Introduction

Periodontal disease is a complex chronic infectious disease involving supporting structures of the tooth. First, there is a destruction in periodontal tissues due to inflammatory reaction caused by bacterial infection followed by progressive loss of periodontal support of the tooth, then the tooth becomes mobile and is lost finally. Early detection and prevention of periodontitis is critical as it is the most common cause of tooth loss despite being curable at initial disease phases. According to the current consensus, periodontitis occurs due to multifaceted dynamic interactions of periodontopathogenic bacterial and virus colonization, adaptive and innate immune responses, genetic susceptibility factors, and adverse environmental factors. It is a well-documented fact that smoking is the most important environmental risk factor of periodontitis; it is one of the significant risk indicators of attachment loss and smokers tend to have greater numbers of deeper periodontal pockets than non-smokers.

Smokers do not respond well to non-surgical periodontal therapy as non-smokers; moreover, probing depth (PD) reduction and clinical attachment level (CAL) gain achieved are also less in smokers after periodontal surgery. Improved response to therapy has been demonstrated with doxycycline gel, clarithromycin gel and minocycline microspheres in smokers when delivered locally. These trials indirectly hint that these locally delivered tetracycline group of antibiotics have an antimicrobial action as well as local host modulating action by protecting against some of the destructive/inflammatory responses due to smoking.

Statins are inhibitors of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase help in reduction of serum cholesterol levels and are widely used to prevent cardiovascular diseases. Recent studies have pointed out that statin therapy may also be attributed to mechanisms independent of their cholesterol-lowering effects. They have important anti-inflammatory and antioxidant properties and osteoblastic differentiation.

Keywords:
Clinical trial(s), periodontitis, smoking

Abstract

Background: Etiological factors for periodontal diseases are multifactorial and one of these etiologic agents is bacteria. Mechanical therapy itself may not eliminate the anaerobic infection at the base of the pocket. To overcome this, various drug delivered locally have been used in adjunct to scaling and root planing (SRP). The present trial aims to evaluate the efficacy of 1.2% rosuvastatin (RSV) gel locally delivered as an adjunct to SRP in smokers with chronic periodontitis (CP).

Materials and Methods: A total of 60 patients were randomly divided into two treatment groups: SRP with placebo gel (Group 1) and SRP with 1.2% RSV gel (Group 2). Clinical parameters were evaluated at baseline, 3, 6, and 9 months. Radioic assessment was done at baseline and 6 and 9 months using computer-aided software.

Results: As compared to placebo group, a significant greater mean probing depth reduction and greater mean gain in clinical attachment level were seen in the RSV group at different time periods. Moreover, a greater mean defect depth reduction was found in the RSV group (23.91 ± 1.03, 29.24 ± 0.834) after 6 and 9 months, respectively.

Conclusion: Smokers with CP patients showed significant improvement in evaluated clinical parameters in RSV group with greater percentage of defect depth reduction as compared to placebo group.

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properties by stimulating bone morphogenic protein 2 (BMP-2).\(^\text{[17]}\) They have immune modulation, anti-thrombotic, and endothelium stabilization\(^\text{[18]}\) effects as well. Among all these properties, anti-inflammatory and osteoplastic differentiating properties of statins can be beneficial for the treatment of periodontitis. In recent studies, it has been found out that there is significantly greater decrease in bleeding index and PD and more CAL gain with the use of locally delivered simvastatin (SMV) and atorvastatin (ATV) in smokers with chronic periodontitis (CP).\(^\text{[19,20]}\)

Rosuvastatin (RSV) is a synthetic, sulfur-containing, hydrophilic, second-generation statin.\(^\text{[21]}\) RSV application has shown increase in bone fill and gain in CAL when used in combination with platelet-rich fibrin and hydroxyapatite for mandibular Class II furcation defects and intrabony defects (IBDs) treatment.\(^\text{[22,23]}\)

To date, there has been no study evaluating the adjunctive effects of RSV in smoker patients with CP. Considering the aforementioned facts, this trial was designed to evaluate the efficacy of locally delivered 1.2% RSV in adjunct to mechanotherapy for the treatment of CP in smokers.

Materials and Methods

Data source

In this longitudinal triple masked trial, a total of 70 male smokers with CP were selected from the outpatient department section of the Department of Periodontology, Government College of Dentistry and Research Institute, Bengaluru, India, and followed for 9 months. First, after ethical approval from the institutional ethical committee and review board of the college, written informed consent was taken from all participants of the study. The trial was commenced from June 2015 to April 2016 (Clinical Trials.gov Identifier NCT03043196).

Criteria for selection

Systemically healthy CP patients aged between 30 and 50 years who are current smokers without any periodontal treatment history or antibiotics use in the past 6 months, having sites with IBD depth ≥ 3 mm (alveolar crest to base of the defect distance on intraoral periapical radio) along with PD ≥ 5 mm or CAL ≥ 3 mm in an asymptomatic tooth were included in this trial. A questionnaire was given to obtain smoking history. If a patient smoked more than 10 cigarettes/day regularly for a minimum of 5 years, then it was considered as a current smoker.\(^\text{[24]}\) Former smokers were patients who previously been smoked but stopped currently, and non-smokers were not included. Patients allergic to statins, on systemic statin therapy, with any known systemic disease or any other inflammation/infection systemically which could alter periodontal disease course and tobacco users in any form other than cigarettes were not included in the study.

Patient grouping

After patient’s selection (by Avani Raju Pradeep (ADD)), 60 patients were divided randomly into two groups, i.e., RSV group (Group I) and placebo group (Group II). A computer-generated random using statistical unit was used for the randomization and investigators were unaware in the randomization process and assigned group in all evaluations of outcome. Proper oral hygiene instructions were given to each patient. They were advised to brush twice daily and do not use any other oral hygiene aid. Before local delivery of respective drugs into the site, scaling and root planing (SRP) was performed for every patient at baseline. In Group I patients (30), 1.2% RSV gel was applied into the sites after SRP and in Group II patients (30), placebo gel was placed after SRP. After therapy, no antibiotics or anti-inflammatory agents were prescribed.

Evaluation of clinical and radiographic parameters

Modified sulcus bleeding index\(^\text{[25]}\) (mSBI), full-mouth plaque index (PI) score,\(^\text{[26]}\) PD, and CAL were assessed at baseline first, followed by 3, 6, and 9 months duration. A color-coded periodontal probe\(^\text{[1]}\) was used to measure PD and CAL. Examiner (AR) who was blinded to the treatment given to the patients measured all the clinical parameters and a different clinician treated all the patients.

Intraexaminer calibration

Twenty patients were examined twice for intraexaminer calibration, 24 h apart before commencing the study. If measurements at baseline and 24 h were similar to 1 mm at the 95% level, calibration was accepted.

1.2% RSV gel formulation

RSV gel was prepared as used in our studies previously.\(^\text{[22,23]}\)

Local drug application

Using a blunt cannula syringe, 0.1 ml prepared RSV/Placebo gel (1.2 mg/0.1 ml) was injected into the periodontal pockets. Participants were advised not to chew any sticky or hard food items or brush the treated sites. For a week, usage of any interdental aid was refrained. During recall visits, any adverse effects, if at all were noted and removed any present supragingival deposits.

IBDs assessment

Defect depth reduction was assessed using image analyzer\(^\text{[1]}\) at baseline and 6 and 9 months. Bone defect depth was assessed by crest of the alveolar bone to the base of the defect vertical distance measurement on radiograph. Customized bite blocks with parallel angle technique were used to obtain films as reproducible as possible. Masked evaluator (ARP) reviewed all radios in a single reference center. For analyzation, radiographs were scanned with a scanner\(^\text{[1]}\) at 6400 dots per inch and computer-aided software\(^\text{[1]}\) was used for bone defect evaluation.

1.2% rosuvastatin gel as a local drug delivery agent Kanoriya, et al.
Primary and secondary outcome measures
Radiographic defect depth reduction was the primary outcome of the study. The secondary outcomes were probing pocket depth, CAL, mSBI, and PI.

Statistical analysis
Statistician, who was blind to the study groups done the statistical analysis. The study power calculation was done on the basis of previous study. Full-mouth PI, mSBI, PD, CAL, and bone defect depth were expressed as mean ± standard deviation. For statistical comparison of mean between the treatment groups, Student’s \( t \)-test was applied and \( P < 0.05 \) was considered statistically significant. Changes in each period were calculated from baseline. Data analysis was done using Statistical Package for the Social Sciences v. 20.0, IBM, Chicago, IL.

Results
Sixty of 70 male smokers who were initially enrolled for the study completed the study [Figure 1]. Drugs were well tolerated by all the patients, no adverse reactions; complications were noted. Soft tissue healing was uneventful with no significant differences visually. There was improvement in full-mouth plaque score in both the groups after 3, 6, and 9 months which was statistically insignificant between the groups [Table 1].

Improvement in mSBI was more in RSV group than placebo during all intervals and it was statistically significant [Table 1]. At baseline, there was no difference between two treatment groups for clinical parameters such as PD and CAL; however, RSV group showed statistically significant more reduction in PD and gain in CAL at all intervals as compared to placebo group [Tables 2 and 3]. Radiographic parameter, i.e., bone defect depth showed a significant mean reduction of 1.12 ± 0.04 and 1.39 ± 0.05 statistically at 6 months and 9 months with the use of RSV as compared to placebo gel (0.186 ± 0.08 and 0.243 ± 0.10) [Table 3]. Percentage defect depth reduction was also significantly greater with the use of RSV gel in smokers at 6 and 9 months (23.91 ± 1.03 and

| Group index | Baseline | 3 months | 6 months | 9 months |
|-------------|----------|----------|----------|----------|
| Full-mouth PI | Placebo | 2.40±0.20 | 1.01±0.13 | 0.99±0.16 | 0.95±0.18 |
| | 1.2% RSV | 2.34±0.19 | 0.98±0.12 | 0.94±0.17 | 0.91±0.21 |
| \( P \) value\( ^{†} \) | 0.249 | 0.379 | 0.195 | 0.365 |
| mSBI | Placebo | 2.16±0.24 | 1.44±0.26 | 1.22±0.34 | 1.11±0.28 |
| | 1.2% RSV | 2.25±0.23 | 1.19±0.20 | 0.93±0.23 | 0.79±0.19 |
| \( P \) value\( ^{†} \) | 0.176 | <0.010* | <0.010* | <0.010* |

\*Statistically significant at \( P<0.05 \), \( ^{†} \)t test. PI: Plaque index, mSBI: Modified sulcus bleeding index, RSV: Rosuvastatin, SD: Standard deviation

Table 2: Mean±SD values of PD, CAL, and IBD depth at different time intervals for 1.2% RSV and placebo groups

| Parameter | Placebo | 1.2% RSV | \( P \) value\( ^{†} \) |
|-----------|---------|----------|------------------------|
| PD (mm)   | Baseline | 7.65±1.15 | 7.83±1.12 | 0.499 |
|           | 3 months | 6.56±1.67 | 5.73±1.11 | <0.005 |
|           | 6 months | 5.96±1.06 | 4.63±1.18 | <0.0001* |
|           | 9 months | 6.13±1.13 | 4.16±1.23 | <0.0001* |
| CAL (mm)  | Baseline | 5.90±1.29 | 6.06±1.11 | 0.595 |
|           | 3 months | 4.93±1.11 | 3.93±1.20 | <0.0001* |
|           | 6 months | 4.26±1.14 | 3.10±0.92 | <0.0001* |
|           | 9 months | 4.40±1.19 | 2.80±0.80 | <0.0001* |
| IBD depth (mm) | Baseline | 4.68±0.16 | 4.75±0.14 | 0.093 |
|             | 6 months | 4.50±0.21 | 3.62±0.13 | <0.0001* |
|             | 9 months | 4.44±0.22 | 3.36±0.11 | <0.0001* |

\*Statistically significant at \( P<0.05 \), \( ^{†} \)t test. PI: Plaque index, mSBI: Modified sulcus bleeding index, RSV: Rosuvastatin, SD: Standard deviation

Table 1: Full-mouth PI and mSBI (±SD) for 1.2% RSV and placebo groups at different time intervals

Assessed for Eligibility (N=70)
Excluded (N=5)
Not meeting inclusion criteria (N=2)
Refuse to participate (N=3)
By inclusion exclusion criteria 60 patients were randomized

Based on inclusion exclusion criteria 60 patients were randomized

SRP+PLACEBO gel (Group I)
\( N=30 \)
Sites=30
Failed to follow-up
\( N=0 \)
Sites=0
Analysed
\( N=30 \)
Sites=30

SRP+RSV gel (Group II)
\( N=30 \)
Sites=30
Failed to follow-up
\( N=0 \)
Sites=0
Analysed
\( N=30 \)
Sites=30

Failed to follow-up
\( N=0 \)
Sites=0

Figure 1: Study flowchart
Table 3: Mean change (mean ± SD) in PD, CAL, IBD, and DDR% reduction in 1.2% RSV and placebo groups at different time intervals

| Parameter       | Placebo     | 1.2% RSV    | P value* |
|-----------------|-------------|-------------|----------|
| PD (mm)         |             |             |          |
| 3 months        | 1.06 ± 0.36 | 2.10 ± 0.30 | <0.0001* |
| 6 months        | 1.66 ± 1.18 | 3.20 ± 0.41 | <0.0001* |
| 9 months        | 1.50 ± 0.50 | 3.66 ± 0.47 | <0.0001* |
| CAL (mm)        |             |             |          |
| 3 months        | 0.96 ± 0.59 | 2.13 ± 0.34 | <0.0001* |
| 6 months        | 1.63 ± 0.61 | 2.96 ± 0.49 | <0.0001* |
| 9 months        | 1.50 ± 0.65 | 3.26 ± 0.69 | <0.0001* |
| IBD depth (mm)  |             |             |          |
| 6 months        | 0.186 ± 0.08| 1.12 ± 0.04 | <0.0001* |
| 9 months        | 0.243 ± 0.10| 1.39 ± 0.05 | <0.0001* |
| Radiographic DDR%|         |             |          |
| 6 months        | 4.00 ± 1.97 | 23.91 ± 1.03| <0.0001* |
| 9 months        | 5.21 ± 2.18 | 29.24 ± 0.834| <0.0001* |

*Statistically significant at P<0.05. †t test. IBD: Intrabony defect, CAL: Clinical attachment level, PD: Probing depth, DDR: Defect depth reduction, SD: Standard deviation, RSV: Rosuvastatin

29.24 ± 0.83) as compared to placebo gel (4.00 ± 1.97 and 5.21 ± 2.28) [Table 3].

Discussion

The current trial evaluated the clinical effectiveness of 1.2% RSV gel delivered locally for the treatment of CP in smokers in adjunct to mechanotherapy. Results of this trial showed significant defect depth reduction (radiographic) and clinical parameters improvement in comparison to placebo. To the best of our current knowledge, no studies have been done evaluating the clinical efficacy of 1.2% RSV in smokers for CP treatment; however, statins have been used as Local drug delivery (LDD) agents in the previous studies. About 1.2% RSV gel delivery into pockets locally results in more reduction in PD and gastrointestinal, along with increased CAL gain.[3] Other statins such as SMV and ATV have also shown a significant radiographic bone fill, PD reduction, and CAL gain in adjunct to mechanotherapy in CP patients.[21,28] It is very well known that smoking is one of the most important environmental risk factors for CP and smokers tend to have more attachment loss than non-smokers.[4] A significant association between smoking and poorer levels of periodontal status was reported by Ismail et al.[29] Significant relationship between smoking and attachment loss can be attributed to the vasoconstrictive effects of nicotine and its by production peripheral circulation as well as on gingival, coronary blood vessels. Smoking also hampers leukocytes and macrophages functional activity in salivary and gingival crevicular fluid, decreases PMN chemotaxis and phagocytosis, thereby suppressing protective response mediated by phagocytes to periodontal microorganisms.[30,31] In humans, clinical studies of LDD following non-surgical periodontal therapy in smokers have shown an improved healing.[32,33]

In the current trial, the efficacy of 1.2% RSV in smokers with CP has been evaluated as LDD agent. LDD gives the advantage of higher concentration of drug at the sites of target with reduced dosages, limited side effects and it does not need to be administered.[34] LDD offers benefits in terms of higher patient acceptability, improved patient compliance as reported in previous studies.[27,28] Decrease in mSBI with the use of RSV gel can be linked to anti-inflammatory action exerted by RSV which might be due to endothelial cell adhesion molecule expression inhibition caused by nitric oxide release by vascular endothelium or due to reduced availability of mevalonic acid within endothelial cells.[35] RSV expresses anti-inflammatory activity by suppressing levels of important inflammatory marker C-reactive protein.[36] Significant radiographic defect depth reduction, PD reduction, and CAL gain with the use of RSV can be attributed to the osteoblastic properties exerted by RSV. It is now proven that statins on bone act by mevalonate pathway and BMP-2 induction.[37] RSV is a highly potent and efficacious hydrophilic statin as compared with other statins, capable of inhibiting HMG-CoA reductase at lower pharmacological doses. A correlation between the HMG-CoA reductase inhibition and action on bone has been proven.[38] Several studies[27,28] have reported in vitro induction of osteoblastic differentiation with lipophilic statins, whereas with hydrophilic statin like RSV, carrier-specific molecules mediate their entrance into the osteoblastic cellular membrane. Recently, Monjo et al. showed that RSV enters the osteoblastic membrane mediated through an active transport mechanism through solute carrier (SLC) transporters from the SLC22, SLC21/SLCO, and SLC16 gene family, specifically Slc22a8, Slco1a1, Slc2b1, and Slc16a1. It was also showed that RSV increased BMP-2 gene expression and secretion, thus induce osteoblast differentiation and alkaline phosphatase activity in MC3T3-E1 osteoblast cells and helps in expression of Scl01a1 regulation which paves the way for RSV entrance across the membrane in mature osteoblastic cell.[39]

Results of the current trial are similar with the previous studies,[19,20] in which the use of other statins such as SMV[19] and atorvastatin[20] in smokers with CP in adjunct to mechanotherapy resulted in significant reduction in bleeding index, radiographic defect depth reduction, PD reduction, and CAL gain was found.

Conclusion

It can be concluded that 1.2% RSV gel delivered locally into periodontal pockets of smokers with CP patient results in a significant improved clinical as well as radiographic parameters when compared to placebo in adjunct to mechanical therapy. Hence, it can be a new approach to achieve periodontal regeneration in smokers who are otherwise more prone to periodontal destruction. However, multicentered randomized trials with larger sample size and long-term follow-up are needed to validate the finding of this trial.
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