Subgingivally Delivered 3% Satranidazole in the Treatment of Chronic Periodontitis among Smokers: A Randomized, Controlled Clinical Trial

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Abstract

Background: The present clinical trial was designed to investigate the effectiveness of subgingivally delivered satranidazole (SZ) gel as an adjunct to scaling and root planing (SRP) in the treatment of smokers with chronic periodontitis.

Methods: Sixty smoker subjects with probing depth (PD) ≥ 5 mm were selected. Thirty subjects each were randomly assigned to SRP + placebo and SRP + SZ. SZ or placebo (0.1 mL) was injected into the pocket using a syringe with a blunt cannula. The clinical outcomes evaluated were plaque index (PI), gingival index (GI), clinical attachment level (CAL) and PD at baseline, 1 month, 3 months and 6 months.

Results: At 6 months, SRP + SZ resulted in greater mean reduction (3.05 mm) in PD as compared to SRP + placebo (1.97 mm; $p < 0.05$) and also a greater mean CAL gain (2.89 mm) in SRP + SZ as compared to SRP + placebo (1.88 mm; $p < 0.05$).

Conclusion: When compared to the placebo, the adjunctive use of 3% SZ resulted in significant improvement in clinical outcome in the treatment of chronic periodontitis among smokers.

Keywords: Satranidazole, chronic periodontitis, local drug delivery, smokers

Introduction

Periodontitis is a chronic inflammatory condition characterized by acute episodes of periodontal destruction occurring in response to an elevated bacterial load in a susceptible host (Offenbacher, 1996). The importance of bacteria in the aetiology of periodontal pockets has been clearly established (Slots, 1979; Moore, 1987). As a result, therapy is necessarily directed at controlling the bacterial flora associated with the periodontium/tooth interface.

Smoking is known as a major risk factor for increasing the prevalence and severity of periodontal destruction (Papapanou, 1996). There is a fairly well established biologic rationale for the negative effects of cigarette smoking on periodontal tissues. In general, studies have shown that smoking increases the risk for developing

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periodontal disease by two- to five-fold, and these effects seem to be dose-dependent (McGuire and Nunn, 1999; Johnson and Hill, 2004).

Non-surgical periodontal therapy eliminates or suppresses the putative periodontal microorganisms in the subgingival area. It is effective in reducing the probing depth and improving the clinical attachment gain in the majority of periodontitis cases (Badersten *et al*., 1984); however, other cases, such as in smokers, respond less favourably to non-surgical periodontal therapy (Grossi *et al*., 1997).

Recent studies on the local delivery of doxycycline gel (Ryder *et al*., 1999), clarithromycin gel (Agarwal *et al*., 2012) and azithromycin gel (Pradeep *et al*., 2013) reported an improved response to therapy in smokers. These recent studies indirectly support the concept that the locally applied antibiotics may not only have an antimicrobial effect, but may also exert a local host modulating effect by protecting against some of the effects of smoke on the destructive/inflammatory arm of the host response.

Satranidazole (SZ) is another antibiotic that belongs to the 5-nitroimidazole group. Satranidazole, [1-methylsulphonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone] is a novel nitroimidazole that differs from other 5-nitroimidazoles such as metronidazole (MTZ), ornidazole, and tinidazole in that the 2C of the imidazole ring is connected via a nitrogen to a substituted imidazolidinone moiety (Nair and Nagarajan, 1983). Pharmacokinetic studies of SZ in humans have demonstrated a longer half-life (SZ 14 hours; MTZ 8 hours) and higher blood levels than MTZ. This necessitates less frequent dosing of SZ as compared to MTZ. These factors, combined with its greater potency, are believed to contribute to its therapeutic efficacy (Nair and Nagarajan, 1983).

Previous studies have demonstrated that subgingivally delivered SZ improves some clinical parameters in patients with chronic periodontitis (Priyanka *et al*., 2015a) and in type 2 diabetes patients with chronic periodontitis (Priyanka *et al*., 2015b). To the best of our knowledge, there is no published literature on evaluation of the clinical efficacy of *in situ* gel using SZ in smoker subjects with chronic periodontitis. Keeping the above facts in mind, the aim of this double-blinded, placebo-controlled randomized clinical trial was to evaluate the clinical efficacy of subgingivally delivered SZ in smoker subjects with chronic periodontitis.

Material and methods

Source of data

In this 6-month follow-up longitudinal interventional study, a total of 60 male smoker subjects (age range 30–50 years) with chronic periodontitis were selected from the outpatient section of the Department of Periodontics, Government Dental College and Research Institute, Bangalore, India. It was made clear to the potential subjects that participation was voluntary. The authors declare that this experiment on subjects was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from subjects, and ethical clearance for the study was received from the Institutional Ethical Committee and Review Board, Government Dental College and Research Institute.

Selection criteria

Systemically healthy subjects with probing depth (PD) ≥ 5 mm or clinical attachment level (CAL) ≥ 4 to 6 mm and vertical bone loss ≥ 3 mm on intraoral periapical radiographs with no history of periodontal therapy or use of antibiotics in the preceding 6 months were included. Smoking history was obtained using a questionnaire. No attempt was made to validate the smoking history by measures such as serum cotinine levels. A subject was classified according to their pack history as current smoker if he or she regularly smoked more than 10 cigarettes/day for a minimum of 5 years. Non-smokers were subjects who had never smoked (Kamma *et al.,* 2004). Former smokers, i.e., subjects who had previously been smokers but had stopped their habit, were excluded. Patients with known or suspected allergy to the SZ group, those on systemic antimicrobial therapy, patients with aggressive periodontitis, diabetics, alcoholics, immunocompromised patients, and pregnant or lactating females were excluded.

Seventy-two subjects were initially analyzed for the study. Twelve subjects were excluded because they did not meet the inclusion criteria. After subject selection (by PR), thirty subjects were randomly (by computer generated system) assigned to each treatment group, and one site per subject was treated with scaling and root planing (SRP) plus placebo gel or SRP plus SZ (3%/0.1 mL) *in situ* gel. In this double-blinded, placebo-controlled randomized clinical trial the treatment group was concealed from the patient, clinical examiner and/or the operator. Scaling and root planing was performed at baseline until the root surface was considered smooth and clean by the operator (NP). No antibiotics or antiplaque and anti-inflammatory agents were prescribed after treatment.

Clinical parameters, including gingival index (GI) and plaque index (PI; Loe, 1967), PD, and CAL were recorded at baseline (before SRP) and at 1, 3 and 6 months. A custom-made acrylic stent and a University of North Carolina no. 15 color-coded periodontal probe (UNC 15 periodontal probe, Hu-Friedy, IL, USA) were used to standardize the measurement of PD and CAL. Clinical attachment loss was calculated by measuring the distance from the stent (apical extent) to the base of the pocket minus the distance from the stent to the cemento-enamel junction.

A single clinician (NP) provided treatment to both groups, and all pre- and post-treatment clinical parameters were recorded by another examiner (PR) who was masked to the type of treatment received by the subjects.

Intra-examiner calibration

Intra-examiner calibration was achieved by examination of 20 patients twice, 24 h apart before beginning the study. Calibration was accepted if measurements at baseline and 24 h were similar to 1 mm at the 95% level.

Primary and secondary outcome measures

The primary outcome of the study was CAL. The secondary outcomes included PI, GI and PD.

Formulation of 3% SZ in situ gel

After intensive *in vitro* investigations for optimization and stability at the collaborative centre (Department of Pharmaceutics, Al-Ameen College of Pharmacy, Bangalore, India), the following formulation was developed.

The SZ gel (3%) was prepared as described in our previous study (Priyanka *et al*., 2015). Weighed carbopol 934P was dissolved in 50 mL of McIlvaine buffer pH 6.6. The SZ drug was also dissolved in about 25 mL of McIlvaine buffer pH 6.6. This solution of SZ was slowly added to the solution of CB 934P with stirring. Then, the gelling agent sodium carboxy methylcellulose (SCMC) was added slowly under continuous magnetic stirring at 100 rpm. The volume was made up to 100 mL with McIlvaine buffer pH 6.6. The prepared gel was kept for 24 h at room temperature for complete polymer dissolution. Thus, the SZ *in situ* gel was prepared with a concentration of 3%.

Local drug delivery (LDD)

For standardization, 0.1 mL of prepared SZ gel (3%) was injected into the periodontal pockets using a syringe with a blunt cannula. No periodontal dressing was 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 *in situ* gel, subjects were instructed to refrain from chewing hard or sticky foods, brushing near the treated areas, or using any interdental aids for 1 week. Adverse effects were noted at recall visits, and any supragingival deposits were removed.

Statistical analysis

Power analysis calculations were performed before the study was initiated. To achieve 90% power and detect mean differences of the clinical parameters between groups, 30 sites in each group were required. Continuous variables (PI, GI, PD, CAL) were expressed as mean ± standard deviation (SD). Normality assumption was tested using the Shapiro-Wilk W test. Between the treatment groups comparison was carried out using the Mann-Whitney test. The Wilcoxon signed ranks test was used for comparisons within the ,SZ and control groups respectively. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed with statistical software (SPSS version 10.5, SPSS, Chicago, IL).

Results

A CONSORT flowchart exhibiting the number of subjects finally analysed and those dropping out is shown in *Figure 1*. Fifty-five of 60 subjects completed the study. Five subjects did not follow up after the baseline examination. Fifty-five treatment sites (one site/subject) were evaluated for clinical parameters at baseline, 1, 3 and 6 months.

Clinical evaluation

No adverse reaction was observed in any subject from the SRP + SZ group, and no patient reported any discomfort. Healing was uneventful. All subjects tolerated the drug, without any post-application complications. On subjective evaluation, all patients gave positive responses regarding the taste and flavour.

There was reduction but no significant difference was found between the two groups in PI and GI at any point. However, the decrease in GI was statistically significant within both groups at 3 months (*Table 1*). The decrease in PD was statistically significant within both groups compared to baseline at all time intervals (*Tables 2* and *3*). When the groups were compared to each other, the decrease in PD at each time period was statistically significant. The difference in CAL from baseline was statistically significant in both groups, CAL gain was greater in the SRP + SZ group compared to SRP + placebo at all periods, and the differences reached the level of significance (*Tables 2* and *3*).

Table 1. Mean ± SD and *p* values of plaque index (PI) and gingival index (GI) of the two groups at various intervals

Parameter	Visits	SRP + placebo	SRP + SZ	*p* value
PI	Baseline	2.88 ± 0.45	2.86 ± 0.22	NS
	1 month	2.65 ± 0.22	2.53 ± 0.18	NS
	3 months	2.59 ± 0.16	2.45 ± 0.34	NS
	6 months	2.54 ± 0.35	2.50 ± 0.23	NS
GI	Baseline	2.72 ± 0.41	2.77 ± 0.27	NS
	1 month	2.23 ± 0.12	2.20 ± 0.22	NS
	3 months	1.99 ± 0.32	1.67 ± 0.14	0.001*
	6 months	1.75 ± 0.15	1.42 ± 0.11	NS

*$p < 0.05$; NS, not significant; SRP, scaling and root planing; SZ, satranidazole

Table 2. Probing depth (PD) and clinical attachment level (CAL) for SRP + placebo and SRP + SZ (mean ± SD) at different time intervals

Parameter	Visits	SRP + placebo	SRP + SZ
PD (mm)	Baseline	8.99 ± 1.44	8.78 ± 1.38
	1 month	7.88 ± 1.33	6.99 ± 1.41
	3 months	6.20 ± 1.35	4.62 ± 1.11
	6 months	4.23 ± 1.23	1.57 ± 1.21
CAL (mm)	Baseline	7.57 ± 1.51	7.92 ± 1.34
	1 month	6.85 ± 1.22	6.11 ± 1.11
	3 months	5.21 ± 1.13	4.00 ± 1.23
	6 months	3.33 ± 1.25	1.11 ± 1.22

SRP, scaling and root planing; SZ, satranidazole

Table 3. Decrease in probing depth (PD) and clinical attachment level (CAL) gain from baseline (mean ± SD) at different time intervals for the two groups

Parameter	Visits	SRP + placebo	SRP + SZ	*p* value
PD (mm)	1 month	1.11 ± 0.12	1.79 ± 0.02	0.001*
	3 months	1.68 ± 0.23	2.37 ± 0.14	0.001*
	6 months	1.97 ± 0.22	3.05 ± 0.22	0.001*
CAL (mm)	1 month	0.72 ± 0.11	1.81 ± 0.01	0.001*
	3 months	1.64 ± 0.05	2.11 ± 0.21	0.001*
	6 months	1.88 ± 0.21	2.89 ± 0.14	0.001*

*$p < 0.05$; SRP, scaling and root planing; SZ, satranidazole

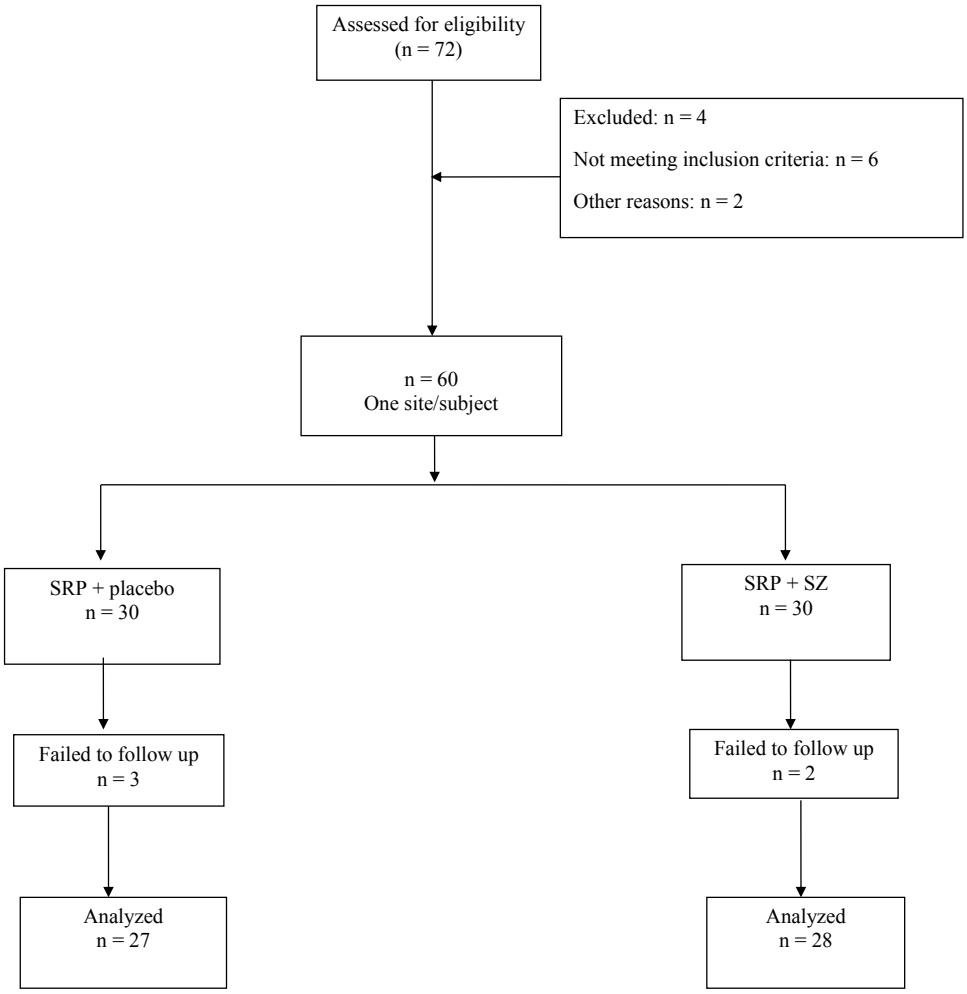

Figure 1. Study flow chart. SRP, scaling and root planing; SZ, satranidazole

Discussion

The present study evaluated the clinical efficacy of 3% SZ *in situ* gel as an adjunct to SRP for the treatment of pockets in smokers with chronic periodontitis and showed significant improvement in clinical parameters compared to the placebo gel. To our knowledge, to date there have been no studies reporting the use of 3% SZ gel as local drug delivery in the treatment of smokers with chronic periodontitis. Therefore, a direct comparison with other studies is not possible.

Tobacco smoking is considered one of the risk factors which can modify the periodontal response to microbial aggression (Bergstrom and Preber, 1994). Smokers are more susceptible than non-smokers to advanced and aggressive forms of periodontitis (Haber *et al*., 1993).

Haffajee *et al.* (2001) have reported significant clinical improvements following SRP in subjects who had never smoked or who were past smokers, but not in current smokers. *Porphyromonas gingivalis, Bacteroides forsythus* (now *Tannerella forsythia*), and *Treponema denticola* were equally prevalent among current, past and 'never' smokers before therapy and decreased significantly post-SRP in all but the current smokers (Haffajee *et al*., 2001). Therefore, the use of antimicrobials as an adjunct to SRP for the treatment of chronic periodontitis in current smokers is imperative.

In our study, in sites with an initial PD of 7 mm or greater, the mean CAL gain was 2.89 mm following SRP + SZ and 1.88 mm following SRP + placebo. The mean amount of PD reduction was 3.05 mm following SRP + SZ and 1.97 mm following SRP + placebo. The results of this study indicate that both therapies resulted in significant improvements, but patients in the SRP + SZ group showed enhanced clinical outcome ($p < 0.05$) over a period of 6 months as compared to SRP + placebo.

Previously in our study we have used 3% SZ gel as local drug delivery for 6 months in the treatment of chronic periodontitis patients (Priyanka *et al*., 2015a), and reported significant improvement in the healing response compared to the placebo group. In a recent study, we reported the use of 0.5% azithromycin (Pradeep *et al*., 2013) as an adjunct to SRP for treating chronic periodontitis smoker subjects and we found that improvement in clinical parameters in the current study were similar. Therefore, it can be proposed that subgingivally delivered SZ as an adjunct to SRP is a better approach for treatment of periodontal pockets in current smokers with chronic periodontitis compared to SRP alone.

The mean concentration of SZ at all observed periods (from baseline to 30 days), as estimated by reverse-phase high performance liquid chromatography (HPLC), provided sufficient anti-inflammatory activity and fulfilled the conditions for a controlled-release device (Priyanka *et al*., 2015). We hypothesize that local drug delivery of SZ resulted in a higher concentration of drug in the periodontal pocket and could be maintained for a longer period, which might have allowed penetration into the periodontal tissues as well. Higher concentrations of SZ in the gingival crevicular fluid enhance its action against microbes (Kim *et al*., 2004) and may mitigate the effects of smoking in the local environment of the pockets (Ryder, 2007). Thus, maintenance of this concentration of the drug locally for a long duration may have been responsible for the additional improvement over SRP.

Heavy smokers (>20 cigarettes per day) usually respond less favourably to treatment than light smokers (Kaldahl *et al*., 1996). Giannopovlou *et al.* (1999) found that nicotine at high concentrations (100 ng/mL to 25 mg/mL) was cytotoxic and inhibited the vacuolation and proliferation of fibroblasts. They also confirmed periodontal ligament cell proliferation and protein synthesis were inhibited in a dose-dependent manner. The current study population consisted mostly of light smokers (<20 cigarettes per day) and thus further studies need to be carried out to determine whether the periodontal healing following SZ gel application was also dependent on levels of tobacco exposure.

Conclusion

This clinical trial demonstrates that local delivery of 3% SZ into the periodontal pocket stimulated a significant increase in the PD reduction and CAL gain, compared to placebo gel as an adjunct to SRP in smoker patients with chronic periodontitis. However, long-term, multicenter, longitudinal studies, using different vehicles and concentrations of SZ, should be carried out to affirm the observations of our study.

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