



GEL LOCAL DRUG DELIVERY AND REDELIVERY OF ROSUVASTATIN IN THE TREATMENT OF CLASS II FURCATION DEFECTS

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ABSTRACT

Periodontitis is highly widespread disease characterized by chronic inflammatory process. One of the lipid-lowering drugs is Statins that help in lowering cholesterol levels in the man by specifically inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is a cholesterol synthesis limiting enzyme. Rosuvastatin (RSV) has shown bone stimulatory and anti-inflammatory effects. The current study intends to inspect effectiveness of 1.2% RSV gel as a local drug delivery and redelivery supplement to scaling and root planning (SRP) for treatment of Class II mandibular furcation defects. Fifty patients with mandibular buccal Class II furcation involvement were randomly chosen to two treatment groups: 1) SRP with placebo gel (control group) and 2) SRP with 1.2% RSV gel (study group). Clinical and radiographic parameters were measured at baseline and after 6, 9 months. Gels were redelivered at the treated sites at a 6-month recall visit. Greater mean probing pocket depth (PPD) reduction and greater mean gain in vertical clinical attachment level (VCAL) and horizontal clinical attachment level (HCAL) were seen in the RSV group at 6 and 9 months. Significantly greater of bone fill was found in the RSV group. The RSV group shows significant improvement in all clinical and radiographic parameters and compared with the control group in treatment of mandibular Class II furcation defects as an adjunct to SRP.

KEY WORDS: RSV, reductase inhibitors, periodontitis, placebo, statins.

INTRODUCTION

Periodontitis is a set of inflammatory diseases affecting the tissues surrounding the teeth reasoned by infection of bacteria that adhere and grow on the surfaces of the tooth^[1]. Periodontitis affects the root trunk of multi-rooted teeth, which is the join point of two or more roots^[2], first there is tissue destruction and gradually furcation involvement. Nabers probe is used to check for furcation involvement clinically. Recently, cone beam computerised technology (CBCT) has also been utilized to detect furcation. Periapical and interproximal intraoral radiographs can help diagnosing and locating the furcation. Treatment objectives are to eradicate the bacteria from the uncovered root (s) surface and to re-establish the anatomy of the tooth, so that improvement of plaque control can be achieved. Success rate in furcation lesions management is low owing to imperfect removal of subgingival plaque and calculus in the interradicular area^[3, 4]. Treatment plans for patients differ depending on the local and anatomical factors.

- For Grade I furcation, scaling, root surface debridement or furcation plasty could be done.
- For Grade II furcation, furcation plasty, open debridement, tunnel preparation, root resection, extraction, guided tissue regeneration (GTR) or enamel matrix derivative could be considered.
- For Grade III furcation, open debridement, tunnel preparation, root resection, GTR or tooth extraction could be performed if appropriate^[4, 5].

Statins also known as HMG-CoA reductase inhibitors (3-hydroxy-3-methylglutaryl coenzyme A), are a class of lipid-lowering drugs which is a rate-limiting enzyme for cholesterol fabrication^[6].

Statins help in promoting angiogenesis^[7], they provoke production of bone morphogenetic proteins (BMPs) and assist in osteoblastic differentiation^[8]. They have immunomodulatory, anti-inflammatory, antioxidant, antithrombotic. Osteoblastic differentiation and anti-inflammatory activity which is employed in periodontal diseases treatment^[8, 9].

Rosuvastatin (RSV) marketed under the trade name Crestor, is a member of the drug class of statins, used in combination with exercise, diet, and weight-loss to treat high cholesterol and related conditions, and to prevent cardiovascular disease. It was developed by Shionogi in 2013^[10].

Rosuvastatin contains sulfur (in sulfonyl functional group) is a second-generation sulfur containing, synthetic, hydrophilic statin^[11]. It has proficient anti-inflammatory activity^[12] and aids in osteoblastic differentiation and amplification of alkaline phosphatase action^[13]. RSV, joined with platelet-rich fibrin (PRF) and hydroxyapatite bone grafts, has shown gain in attachment level and increase in bone height compared with open-flap surgery alone in lower Class II furcation defects and intrabony defects^[14, 15]. With use of RSV in Class II furcation defects, the clinical parameters have been bettered^[14]. This study is conducted as a randomized controlled clinical trial to inspect clinical and radiographic influences of 1.2% RSV gel that was given at local sites as auxiliary

to non-surgical treatment in patients with Class II furcation defects.

MATERIALS & METHODS

For this 9-month longitudinal study, participants were chosen from patient seeking treatment in the Department of Periodontology, College of Dentistry- University of Baghdad. Fifty subjects with chronic periodontitis (23 males and 27 females, aged 35 to 55 years; mean age: 39.2 years) with mandibular Class II furcation defects were examined for this study. All the individuals were informed about the purpose of these investigations and consented to its protocol. Written informed consent was obtained from all patients.

Systemically healthy patients with mandibular Class II furcation defects mandibular molars with PPD \geq 5 mm and horizontal PD \geq 3mm and with no history of antibiotic or periodontal therapy in the past 6 months were included in the study. Patients with any known systemic disease, allergy to statins, systemic statin therapy, or alcoholic or smoking and pregnant or lactating women were excluded from this study.

The subjects were divided into study and control groups, 25 patients in each group. Instructions on proper oral hygiene measures were given to each patient and scaling and root planning (SRP) was done at baseline. Control group patients were treated with SRP followed by placebo gel local drug delivery; study group with SRP followed by 1.2% RSV gel local drug delivery.

Antibiotics or anti-inflammatory agents were not prescribed after therapy.

Clinical periodontal parameters measured at baseline included:

- 1) Plaque index (PLI)
- 2) Gingival index (GI)
- 3) Probing pocket depth (PPD)
- 4) Vertical CAL (VCAL)
- 5) Horizontal CAL (HCAL).

SRP was done, followed by gel placement for each patient. All parameters were measured again at 6 and 9 months using Michigan O periodontal probe and acrylic stent to standardize measurement of PPD and VCAL. VCAL was calculated by measuring the distance from the stent to the base of the pocket, subtracting the distance from the stent to the cemento-enamel junction. HCAL was measured using a periodontal probe from the stent to the deepest horizontal point of the periodontal pocket.

Use radiographs to measure bone defect depth (BDD) which was measured as the distance from the furcation fornix to the base of the defect by using parallel angle technique.

RSV gel (1.2 mg) was prepared as mentioned in studies by Pradeep et al.^[14] and Thylin et al.^[16]. For preparation of

1.2% RSV gel, a suitable non-toxic, non-allergenic medium of methylcellulose was used. To prepare methylcellulose in situ gel, the required amount of biocompatible solvent was added to a weighed quantity of methylcellulose. The vial was heated at temperatures of 50 to 60 and was agitated using a mechanical shaker to obtain a clear solution. A weighed amount of RSV was added to this mixture and dissolved completely to gain a homogeneous phase of polymer, solvent, and drug. 1.2% RSV in situ gel was prepared to treat patients in study group. Placebo gel delivered to patients in control group contained the same methylcellulose gel without RSV.

RSV or placebo gel (1.2 mg/0.1mL) was injected into periodontal pockets (one site per patient) by syringe with a blunt cannula. Patients were instructed not to eat any hard or sticky foods. They were also insured not to brush or to use any interdental aids near the treated site for 1 week. At a 6-month recall appointment, clinical and radiographic parameters were measured, and gels were redelivered to the same sites using the same method. At a 9-month recall, all parameters were measured. During recall visits, proper oral hygiene instructions were given to all patients and supragingival plaque or calculus was removed.

Statistical analysis was performed using independent sample t-test, repeated measure anova and SD was used to express differences and continuous variables of PPD, VCAL, HCAL, BDD, GI and PI. Data were analyzed using statistical software, SPSS with all significance levels set at $P < 0.05$.

RESULTS

In the current results there was significant improvement in PI and GI in all groups during the visits (Table 1). No side effects or allergic symptoms of the drugs were seen or noted. GI scores at baseline showed no difference in two groups, but a statistically significant difference in the decrease in GI scores from base line to 6 and 9 months was found in control and study groups. The decrease in GI score was statistically significantly greater in the RSV group than placebo group at 6 and 9 months at $P < 0.05$ (Table 1).

There was no difference in clinical parameters at baseline of PPD, HCAL, and VCAL in groups. Significant difference in the decrease in PPD, HCAL, and VCAL was observed in study group compared with control group from baseline to 6 and 9 months (Table 1). In RSV group, the difference from baseline was statistically highly significant in PPD, VCAL, and HCAL at each time period ($P < 0.05$), as shown in (Table 2). For radiographic parameters, BDD showed significantly greater reduction at 6 and 9 months in the RSV (1.28 ± 0.43 , 1.73 ± 0.38) group than in the placebo group (0.26 ± 0.16 , 0.3 ± 0.17) (Table 2).

TABLE 1: Mean and standard deviation of clinical periodontal parameters and BDD for each group with comparison of significance

Parameter	Visit	Control	Study	P value
PLI	Baseline	1.81 ± 0.31	1.85 ± 0.33	0.82
	3 Months	1.11 ± 0.23	1.1 ± 0.24	0.86
	6 Months	0.91 ± 0.26	0.80 ± 0.22	0.34
	9 Months	0.69 ± 0.21	0.59 ± 0.19	0.46
Significant		HS	HS	
GI	Baseline	2.1 ± 0.56	2.2 ± 0.59	0.77
	3 Months	1.33 ± 0.31	1.06 ± 0.27	S
	6 Months	0.95 ± 0.30	0.79 ± 0.15	S
	9 Months	0.87 ± 0.26	0.60 ± 0.19	S
Significant		HS	HS	
PPD	Baseline	6.6 ± 1.16	6.2 ± 1.19	0.51
	3 Months	5.41 ± 1.41	3.61 ± 0.92	S
	6 Months	5.1 ± 1.17	3.01 ± 1.01	S
	9 Months	4.90 ± 1.43	2.17 ± 1.16	S
Significant		HS	HS	
VCAL	Baseline	7.80 ± 1.06	7.76 ± 1.18	0.58
	3 Months	6.82 ± 1.01	4.97 ± 1.22	S
	6 Months	6.1 ± 0.87	4.1 ± 1.21	S
	9 Months	5.87 ± 0.78	3.2 ± 1.31	S
Significant		HS	HS	
HCAL	Baseline	7.40 ± 1.01	7.66 ± 1.08	0.79
	3 Months	6.42 ± 1.21	4.95 ± 1.32	S
	6 Months	5.55 ± 0.99	4.11 ± 1.21	S
	9 Months	5.1 ± 1.12	3.3 ± 1.39	S
Significant		HS	HS	
BDD	Baseline	3.21 ± 0.36	3.2 ± 0.56	0.24
	6 Months	2.95 ± 0.30	1.92 ± 0.30	S
	9 Months	2.91 ± 0.27	1.47 ± 0.26	S
Significant		HS	HS	

S: Significant at P<0 .05. HS: Highly Significant at P<0.001

TABLE 2: Mean Change from Baseline in PPD, VCAL, HCAL and BDD at 6 and 9 Months

Parameter	Visit	Control	Study	P value
PPD	Baseline to 6 Months	1.5 ± 0.48	3.19 ± 0.47	HS
	Baseline to 9 Months	1.7 ± 0.84	4.03 ± 0.53	HS
VCAL	Baseline to 6 Months	1.7 ± 0.41	3.66 ± 0.54	HS
	Baseline to 9 Months	1.93 ± 0.49	4.56 ± 0.75	HS
HCAL	Baseline to 6 Months	1.85 ± 0.58	3.55 ± 0.55	HS
	Baseline to 9 Months	2.3 ± 0.48	4.36 ± 0.72	HS
BDD	Baseline to 6 Months	0.26 ± 0.16	1.28 ± 0.43	HS
	Baseline to 9 Months	0.3 ± 0.17	1.73 ± 0.38	HS

HS : Highly Significant at P<0.001

DISCUSSION

Regenerative technique has been believed as a good method to reestablish missing periodontal structure and apparatus of functional attachment through the reformation of cementum, periodontal ligament, and alveolar bone^[17]. High concentration of drug can be achieved with local drug delivery by putting the drug to its target site; adverse effects associated with systemic therapy can be avoided^[18]. Local drug delivery has been established to be an effective treatment modality for periodontal regeneration^[19]. This study evaluates the effectiveness of 1.2% RSV gel to treat mandibular Class II furcation defects in persons with chronic periodontitis when used in addition to SRP. There was significant betterment in all clinical periodontal parameters and significantly decrease BDD with use of 1.2% RSV drug

compared with use of placebo. Statins (HMG-CoA reductase inhibitors) are generally used for management of hypercholesterolemia by decreasing cholesterol level^[20]. Other helpful influences of statins are: decreasing in low-density lipoprotein (LDL) oxidation, bone stimulation, and diminish the inflammation^[8,21]. These statins characteristics of anti-inflammatory and bone-stimulating features are useful for patients with chronic periodontitis. Rosuvastatin is a competitive inhibitor of the enzyme HMG-CoA reductase, having action mechanism similar to that of other statins, by Lowering high cholesterol and triglycerides levels and increasing of high-density lipoprotein (HDL) cholesterol in certain patients; Therefore it can be used to limit atherosclerosis in those with elevated levels of blood cholesterol and to diminish the risk of heart attack or stroke^[22].

RSV also has osteoblastic properties^[23], so the use of RSV as a local delivery drug agent in combination with plasma rich fibrin and bone graft in mandibular Class II furcation defect, there was improvement in bone gain that guide to enhance the reduction in PPD and more achievement in CAL^[14,15].

Results obtained from this study were similar with some previous studies Pradeep *et al.*, Garg and Pradeep^[15, 24], that showed more reduction in PPD and gingival index with increased gain in clinical attachment level in patients with CP by using of 1.2% RSV gel in comparable to control patients.

In this study, drugs were re-delivered at the same treated sites at a 6-month recall appointment, and there were additional beneficial effects of the drugs as higher concentrations at sites for a longer period. Clinically, considerable advantages of RSV in comparable to placebo, can be explained by anti-inflammatory action of RSV due to effective decrease in C-reactive protein levels^[25].

CONCLUSION

There is in clinical and radiographic parameters enhancement by utilizing of RSV gel local delivery and re-delivery with SRP in persons that have CP with mandibular Class II furcation defects. Results with RSV gel delivery were notably superior to placebo gel. Further study need long term for evaluation after second application.

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