing heterogeneity.

The results of our study showed a considerable change in PI, GI, and statistically significant changes in PPD, RAL and RGML.

Nevertheless, further long-term, multicenter, randomized, controlled clinical trials will be required to know its clinical and histologic effects as well as radiographic changes in the bone.

6.2 Implications for Future Research

Efficacy of Simvastatin and Metformin as LDD can be studied and compared to other drugs in other forms of periodontitis in patients with or without underlying systemic conditions.

Different vehicles and concentrations of the drugs are also needed to be researched.

Future focus is directed to develop novel agents which are low of cost, readily available, without any side effects and beneficial to the patients in terms of disrupting the nature and cause of the disease.

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