Research Article

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Comparative Evaluation of Locally Delivered Statins (1.2% Atorvastatin) and Antibiotic (1% Ornidazole) Gel in the Treatment of Chronic Periodontitis: A Clinico-Biochemical Study

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ABSTRACT

Background: The local delivery of therapeutic agents to periodontal pockets has the benefit of administering more drugs at the target site, thus achieving high intrasulcular drug concentrations, avoiding its systemic side effects, and a better patient compliance. This present study was conducted to evaluate the efficacy of locally delivered 1.2% atorvastatin Gel in comparison to 1% ornidazole gel in the treatment of chronic periodontitis.

Materials and Methods: 44 Subjects selected on the basis of inclusion criteria were categorized into two treatment groups. GROUP I (n=22): Patients treated by SRP with subgingival 1.2% Atorvastatin gel. GROUP II (n=22): Patients treated by SRP with subgingival 1% ornidazole gel. Clinical parameters of mean sulcular bleeding index, probing depth, relative attachment level were recorded at baseline, 1 month and 3 months and GCF TNFα levels were recorded at baseline and 1 month.

Result: Overall observation in the present study on the basis of clinical and biochemical results achieved has revealed that in both Group A (SRP + 1.2% Atorvastatin) and Group B (SRP + 1% Ornidazole), there was statistically significant reduction in clinical parameters (m SBI, PD), gain in RAL at 1 and 3 months postoperatively, along with the GCF TNF-α levels. On comparison between Group A and Group B, both the Groups exhibited similar significant improvement in all the clinical parameters but group A exhibited more significant reduction in GCF TNF α levels as compared to group B.

Conclusion: The results of the present study favour the use of both locally delivered atorvastatin and ornidazole in the treatment of chronic periodontitis.

Keywords: Chronic periodontitis, statins, ornidazole, local drug delivery, TNF alpha.

INTRODUCTION

Periodontal disease is a general term which encompasses several pathological conditions affecting the tooth supporting structures[1]. Periodontitis is defined as an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or group of specific microorganisms resulting in progressive destruction of the periodontal ligament and alveolar

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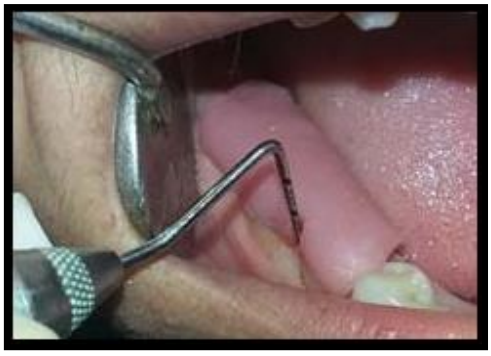
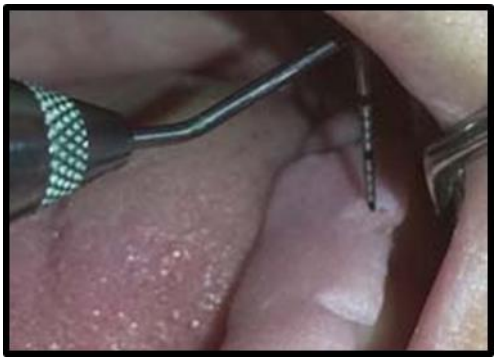
GROUP I (1.2 % ATORVASTATIN)

FIGURE 1



GROUP II (1% ORNIDAZOLE)

FIGURE 2



Preoperative clinical measurements

FIGURE 3

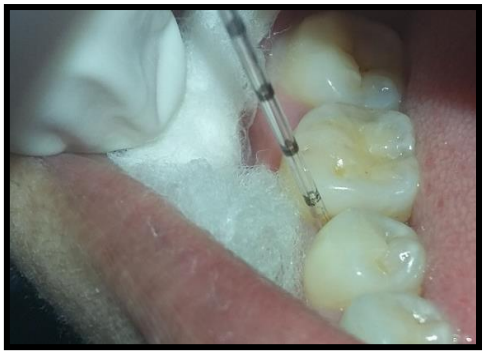
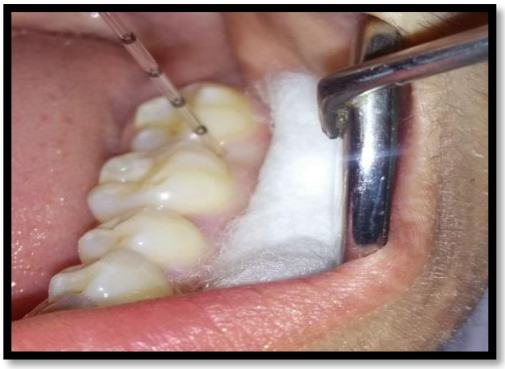
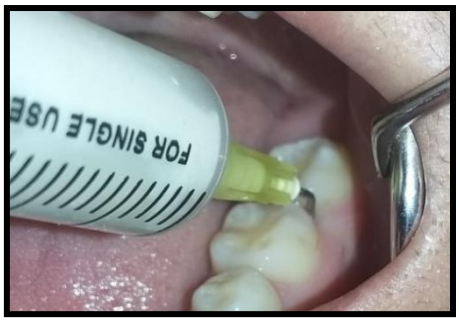


FIGURE 4



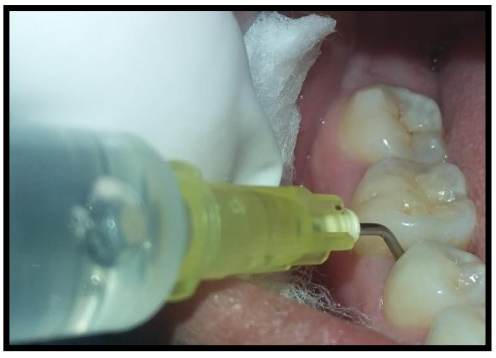
Preoperative GCF collection

FIGURE 5



Subgingival delivery of 1.2% Atorvastatin

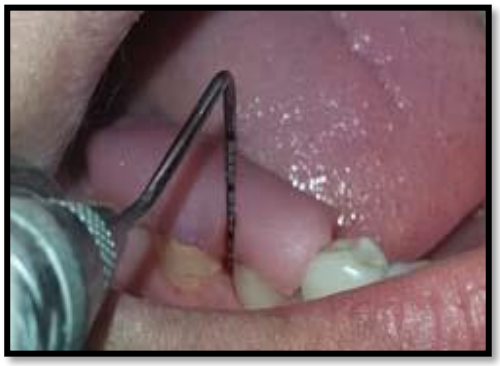
FIGURE 6

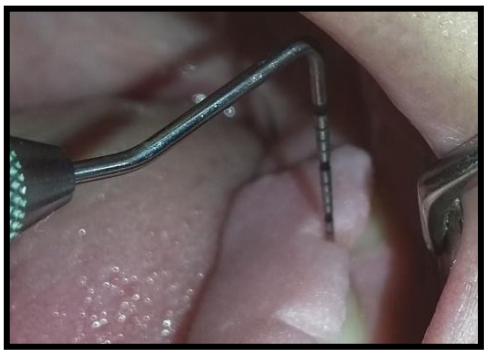


Subgingival delivery of 1% Ornidazole

FIGURE 7

FIGURE 8





Postoperative clinical measurements

FIGURE 9

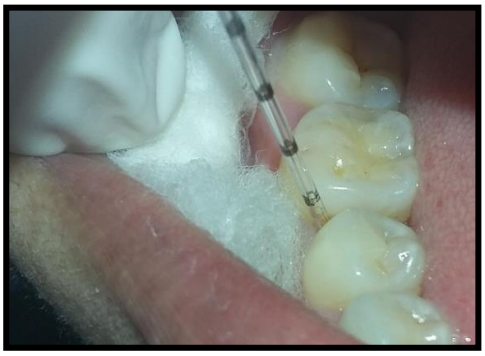
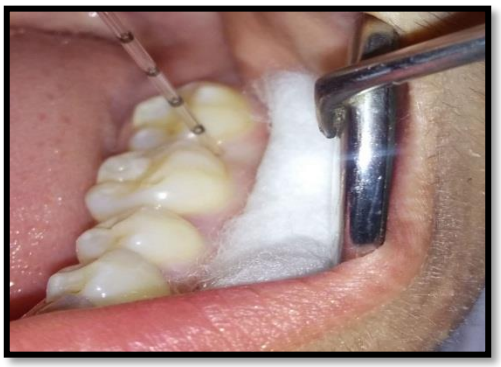


FIGURE 10



Postopertive GCF collection

bone with increased probing depth formation, recession or both[2]. The clinical signs of periodontitis are changes in the morphology of gingival tissues, bleeding upon probing, as well as periodontal pocket formation[3]. Traditional therapies for periodontal disease have included mechanical debridement to disrupt the subgingival flora and provide clean, smooth and biologically compatible root surfaces[1]. The concept of local drug delivery was championed by Dr . Max Goodson in the year 1979. Local drug delivery allows the use of concentrations of approximately 100 times higher that does systemic administration.

Various agents have been used and investigated as local drug delivery in the treatment of periodontal disease. The present study is designed to investigate the effectiveness of locally deliverd statins (1.2% Simvastatin) in comparison to an antibiotic (1% Ornidazole) gel in the treatment of chronic periodontitis. Statins are 3 – hydroxy 3- methyl glutryl co enzyme reductase inhibitors describe to prevent cardiovascular and cerebrovascular diseases[4]. Statins inhibil HMG coA reductase and decrease the production of mevalonate, geranyl pyrophosphate and farnesyl pyrophosphate and substituent products on the way to construction of the cholesterol molecule. Thus, statins could inhibit inflammation by inhibition of the cholesterol pathway and intercellularly interfering with Ras superfamily protein function. Statins have pleiotropic effects like anti inflammatory, anti oxidant and anabolic effects on bone apart from lipid lowering action[5].

Atorvastatin has been found to be more effective compared to simvastatin and pravastatin in patents with hyperlipidemia. Atorvastatin therapy decreases tumour necrosis factor TNF alpha) production in lipopolysacchrides – activated monocytes, confirming the anti inflammatory properties of this class of drugs[6]. Antibacterial agents have been used widely in the management of periodontal infection[7]. Scaling and root planning

Table 1: Intragroup Comparison of mSBI Scores Between the Different Intervals: Baseline, 1 Month And 3 Months.

Group I			
	Interval	P value	Significance
Baseline	2.39±0.35	0.001	Significant
1 Month	1.14±0.47		
3 Month	0.93±0.47		
Group II			
Groups	Baseline (Mean±SD)	P value	Significance
Baseline	2.52±0.30	0.001	Significant
1 Month	1.13±0.30		
3 Month	0.93±0.29		

Table 2: Intergroup Comparison of Change In mSBI Index Scores Between The Different Intervals –Baseline, 1 Month And 3 Months.

Baseline and 1 month						
Groups	Baseline (Mean±SD)	1 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	2.39±0.35	1.14±0.47	1.24±0.36	52.96±17.86	0.572	Non –Significant
Group II	2.52±0.30	1.13±0.30	1.38±0.20	55.48±10.70		
Baseline and 3 months						
Groups	Baseline (Mean±SD)	3 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	2.39±0.35	0.93±0.47	1.45±0.36	61.86±17.99	0.725	Non -Significant
Group II	2.52±0.30	0.93±0.29	1.58±0.21	63.46±11.09		
1 Month and 3 Month Interval						
Groups	1 Month (Mean±SD)	3 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	1.14±0.47	0.93±0.47	0.21±0.04	22.04±10.63	0.392	Non -Significant
Group II	1.13±0.30	0.93±0.29	0.20±0.05	19.48±8.91		

Table 3: Intragroup Comparison of PD Scores Between the Different Intervals –Baseline, 1 Month And 3 Months.

Group I			
Intervals	Mean ±SD	P value	Significance
Baseline	6.44±0.83	0.001	Significant
1 Month	4.19±0.83		
3 Month	3.14±0.90		
Group II			
Intervals	Mean ±SD	P value	Significance
Baseline	6.23±0.89	0.001	Significant
1 Month	4.06±0.90		
3 Month	2.95±0.92		

Table 4: Groupwise comparison of change in PD scores between the different intervals –baseline, 1 month and 3 months.

Baseline and 1 month						
Groups	Baseline (Mean±SD)	1 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	6.44±0.83	4.19±0.83	2.24±0.24	35.33±5.46	0.861	Non -Significant
Group II	6.23±0.89	4.06±0.90	2.17±0.06	35.62±5.26		
Baseline and 3 months						
Groups	Baseline (Mean±SD)	3 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	6.44±0.83	3.14±0.90	3.29±0.38	52.05±8.97	0.560	Non -Significant
Group II	6.23±0.89	2.95±0.92	3.28±0.28	53.59±8.48		
1 Month and 3 Month Interval						
Groups	1 Month (Mean±SD)	3 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	4.19±0.83	3.14±0.90	1.05±0.30	26.27±9.31	0.443	Non -Significant
Group II	4.06±0.90	2.95±0.92	1.10±0.26	28.35±8.46		

Table 5: Intragroup comparison of RAL index scores between the different intervals –baseline, 1 month and 3 months.

Interval	Mean ± SD	P value	Significance
Baseline	6.10±0.94	0.001	Significant
1 Month	3.38±0.97		
3 Month	1.93±0.92		
Group II			
Interval	Mean ± SD	P value	Significance
Baseline	5.80±0.93	0.001	Significant
1 Month	2.91±0.97		
3 Month	1.55±0.79		

P*<0.005- significant

Table 6: Intergroup comparison of change in RAL scores between the different intervals –baseline, 1 month and 3 months.

Baseline and 1 month						
Groups	Baseline (Mean±SD)	1 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	6.10±0.94	3.38±0.97	2.72±0.37	45.56±8.91	0.05	Non -Significant
Group II	5.80±0.93	2.91±0.97	2.89±0.20	51.10±9.34		
Baseline and 3 months						
Groups	Baseline (Mean±SD)	3 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	6.10±0.94	1.93±0.92	4.16±0.62	69.38±11.42	0.111	Non -Significant
Group II	5.80±0.93	1.55±0.79	4.25±0.37	74.48±9.26		
1 Month and 3 Month Interval						

Groups	1 Month (Mean±SD)	3 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	3.38±0.97	1.93±0.92	1.44±0.60	44.33±16.02	0.299	Non -Significant
Group II	2.91±0.97	1.55±0.79	1.36±0.37	48.67±10.86		

Table 7: Intragroup comparison of GCF TNF α levels between the different intervals –baseline, 1 month.

Group I			
Interval	Mean±SD	P value	Significance
Baseline	77.41±6.30	0.001	Significant
1 Month	14.09±3.09		
Group II			
Interval	Mean±SD	P value	Significance
Baseline	76.53±6.63	0.001	Non -Significant
1 Month	38.05±6.89		

Table 8: Groupwise comparison of change in GCF TNF α scores between the different intervals –baseline, 1 month.

Baseline and 1 month						
Groups	Baseline (Mean±SD)	1 Month Interval (Mean±SD)	Mean Change b/w intervals	%change b/w the intervals	Independent t Test for significance of change	
					P value	Significance
Group I	77.41±6.30	14.09±3.09	63.32±7.65	81.58±4.72	0.001	Significant
Group II	76.53±6.63	38.05±6.89	38.48±8.75	50.05±9.25		

combined with administration of systemic antibiotics as adjunctive antimicrobial therapy has shown a favourable clinical and microbiological outcome in general aggressive periodontitis patients, when compared with scaling and root planing[8]. Nitroimidazole compound is one such agent that acts by inhibiting DNA synthesis. The nitro group gets reduced to anion radicals which causes oxidation of DNA leading to strand breakage and cell death. Hence, it has both anti-microbial and mutagenic effect.

This present study was conducted to evaluate the efficacy of locally delivered 1.2% atorvastatin Gel in comparison to 1% ornidazole gel in the treatment of chronic periodontitis.

AIM

The aim of the present study is to evaluate and compare the clinical efficacy of locally delivered statins (1.2% Atorvastatin) with antibiotic (1% ornidazole) gel in the treatment of chronic periodontitis and their effect on GCF TNF α.

MATERIAL AND METHOD

Forty four Patients with in age range of 25-55 years of both the sexes were selected from the Out Patient Department of Periodontology of DJ College of Dental Sciences and Research, Modinagar, Uttar Pradesh. Each patient was given a detailed verbal and written description of the study.

Inclusion Criteria

1. Systemically healthy patients with chronic periodontitis having a pocket depth of ≥5mm
2. No history of antibiotic or periodontal therapy in the preceding 6 months.
3. Age group of 25 – 55 years.

Exclusion Criteria

1. Patients with aggressive periodontitis, smokers, alcoholics, diabetes, hypertension, immunocompromised patients, and pregnant or lactating mothers.

2. Patients with dental infections like chronic peri-apical lesions, apthous stomatitis, and oral lichen planus.
3. Patients with known or suspected allergy to the atotvastatin group or ornidazole group.
4. Patients on systemic statin therapy or antibiotic therapy.

Subjects selected on the basis of inclusion criteria were categorized into two treatment groups. GROUP I (n=22): Patients treated by SRP with subgingival 1.2% Atorvastatin gel. GROUP II (n=22): Patients treated by SRP with subgingival 1% ornidazole gel

Clinical measurements

At each patient's initial appointment, baseline data were obtained on modified Sulcus Bleeding Index (mSBI) on four posterior teeth in each quadrant. Probing depth (PD), Relative attachment level was measured for same teeth. GCF samples were taken at 16 sites for each patient. These sites were the mesio-buccal surfaces of the above stated 4 posterior teeth in each upper quadrant and at the mesio-lingual surfaces of same in each lower quadrant. GCF sample was collected for 15 seconds by calibrated volumetric microcapillary pipettes immediately after the area has been isolated with cotton rolls, dried, and supragingival plaque has been removed with a sterile Gracey curette. pipettes were immediately transferred to plastic vial then stored at -70°C till the time of assay. Pipettes contaminated with blood and saliva were excluded from the sampled group. Scaling and root planing were performed in both the groups. No antibiotics or anti-plaque and anti-inflammatory agents were prescribed after treatment. (figure 1-10)

Formulation of Atorvastatin gel

Atorvastatin gel was prepared in the Department of Pharmacology, DJ College of Dental Sciences and Research, Modinagar. 105mg of Methylcellulose was added into 5ml of distilled water and constirring was done at 50°-60° C to make a gel form (Solution A). A weighed amount of ATV was added to the above solution and dissolved completely to obtain a homogeneous phase of polymer, solvent, and drug. Thus, the ATV in situ gel was prepared with a concentration of 1.2%

Local Drug Delivery

For standardization, atorvastatin gel (1.2%) was injected into the periodontal pockets using a syringe with a blunt cannula in Group I and ornidazole gel (1%) was injected into the Group II. No periodontal dressing applied after delivery of the drug because the prepared formulation decreases in viscosity, which causes swelling and occlusion of the periodontal pocket. After placement of the gel in situ, patients instructed to refrain from chewing hard or sticky foods, brushing near the treated areas, or using any interdental aids for 1 week. One and three months later all clinical measurements were repeated for both the groups and GCF samples were evaluated again after 1 month.

RESULTS

Intra group comparison of Group I (Atorvastatin) and group II (Ornidazole) between the different intervals shows that there is significant reduction in mean scores of m SBI, PD and RAL at baseline, 1 month and 3 months. Thus, it shows that both Atorvastatin and Ornidazole are efficient in reducing gingival bleeding, probing depth and relative attachment levels. **(Table 1,3,5).** Independent t Test for significance of change in m SBI, PD and RAL in intergroup analysis shows that there is statistically non significant differences in both Atorvastatin and Ornidazole group. Thus, both Atorvastatin and Ornidazole are efficient in decreasing gingival bleeding, probing depth and relative attachment levels **(Table 2,4,6).**

Intra group comparison of Group I (Atorvastatin) and Group II (Ornidazole) between the different intervals shows that there is significant reduction in mean scores of GCF TNF α at baseline and 1 month in group I (Atorvastatin) as compared to group II (Ornidazole).

Thus, Atorvastatin is more efficient in reducing GCF TNF α levels than Ornidazole **(Table 7).** Independent t Test for significance of change in GCF TNF α scores in intergroup analysis shows that there is statistically significant differences in Atorvastatin and Ornidazole group . Thus, it shows that Atorvastatin is efficient in decreasing GCF TNF α levels as compared to ornidazole.**(Table 8)**

DISCUSSION

Periodontitis is a multifactorial disease with the presence of pathogenic bacteria being necessary for the initiation of inflammation, but the progression of periodontal disease depends equally on the host response to various pathogenic bacterial products and components. Advances in understanding the etiology and pathogenesis of the periodontal disease have led to increasingly effective pharmacological interventions along with phase I therapy. In this regard, safe and intrinsically efficacious medication can be delivered into periodontal pockets to suppress or eradicate the pathogenic microbiota or modulate the inflammatory response or thereby limiting tissue destruction. The local delivery of therapeutic agents to periodontal pockets has the benefit of administering more drugs at the target site, thus achieving high intrasulcular drug concentrations, avoiding its systemic side effects, and a better patient compliance.

In this study, Atorvastatin a new generation HMG-Co-A reductase inhibitor, has been compared with ornidazole belonging to the 5-nitroimidazole group to treat periodontal pocket with the purpose to evaluate their clinical efficacy on GCF TNF-α levels and correlating with the clinical parameters in chronic periodontitis patients before and after scaling and root planing. Atorvastatin, an inhibitor of HMG- CoA reductase enzyme has been widely used on clinical practice in order to prevent cardiovascular accidents[9]. Studies investigating Atorvastatin have shown that its treatment leads to significant reductions in the levels of proinflammatory cytokines (TNF, IL-1 and IL-6)[10]. In another study, Atorvastatin significantly decreased bone resorption markers, including levels of serum IL-6[11]. Atorvastatin also decreased COX-2 expression within peripheral blood monocytes in patients with acute myocardial infarction[12] and increased IL-10 levels in a dose-dependent manner[13]. Atorvastatin has also been used to inhibit metalloproteinases[14], osteoclastogenesis and bone destruction, and the expression of the receptor activator of nuclear factor- kappa B ligand (RANKL)[15] .

Fajardo M E, Sanchez-Marin F J, Espinosa-Chavez E J. (2010)[16] investigated the effect of Atorvastatin on chronic periodontitis and they concluded that Atorvastatin might have beneficial effects on bone alveolar loss and tooth mobility in subjects with periodontal disease.

Another study by Pradeep AR et al (2013)[17] investigated the clinical efficacy of Subgingivally Delivered 1.2% Atorvastatin in Chronic Periodontitis. They found that mean PD reduction and mean CAL gain were greater in the ATV group than the placebo group at 3, 6, and 9 months. A significantly greater mean percentage of radiographic bone fill was found in the ATV group compared to the placebo group (1.82% – 1.32%) after 9 months. Ornidazole, a Nitroimidazole compound is one such agent that acts by inhibiting DNA synthesis. A recent report (Saxer & Guggenheim 1983)[18] provided data to support the hypothesis that Ornidazole might be a valuable adjunctive chemotherapeutic agent in the treatment of post-juvenile and rapidly progressive periodontitis.

Another study by Mombelli A et al[19] concluded that the combination of Ornidazole and mechanical retreatment has a beneficial effect on the majority of failing sites, and it appears reasonable to initiate a combined therapy, if with repeated scaling, infection and progression cannot be controlled successfully by mechanical means alone.

Thus, use of Atorvastatin and ornidazole in the local drug delivery system, may be advantageous against the periodontal pathogens or modulating the inflammatory response as well as assessing the levels of proinflammatory cytokines in the gingival crevicular fluid in the future potential applications of periodontal therapy. Therefore, present study was conducted to compare the clinical effectiveness of subgingivally delivered 1.2% Atorvastatin gel and 1% ornidazole gel incorporated into the periodontal pockets, as an adjunct to scaling and root planing for treatment of chronic periodontitis patients and its effects on GCF TNF-α levels.

In present study, in Group I, there was statistically significant reduction ($p<0.05$) in mean m SBI, PD, gain in RAL post-operatively at 1 and 3 months from baseline which is in accordance with the findings of the study by Pradeep AR et al

(2010)[20] who observed the significant improvement in PI, GI, PPD and CAL six months postoperatively on use of subgingivally delivered simvastatin gel as an adjunct to SRP in treating chronic periodontitis. In **Group II, t**here was also statistically significant reduction ($p<0.001$) in mean m SBI, PD and gain in RAL score post-operatively at 1 and 3 months from baseline which was in accordance with the findings of the study by Mombelli et al[19] who observed that ornidazole has an additional, beneficial clinical and microbiological effect when used as an adjunct to mechanical re- treatment of recurrent periodontitis.

Intergroup analysis shows that there is statistically non significant differences in the reduction of m SBI, PD and CAL scores in both Atorvastatin and Ornidazole group. Thus, both Atorvastatin and Ornidazole are efficient in decreasing gingival bleeding, probing depth and relative attachment level. In Group I, there was statistically significant reduction ($p<0.05$) in mean TNF-α level post-operatively at 1 month from baseline.These observations were similar to the study by Fentoglu O and colleagues (2011),[21] who observed that there was a significant reduction in GCF TNF-α levels in the statin group ($p<0.05$), as compared to the non-statin users.

In Group II, there was also statistically significant reduction ($p<0.001$) in mean TNF-α level post-operatively at 1 month from baseline. On comparison, Group A showed a statistically significant reduction in GCF TNF-α levels when compared with Group B. Overall observation in the present study on the basis of clinical and biochemical results achieved has revealed that in both Group A (SRP + 1.2% Atorvastatin) and Group B (SRP + 1% Ornidazole), there was statistically significant reduction in clinical parameters (m SBI, PD), gain in RAL at 1 and 3 months postoperatively, along with the GCF TNF-α levels. On comparison between Group A and Group B, both the Groups exhibited similar significant improvement in all the clinical parameters but group A exhibited more significant reduction in GCF TNF α levels as compared to group B.

CONCLUSION

The results of the present study favour the use of both locally delivered atorvastatin and ornidazole in the treatment of chronic periodontitis. This study indicated that clinical effects achieved with both the agents may reduce the need for further advanced and surgical periodontal treatment which would limit morbidity for the subjects, the time of treatment and cost of the therapy. The results obtained present a valid promise for further studies with a larger sample size.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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