Efficacy of Locally Delivered Antimicrobials in the Management of Periodontal Pocket – A Clinical Evaluation"

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Abstract

Aim: To evaluate the effectiveness of local delivery of antimicrobial agents in the management of periodontal pocket"

Materials and Methods: 30 Patients with persistent periodontal pockets of probing depth ≥5 mm with bleeding on probing were selected and included in this 3 month follow up randomized comparative clinical study. Subjects were divided into three groups, Group I (Scaling and Root planning), Group II(Scaling + Simvastatin gel) and Group III(Scaling + Chitosan hydrogel with tetracycline). clinical parameters like Plaque Index (PI), Gingival index (GI), pocket probing depth (PPD) and clinical attachment level(CAL) were assessed. paired t test & One way ANOVA was used to analyse the significance of changes in clinical parameters over time between and within the groups.

Results: On intragroup comparison, all three groups showed significant PI and GI reduction ($P < 0.001$) after treatment at 3months. In intergroup comparisons, PPD reduction and CAL gain were more significant in test Groups 2(Scaling + Simvastatin gel) at 1 month & 3 month from baseline. Clinical parameters were significantly reduced in test sites.

Conclusion: Local application of simvastatin gel and chitosan hydrogel with tetracycline subgingivally resulted in significant improvement clinically therefore local drug delivery proved to be more convenient, easy-to-use and more effective than only scaling and root planning. These devices also do not probe the risk of overdose or systemic overload, simple for formulation, affordable and easily available.

Keywords: Antimicrobials, Periodontal Pocket, Chronic Periodontitis, Local Drug delivery system, Clinical and Microbiological Study.

INTRODUCTION

Periodontal disease is a general term which encompasses several pathological conditions affecting the tooth supporting structures. These conditions are characterized by destruction of the periodontal ligament, resorption of alveolar bone and migration of the junctional epithelium along the tooth surface. The clinical signs of periodontitis are,

changes in the morphology of gingival tissue, bleeding upon probing, as well as periodontal pocket formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria.[1]

Non-surgical and surgical therapy are both applicable in the treatment of periodontal disease. The gold standard in the treatment of periodontitis is mechanical debridement of the pockets by scaling and root planning (SRP).[2]This approach is a demanding therapeutic procedure and it has limitations, mainly related to the inability to access deep pockets and furcations and elimination of pathogens. To overcome these limitations, different adjunctive therapies have been proposed, mainly the use of systemic or local antimicrobial agents.[3]

Local drug delivery systems with controlled release properties have the potential to be used as a therapeutic component in the management of periodontal disease. The principal requirement for effectiveness of this form of therapy is that the agent should reach the base of the pocket and is maintained there for an adequate time for the antimicrobial effect to occur. In view of their beneficial properties, statins and chitosan hydrogels have been presented as new potential candidates for improving periodontal therapy outcomes.[4] Statins have anti-inflammatory and bone stimulating properties Statins are beneficial in the primary prevention of cardiovascular disease in patients with elevated CRP, but relatively low cholesterol levels. Bone anabolism regulated by statins can be ascribed to three aspects Promoting osteogenesis, inhibiting osteoblast apoptosis and Suppressing osteoclastogenesis.[5]

Hydrogels are high-water content materials prepared from cross-linked polymers that are able to provide sustained, local delivery of a variety of therapeutic agents. The advanced development of chitosan hydrogels has led to new drug delivery systems that release their payloads under varying environmental stimuli. Chitosan hydrogel is an excellent excipient because it is non-toxic, stable, biodegradable, and can be sterilized & are able to provide sustained, local delivery of a variety of therapeutic agents that may positively affect chronic periodontitis. Properties of chitosan that are perhaps the most important to dentistry are bioactivity, anti-inflammatory, wound healing, hemostasis and bone repair.[6]

The current study is a controlled clinical trial to evaluate the efficacy of 1.2% Simvastatin and Chitosan hydrogel with tetracycline as local drug delivery in adjunct to scaling and root planning for the treatment of chronic periodontitis.

MATERIALS AND METHODS

30 Patients were selected from the Outpatient Department of Periodontics, Daswani Dental College & Research Centre, Kota, Rajasthan. The procedures, possible risks/discomforts and benefits were fully explained to the participants. All the patients included in the study satisfied the following inclusion and exclusion criteria.

Inclusion Criteria

Patients with periodontitis, pocket depth >5mm, All medically healthy patients with no recurrent history of any systemic disease.

Exclusion Criteria:

Patients with smoking and drinking habits, receiving surgical treatments, systemic diseases, undergone periodontal treatment in last six months period, Pregnant and lactating female undergoing antibiotic therapy.

Randomization

After enrollment, the patients were randomly assigned into 3 groups**:**

1. Group 1 will received Phase I periodontal therapy i.e. Scaling and Root Planning (SRP).
2. Group 2 will received Phase I periodontal therapy and SIMVASTATIN(SMV)GEL as an adjunct to SRP.
3. Group 3 will received Phase I periodontal therapy and CHITOSAN HYDROGEL with tetracycline as an adjunct to SRP.

Treatment Procedure

At Baseline visit, after thorough Scaling and root planning (to achieve a smooth and clean root surface), LDD was performed by a operator using a blunt cannula syringe (26 gauge), injecting 0.1 ml of the prepared placebo/1.2%simvastatin /1.2% chitosan gel with tetracycline into the periodontal pocket. Following delivery, periodontal dressing was placed.

Clinical Evaluation

Clinical parameters were assessed after thorough SRP at baseline, 1 month & at 3 month using:

1. Plaque Index (Sillness and Loe)[7]
2. Gingival index (Loe and Sillness)[7]
3. Clinical attachment level to be measured with William's Periodontal probe.[8]

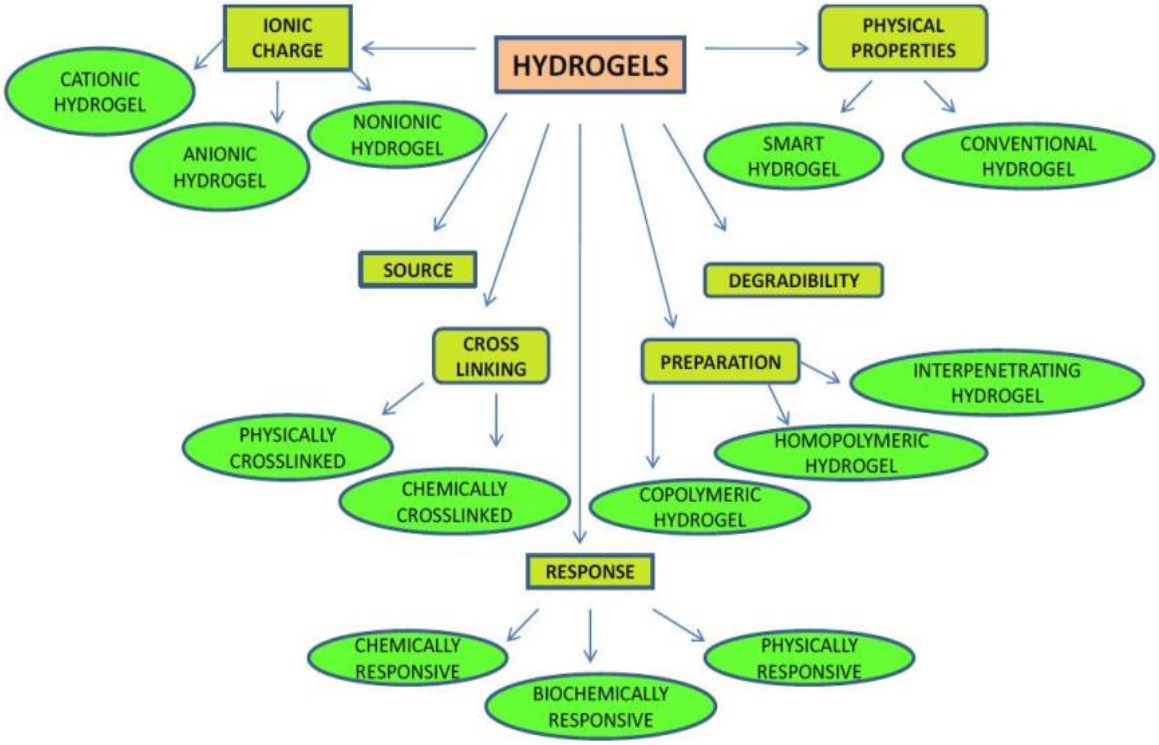
Preparation of Simvastatin Gel

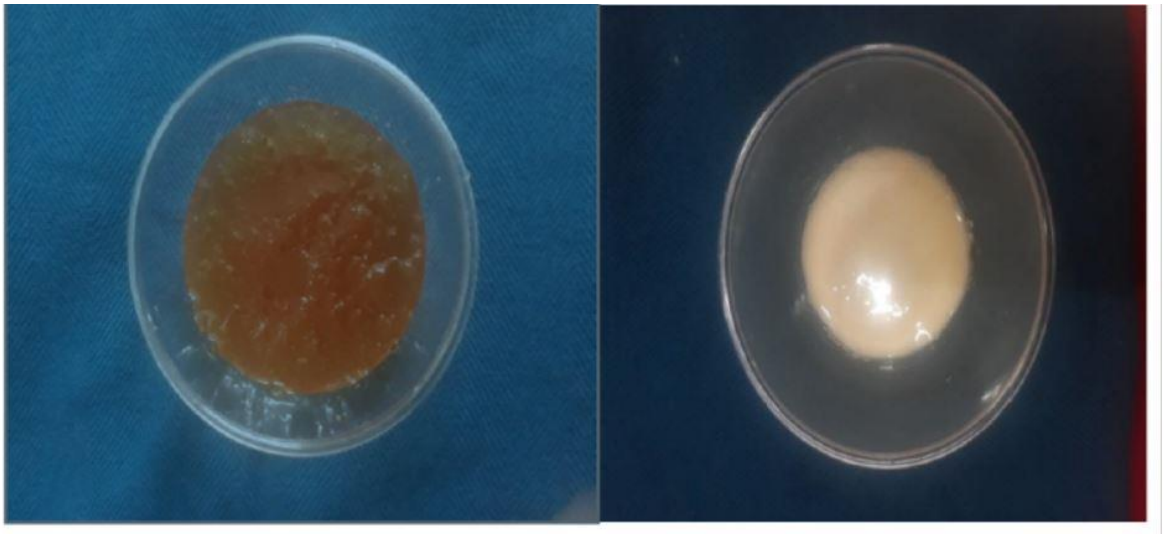
Simvastatin gel was prepared by adding 2.5 g of methylcellulose to 100 g of distilled water slowly and stirring continuously to attain the gel consistency. Once this was prepared, 1.2 g of Simvastatin was added slowly with continuous stirring to get the preparation

Preapration of Chitosan Hygrogel

1gram chitosan powder and 2 gram lactic acid were dissolved in 40ml water (ph between 3-5) and was kept for hydration for 12 hours. The solution was mixed in overhead stirrer for 3 hours. 2ml gluteraldehyde solution (1%w/v) was added dropwise to this solution with continuous stirring for 1hour. Thereafter the solution was poured into petri dishes and allowed to dry in an oven at 45oc.

Post-LDD, patients were instructed to avoid chewing on sticky/hard foodstuff or using toothbrush/interdental aids near the treated areas for 1 week. All patients received the same post-operative instructions and no mouthwashes or antibiotics were prescribed after treatment.





Chitosan Hydrogel **Simvastatin Gel**

RESULT

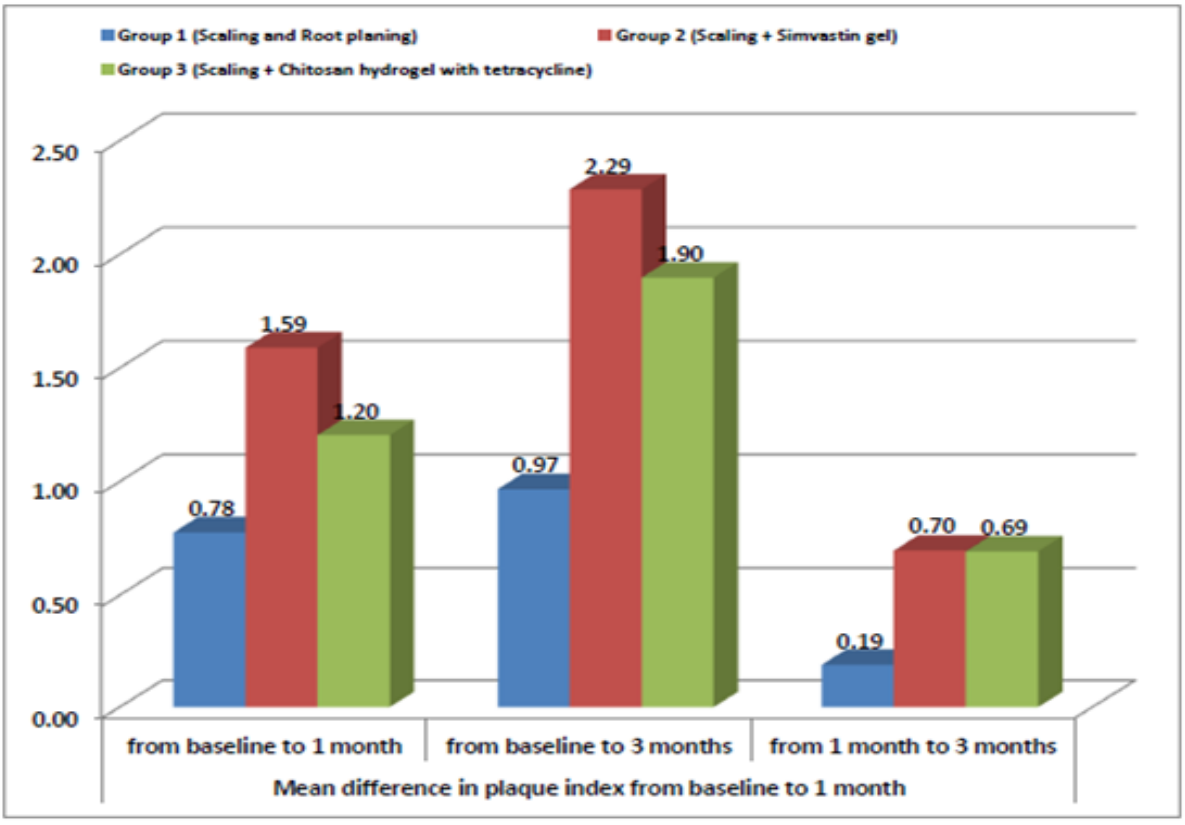
The collected data was subjected to statistical analysis. Based on the distribution of data, the appropriate statistical test was used. The mean PI, GI and CAL were compared between pre-test and post-test in each study group using paired t-test within the group. One way ANOVA was used to analyze the significance of changes in PI and GI over time between groups.

The mean difference in plaque index from baseline to 1 month and from baseline to 3 months was significantly more among Group 2 (Scaling + Simvastatin gel, MEAN±S.D; 1.59± 0.08, 2.29±0.05 respectively) in comparison to Group 3 (Scaling + Chitosan hydrogel with tetracycline, MEAN±S.D;1.20±0.21, 0.97+- 0.04; 1.90+- 0.08 respectively) which was significantly more than Group 1 (Scaling and Root planning, MEAN±S.D; 0.78± 0.02, 0.97±0.04 respectively) (Graph 1,Table1).

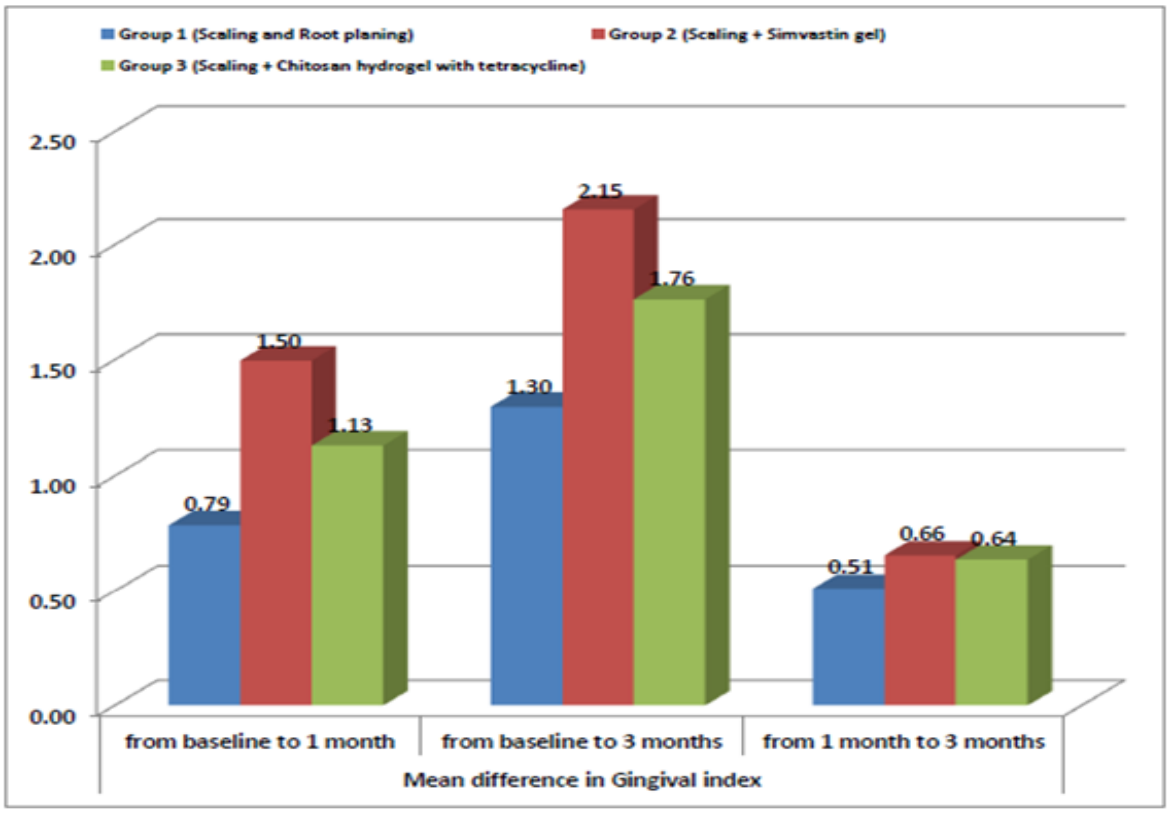
The mean difference in gingival index from baseline to 1 month, from baseline to 3 months and from 1 month to 3 months was significantly more among Group 2 (Scaling + Simvastin gel, 1.50± 0.23mm, 2.15 ± 0.33mm, 0.66± 0.32 mm respectively) in comparison to Group 3 (Scaling + Chitosan hydrogel with tetracycline 1.13± 0.10mm, 1.76±0.22, 0.64± 0.11respectively) which was significantly more than Group 1 (Scaling and Root planning Mean± S.D 0.79±0.03mm, 1.30± 0.12mm, 0.51±0.20mm respectively).(Graph 2,Table 2)

The mean difference in CAL from baseline to 1 month, from baseline to 3 months and from 1 month to 3 months was significantly more among Group 2 (Scaling + Simvastin gel, 0.89 ± 0.29 mm, 2.18 ± 0.36mm, 1.48± 0.41 mm respectively) in comparison to Group 3 (Scaling + Chitosan hydrogel with tetracycline 0.61 ± 0.15mm, 1.12±0.32, 0.98 ± 0.18 respectively) which was significantly more than Group 1 (Scaling and Root planning Mean± S.D 0.30 ±0.06mm, 0.60± 0.11mm, 0.62±0.19mm respectively)(Graph 3,Table 3).

Graph. 1



Graph. 2



Graph. 3

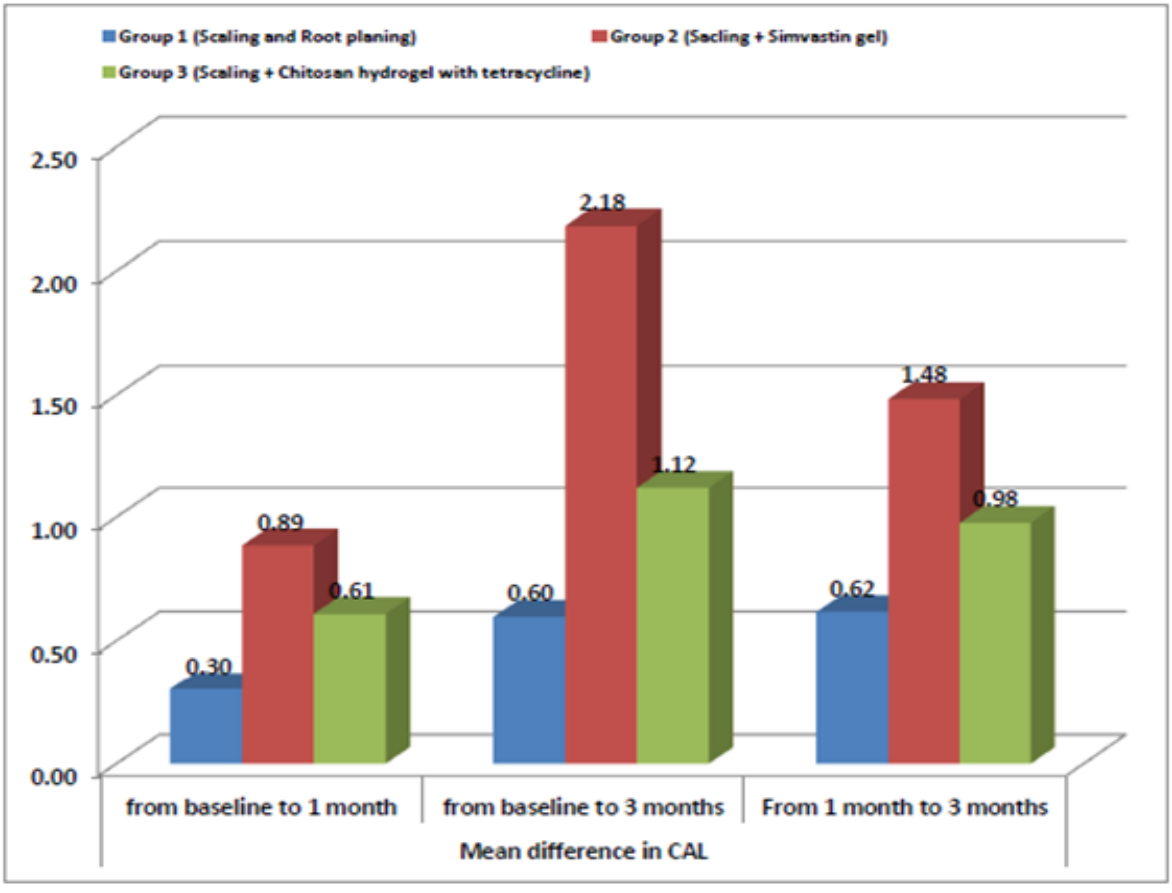


Table. 1

Plaque index		Mean	Std. Deviation	F-value	p-value
At baseline	Group 1 (Scaling and Root planning)	2.86	0.05	2.399	0.311
	Group 2 (Scaling + Simvastatin gel)	2.92	0.02		
	Group 3 (Scaling + Chitosan hydrogel with tetracycline)	2.89	0.10		
At 1 month	Group 1 (Scaling and Root planning)	2.08	0.05	55.3655	<0.001
	Group 2 (Scaling + Simvastatin gel)	1.33	0.06		
	Group 3 (Scaling + Chitosan hydrogel with tetracycline)	1.69	0.25		
At 3 months	Group 1 (Scaling and Root planning)	1.89	0.05	1.062.269	<0.001
	Group 2 (Scaling + Simvastatin gel)	0.64	0.06		
	Group 3 (Scaling + Chitosan hydrogel with tetracycline)	1.00	0.07		

Table. 2

Plaque index		Mean	Std. Deviation	F-value	p-value
At Baseline	Group 1 (Scaling and Root planning)	2.79	0.02	1.505	0.241
	Group 2 (Scaling + Simvastatin gel)	2.81	0.03		
	Group 3 (Scaling + Chitosan hydrogel with tetracycline)	2.84	0.10		
At 1 Month	Group 1 (Scaling and Root planning)	2.01	0.05	43.443	<0.001
	Group 2 (Scaling + Simvastatin gel)	1.32	0.02		
	Group 3 (Scaling + Chitosan hydrogel with tetracycline)	1.71	0.27		
At 3 Months	Group 1 (Scaling and Root planning)	1.50	0.05	322.941	<0.001
	Group 2 (Scaling + Simvastatin gel)	0.66	0.08		
	Group 3 (Scaling + Chitosan hydrogel with tetracycline	1.08	0.08		

Table. 3

Plaque index		Mean	Std. Deviation	F-value	p-value
At Baseline	Group 1 (Scaling and Root planning)	3.69	0.42	0.133	0.876
	Group 2 (Scaling + Simvastatin gel)	3.74	0.40		
	Group 3 (Scaling + Chitosan hydrogel with tetracycline)	3.78	0.29		
At 1 Month	Group 1 (Scaling and Root planing)	3.39	0.41	4.096	0.028
	Group 2 (Scaling + Simvastatin gel)	2.85	0.51		
	Group 3 (Scaling + Chitosan hydrogel with tetracycline)	3.17	0.32		
At 3 Months	Group 1 (Scaling and Root planing)	3.11	0.36	16.777	0.001
	Group 2 (Scaling + Simvastatin gel)	2.26	0.36		
	Group 3 (Scaling + Chitosan hydrogel with with tetracycline	2.80	0.26		

DISCUSSION

Mechanical debridement of periodontal pockets by scaling and root planing is the standard treatment for chronic periodontitis. However, role of mechanical debridement is limited for eliminating pathogens in furcations and deep pockets because these sites are difficult to access. Locally delivered antibiotics can be incorporated directly into the pocket. Hung and Douglass stated that nonsurgical periodontal therapy in combination with drugs locally will provide better clinical outcomes compared to only non-surgical periodontal therapy.[9]

Tetracycline is a wide spectrum antibiotic which may affect anaerobic bacteria. Sachdeva and Agarwal in research on the use of tetracyclines adjunct to scaling and root planing showed a decrease in pocket depth and attachment of epithelium. However, chronic periodontitis is not only an infectious process but also involves inflammation and tissue loss. Consequently, the use of tetracycline to control infection is not sufficient; therefore, in our study a combination of tetracycline with chitosan to enhance tissue regeneration. Chitosan, a non toxic, biodegradable, biocompatible, inexpensive substance, with or without antibiotics has demonstrated effectiveness in the treatment of chronic periodontitis.

Chitosan has mucoadhesive properties, a preliminary requirement for prolonged release of the drug at the site and the ability of gelling at low pH state. In addition to that chitosan has a antacid and antiulcer properties that may reduce the irritation of drug. Chitin and chitosan have been investigated as antimicrobial agents against a broad range of target microorganisms has proven in vitro antimicrobial activity against various pathogenic oral cavities directly involved in plaque formation and periodontal disease such as Actinobacillus actinomycetemcomitans, Streptococcus mutans and P. gingivalis.

Due to concerns regarding the increasing bacterial resistance, antibiotics do not meet widespread acceptance; thus, non-antibiotic alternatives may be a more reasonable approach.

Cytokines, matrixmetalloproteinases (MMPs) are responsible for degradation of extracellular matrix molecules in periodontal disease. Statins have been found to decrease the secretion of MMP-1, MMP- 2, MMP-3 and MMP-9 in vitro.

As mentioned, the ideal objective for using local drug delivery is to control the host-mediated tissue destruction and to regain the lost periodontium. Thus, new drugs have been found to have such effects, out of them statins are opening a new era of interest. Lindy et. al. examined the association of statin use and clinical markers of chronic periodontitis and concluded that patients on statin medication exhibit fewer signs of periodontal inflammatory injury than subjects without the statin regimen. Saxlin et.al. reported that statin medication appears to have an effect on the periodontium that is dependent on the inflammatory condition of the periodontium. [10]The results of Pradeep et al. Subramanian et al. are similar to the results obtained by Lindy et al. regarding the anti-inflammatory effects of the statins. Statins possess potential pleiotropic effects which seem to be beneficial in periodontics. These beneficial effects, include anti-inflammatory, immune-modulatory, antioxidant, antithrombotic, and endothelium stabilization actions.

The adjunctive use of subgingivally delivered biodegradable chitosan base 3% with tetracycline gel 1% and 1.2% Simvastatin gel evaluated in this study is safe and provides statistically significant results. Findings of the study state that both, the PI and GI revealed a significant progressive regression during the entire study period at 1 and 3 months ($P < 0.001$) in all 3 groups.

On intergroup comparision the mean difference in CAL from baseline to 1 month, from baseline to 3 months and from 1 month to 3 months was significantly more among Group 2 (Scaling + Simvastin gel, 0.89 ± 0.29 mm, 2.18 ± 0.36mm, 1.48± 0.41 mm respectively) in comparison to Group 3 (Scaling + Chitosan hydrogel with tetracycline 0.61 ± 0.15mm, 1.12±0.32, 0.98 ± 0.18 respectively) which was significantly more than Group 1 (Scaling and Root planning Mean± S.D 0.30 ±0.06mm, 0.60± 0.11mm, 0.62±0.19mm respectively).

This study was in accordance to the cross sectional study carried out by Sangwan et al. in which the participants underwent periodontal examination which included plaque index, gingival bleeding

index, probing depth and clinical attachment level, the study concluded that statins have a positive effect on periodontal health.

Also, our study was in concordance with the study conducted by Pradeep et al. (2013) who investigated the effectiveness of Simvastatin (SMV), 1.2 mg, and reported that there was a greater decrease in gingival index and probing depth and more CAL gain with significant bone fill at sites treated with SRP plus locally delivered SMV in patients with chronic periodontitis.The results were comparable to the work of Pradeep &Thorat who investigated the efficacy of a 1.2% simvastatin gel as an adjunct to scaling and root planing on chronic PD treatment. The authors concluded that in the sites with chronic PD treated with scaling and root planing and local application of simvastatin gel there was a greater gain of clinical attachment with significant bone fill. Kinra et al. 107 in his study showed that combination of allograft with a solution of simvastatin leads to significantly greater reduction in probing depth, gain in clinical attachment level, and linear defect fill than when the graft is used alone in the treatment of human periodontal infrabony defects.

There are very few studies on applicability of statins in chronic periodontitis in the literature, but results of this study indicate that statins hold beneficial effects. This suggests that this group of drugs might have a great potential to improve the outcomes in the treatment of periodontitis since they are safe and not costly. However, they cannot substitute the standard periodontal treatment, which consists of removing microorganisms, considered to be the primary aetiologic factor of the disease. Thus, on the basis of this study, it can be said that local SMV therapy markedly improves the benefits of SRP, clinically. 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. Local therapy with various controlled release system can be evaluated for maximum benefits. Long-term benefits and safety of the same also need to be evaluated.

CONCLUSION

Sustained release systems prevent the recolonization of pathogens for long period and reduces inflammation. From the findings of the study, we elucidate that treating chronic periodontitis with subgingivally delivered Simvastatin and Chitosan hydrogel as an adjunct to scaling and root planning demonstrated positive results clinically. Clinical parameters were significantly reduced in test sites.

Conflicts of Interest: None

REFERENCES

1. ”Cobb C Non surgical pocket therapy-mechanical. Ann Periodontol.” 1996;1:443–490.
2. “Cobb C et al Clinical significance of non-surgical periodontal therapy: An evidence-based perspective of scaling and root planing. J. Clin. Periodontol.” 2:6-16
3. Pragati S, Ashok S. “Recent advances in periodontal drug delivery systems. Int. J. Drug Deliv 2009;1:1–14.
4. Purushotham S, D'Souza ML, Purushotham R. Statin:” A boon in periodontal therapy.” SRMJ Res Dent Sci 2015;6: 243-9.
5. Gazzerro P, Proto MC, Gangemi G, Malfitano AM, Ciaglia E, Pisanti S, et al. Pharmacol Rev. 2012 Jan;64(1):102-46.
6. Karthiga Devi , Sathish Kumar K, Arivalagan K.” Microwave assisted nanoparticles for drug delivery systems.” Int J Pharma Pharma Sci 2014;6:118-23.
7. Soben Peter. “Indices in dental epidemiology. Essentials of preventive and community dentistry.”4th ed. New Delhi: Arya Publishing house; 2009. p.321-26.
8. Carranza FA, Takei HH, Cochran DL. Clinical diagnosis. In: Newman MG, TakeiHH, Klokkevold PR, Caranza FA, editors. Carranza’s Clinical Periodontology. 10th ed.Noida:Saunders, Reed Elsevier India Private Limited; 2006. p.551-53.
9. “Hung and Douglass Local delivery of antimicrobial agents for the treatment of periodontal disease” August 50(1):83-99.
10. Tuomas Saxlin 1, Liisa Suominen-Taipale, Matti Knuuttila, Pirkko Alha, Pekka YlöstaloJ Clin Periodontol;2009 Dec;36(12):997-1003.