Moxifloxacin *in situ* gel as an adjunct in the treatment of periodontal pocket: A clinico-microbiological study

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**Abstract**

**Context:** Periodontal diseases considered as the infectious condition of the periodontium. The prevalence of these diseases can be reduced by mechanical plaque removal along with systemic and locally delivered antimicrobial agents. Moxifloxacin *in situ* gel was evaluated as an adjunct to scaling and root planing as local drug delivery (LDD) for its efficacy in the treatment of chronic periodontitis.

**Aims:** The aim of the study was to evaluate the efficacy of moxifloxacin as LDD in the treatment of chronic periodontitis.

**Settings and Design:** Study design was randomized control trial.

**Subjects and Methods:** Sixty-seven sites from chronic periodontitis patients of age 25–65 years with a pocket depth of >5 mm, showing radiographic evidence of bone loss were included in the study. The scaling and root planing (SRP) was performed for all the patients and randomly divided into three groups:

- Group A: SRP + moxifloxacin *in situ* gel,
- Group B: SRP + chlorhexidine *in situ* gel,
- Group C: Control group received SRP as monotherapy.

The clinical and microbiological parameters were recorded at baseline, 6th week, and 3 months.

**Statistical Analysis Used:** Data were subjected to statistical analysis with repeated analysis of variance and paired t-test using SPSS (V.22) IBM Corporation, Washington, DC, United States) software.

**Results:** All the three groups showed improvement in both clinical and microbial parameters, but at the end of the 3rd month, Group A showed highly significant results in comparison with Group B and Group C.

**Conclusions:** Moxifloxacin showed more gain in clinical attachment level, and reduction in probing depth and *in situ* gel can be used as a safe vehicle to deliver the drug locally.

**Keywords:** Chronic periodontitis, *in situ* gel, moxifloxacin, periodontal pockets

**INTRODUCTION**

Periodontal diseases are mainly of bacterial etiology in initiation and progression of periodontal diseases. Periodontal treatment aims at reduction of infection and inflammation. Adjunctive use of drugs such as minocycline, doxycycline, amoxicillin, azithromycin, clindamycin, and metronidazole helps in achieving better results in severe periodontitis.

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Moxifloxacin is an antibiotic with broad antimicrobial activity against aerobic and anaerobic bacteria. It acts on bacteria by specifically inhibiting adenosine triphosphate-dependent topoisomerase IV and topoisomerase II (DNA gyrase).[1]

Moxifloxacin has shown better penetration into soft tissues and effective against intracellular periodontal pathogens when used as an adjunct to scaling and root planing (SRP).[2]

Systemic administration of drugs leads to therapeutic concentrations at the site of infection, but for short period, thus forcing repeated dosing for a longer period.[3]

Among various drug delivery systems, gel formulations have advantages of faster drug release ease of preparation and administration. They possess higher biocompatibility and bioadhesive by allowing adhesion to mucosa in the pocket, hence decreasing the risk of dilution of the material by saliva.[3] Hence, this study aims at evaluation of efficacy of moxifloxacin as a local drug delivery (LDD) and use of in situ gel (gellan gum) in the treatment of chronic periodontitis.

SUBJECTS AND METHODS

Five participants aged between 25 and 65 were selected for this clinical trial from the Outpatient Department of Periodontics, with generalized chronic periodontitis having probing pocket depth (PPD) of ≥5 mm in >30% of sites randomly by chit method.

Inclusion criteria
Systemically healthy participants having a minimum of 12 natural teeth with radiographic evidence of bone loss were included in the study.

Exclusion criteria
Patients allergic to quinolones or on any medication which interact with moxifloxacin, antibiotic coverage in past 6 months preceding the study, and pregnant and lactating mothers were excluded from the study.

The study protocol was approved by the Institutional Ethics Committee. Informed written consent was obtained from each participant.

Study design
Participants were randomly allocated to:
- Group A: SRP + moxifloxacin in situ gel (MOX) 28 sites
- Group B: SRP + chlorhexidine in situ gel (CHX) 22 sites
- Group C: SRP alone (CTRL) 17 sites.

All the participants received oral hygiene instructions and SRP and recalled for appropriate LDD except control group. At the end of 1 week, Group A received two drops of moxifloxacin (50 μg) and Group B received chlorhexidine (500 μg) in situ gel. Drugs were delivered with preloaded sterile syringes deep into periodontal pockets of Group A and Group B using a 31-gauge needle. Controls received no antibiotic or placebo.

At baseline, 6th week, and 3rd month after SRP, periodontal parameters were recorded and subgingival plaque samples were collected for microbiological analysis.

Clinical measurements included plaque index (PI), papillary bleeding index (PBI), PPD, and periodontal clinical attachment level (CAL). PPD and CAL were recorded to the nearest millimeter at six sites per tooth (mesiobuccal, buccal, distobuccal, distolingual, lingual, and mesiolingual) using a manual periodontal probe. For standardization of the PPD and CAL measurements, customized acrylic stents were fabricated [Figure 1].

Microbial sampling
At baseline, 6th week, and 3rd month, a subgingival plaque was collected using sterile Gracey curette, by inserting the curette subgingivally into the deepest portion of the periodontal pocket parallel to long axis of the tooth and scraping coronally along the root surfaces.[4] The samples were analyzed using a BANA analysis kit, a chair-side test for the detection of red complex periodontal pathogens. The plaque sample was also immediately pooled into a vial containing 250 μl of phosphate-buffered solution and homogenized using syringe technique.[5]

Phase-contrast microscope (×40 magnification in Phase 2) was used for the evaluation of spirochetes. The first 10 high-power fields were enumerated.[6]
Gram-negative cocci and rods were counted in five randomly selected microscopic fields. Microbiological status was graded as follows: ⁰(a) <5 organisms, +; (b) five to 15 organisms, ++; (c) 15–20 organisms, +++; and (d) >20 organisms, ++++.

Drug formulation and release
Three formulations of in situ gel of moxifloxacin and chlorhexidine with gellan gum polymer were made at different concentrations. They were as follows: formulation code Group 1 – 0.4% gellan gum (% w/v) and 50 μg of moxifloxacin or 500 μg of chlorhexidine; Group 2 – 0.5% gellan gum (% w/v) and 50 μg of moxifloxacin or 500 μg of chlorhexidine; and Group 3 – 0.6% gellan gum (% w/v) and 50 μg of moxifloxacin or 500 μg of chlorhexidine.

The concentration of the drug was based on each drug’s minimum inhibitory concentration (MIC). MIC of moxifloxacin ranges from 0.01 to 10 MIC and MIC of chlorhexidine ranges from 2.67 to 80.00 μg/ml. Optimal gelation was noticed with 0.6% w/v concentration.

The in situ gelling system using gellan gum was prepared by adding the gum to deionized water containing 0.17% w/v sodium citrate and heating to 90°C while stirring. After cooling to below 40°C, the drugs were dissolved in ethanol–water and then added to the solution. The mixture was thoroughly mixed using a magnetic stirrer.

The release of drug from these gels was characterized by an initial phase of high release (burst effect); the remaining drug was released at a slower rate (second phase). This biphasic pattern of release is a characteristic feature of matrix diffusion kinetics.¹

Statistical analysis
Differences in clinical parameters among the treatment groups were analyzed using analysis of variance with univariate repeated measurements. ⁰P<0.05 was considered statistically significant. Differences between the groups were analyzed using a paired t-test. Changes in the microbiological parameters between baseline, week 6, and month 3 were analyzed using a contingency coefficient test by cross-tabulations. Analyses were performed using statistical software. All data were expressed as the mean ± standard deviation.

RESULTS

Plaque index
The mean PI score at baseline was 1.92 ± 0.59 for the MOX group, 2.08 ± 0.52 for CHX, and 1.41 ± 0.39 for CTRL, whereas the values after 3 months were, respectively, 0.26 ± 0.41, 0.33 ± 0.39, and 0.26 ± 0.39. The mean reduction in PI score from baseline to 3 months was 1.66 ± 0.20 for MOX, 1.75 ± 0.13 for CHX, and 1.15 ± 0.00 for CTRL. PI scores were significantly reduced during the oral hygiene educational phase in all groups (⁰P< 0.05).

Papillary bleeding index
No statistically significant differences in changes in bleeding on probing were detected among the groups. PBI scores at 6 weeks and 3 months after therapy were significantly reduced compared with baseline in all treatment groups (⁰P< 0.05). SRP alone led to a reduction in bleeding on probing from 2.35 ± 0.78 at baseline to 0.28 ± 0.46 for the MOX group, from 2.04 ± 0.66 to 0.38 ± 0.49 for CHX, and from 1.58 ± 0.61 to 0.35 ± 0.49 for CTRL. The mean reduction in PBI score from baseline to 3 months was 2.07 ± 0.32 for MOX, 1.66 ± 0.17 for CXH, and 1.23 ± 0.12 for CTRL.

Probing pocket depth
All three treatment modalities led to significant decreases in PPD over the course of the study (⁰P< 0.05; Table 1). Intragroup analyses demonstrated a significant reduction in PPD in every group between the baseline visit and the 3-month follow-up visit [Figure 2]. PPD reductions were significantly greater in the MOX group than in CTRL or CHX at 3 months (⁰P< 0.01).

Clinical attachment level
Statistically significant gains in CAL were seen in all three groups during the study period [Table 1 and Figure 3].

Table 1: Probing pocket depth and clinical attachment level during 3 months mean ± standard deviation*

<table>
<thead>
<tr>
<th>Group</th>
<th>PPD (mm)</th>
<th>CAL (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 6</td>
</tr>
<tr>
<td>Group A (moxifloxacin)</td>
<td>6.50±1.20</td>
<td>4.85±0.89</td>
</tr>
<tr>
<td>Group B (chlorhexidine)</td>
<td>6.61±1.11</td>
<td>5.33±1.06</td>
</tr>
<tr>
<td>Group C (controls)</td>
<td>6.88±1.40</td>
<td>6.00±1.32</td>
</tr>
</tbody>
</table>

*All posttreatment values for both PPD and CAL for all three groups were significantly reduced compared with baseline (⁰P<0.05). PPD: Probing pocket depth, CAL: Clinical attachment level.

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CAL gains were significantly greater in the MOX group compared with CTRL ($P < 0.01$).

**Microbiological analysis**

The percentage of red complex organisms in the MOX group that tested positive for BANA was 89.3% at baseline and 0% after 3 months; the percentage of these organisms that tested negative for BANA was 67.9% after 3 months. In CHX, the percentage of red complex organisms at baseline that tested positive for BANA was 85.7%, whereas, after 3 months, the percentage that tested negative for BANA was 57.1% (0% tested positive for BANA). For CTRL, the percentage of BANA-positive red complex organisms at baseline was 70.6%, whereas the percentage of BANA-negative red complex organisms after 3 months was 35.3%, with 0% testing positive for BANA. On intergroup analysis, all groups showed a highly significant ($P < 0.01$) reduction in red complex organisms from baseline to 3 months. However, the MOX group, followed by CHX, showed maximum sites that tested negative for BANA at the end of 3 months compared with CTRL [Figure 4].

The total spirochetal count was measured using phase-contrast microscopy. At baseline, the mean spirochetal count was 274.00 ± 43.60 for the MOX group, 282.85 ± 19.21 for CHX, and 313.52 ± 47.28 for CTRL. The value after 3 months was 111.17 ± 27.01 for MOX, 143.04 ± 13.68 for CHX, and 181.88 ± 17.33 for CTRL. Analyses of changes within the groups demonstrated that a significant reduction in total spirochetal count occurred in every group between baseline and the 3-month visit. The mean spirochetal reduction from baseline to 3 months was 162.83 ± 16.59 for the MOX group, 139.81 ± 5.53 for CHX, and 131.64 ± 29.95 for CTRL, which was highly significant [$P < 0.01$; Figure 5].

The percentage change in Gram-positive and Gram-negative organisms from baseline to 3 months was measured. The mean percentage increase in the number of Gram-positive organisms in the MOX group from baseline to 3 months was 75.35% ± 23.40%, and the mean percentage decrease in the number of Gram-negative organisms during the 3-month period was 46.40% ± 6.56%. For the CHX group, the mean percentage increase in the number of Gram-positive organisms from baseline to 3 months was 71.42% ± 21.33%, and mean percentage decrease in the number of Gram-negative organisms during the same period was 22.19% ± 15.11%. For CTRL, the mean percentage increase in the number of Gram-positive organisms from baseline to 3 months was 29.90% ± 22.83%, and mean percentage decrease in the number of Gram-negative organisms was 20.48% ± 7.91%. The mean percentage change in Gram-positive and Gram-negative organisms compared between all groups at 3 months was significant ($P < 0.01$).
DISCUSSION

Elimination or adequate suppression of putative periodontopathic microorganisms in the subgingival microbiota is essential for periodontal healing. Antimicrobial treatments in periodontics range from mechanical and/or surgical debridement of tooth surfaces and at-home plaque removal to the local and systemic delivery of chemical antimicrobial agents.

Conventional mechanical-surgical root debridement does not usually eradicate Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Escherichia coli microbacteria, Enteric rods, and probably additional microbial taxa from the subgingival ecosystem.[7] Periodontal debridement may not eradicate these species because of their invasive potential into gingival epithelial cells and subepithelial connective tissues and their high affinity for crevicular epithelium and dentinal tubules. It is possible that chemical antimicrobial agents locally applied into periodontal pockets will further suppress periodontal pathogens and thereby augment the effects of conventional mechanical periodontal therapy.[7]

Miller[8] was among the first to suggest that antiseptics applied topically or through mouth rinsing might be useful in the treatment of periodontal diseases. The results of well-conducted clinical trials demonstrated that topically applied antiseptics, particular chlorhexidine, were highly effective in the treatment and prevention of gingivitis.[8] Results of many clinical trials indicated that irrigating or rinsing with antimicrobial agents as stand-alone treatments for periodontitis was insufficient to eliminate or control periodontal infections because of the inherent antimicrobial resistance of biofilms, as well as difficulties in delivering the drugs to subgingival sites.

Pitcher et al.[10] reported that vigorous swishing with mouth rinses did not impel the antiseptics into subgingival-infected sites. They found that direct irrigation of pockets ≥5 mm using a handheld syringe had a penetration depth of 1.8 mm versus 0.2 mm by mouth rinsing. The limited adjunctive effects of antimicrobial agents in treating these infections are enhanced by placing slow-releasing vehicles' preparations for direct application into the periodontal pocket.[11]

A success of any antimicrobial agent depends on its ability to achieve bacteriostatic or bactericidal concentrations at the base of the pocket and to facilitate retention of the medication long enough in the pocket. Systemic antibiotics require the administration of large doses to gain sufficient concentrations at disease sites and suffer from the potential for bacterial resistance, side effects, drug interactions, or inconsistent patient compliance.[12] The limitations of systemic or topical chemotherapies led to the development of local delivery systems for the administration of antimicrobials directly into the periodontal pockets. This form of therapy offers little or no systemic drug uptake, reduced risk of drug resistance, reduced side effects, and high concentrations at the targeted site. Numerous studies have evaluated the effect of the treatment modality during the initial or maintenance phase of periodontal therapy.

Various LDD systems are available for treating periodontitis including fibers, films, strips, and gels. Among these options, gel formulations have some advantages over conventional dosing forms because of the sustained and prolonged release of the drug, good stability, and biocompatibility which makes in situ gel more reliable. Use of biodegradable and water-soluble polymers can make in situ gel formulations more acceptable and excellent drug delivery systems.[3] This is in agreement with results of studies conducted by Ossama M. Gouda et al.[13] on local delivery of doxycycline gel as additive in the management of periodontitis. Nine-month controlled clinical trials showed that subgingival application of the resorbable doxycycline gel results in significant pocket depth reduction of 1.33 and 0.8 mm gain in CAL and statistically significant reduction in microbiological counts. Madan et al.[14] in 2009, reviewed in situ forming polymeric systems. They concluded that in situ gels can be administered by oral, ocular, rectal, vaginal, injectable, and intraperitoneal routes. It gives the advantage of sustained and prolonged action compared with conventional drug delivery systems.

Moxifloxacin, fourth-generation fluoroquinolone in the present study, was formulated to evaluate in situ gel for the treatment of periodontitis, based on the concept of ion-activated systems. The system used polymers that exhibited
sol-to-gel phase transition because of changes in specific physical–chemical parameters. Sol-to-gel transformation occurred in the presence of monovalent/divalent cations. It was found that an increase in the concentration of calcium ions produced stronger gels. Formulations were evaluated for gelling capacity, drug content, clarity, viscosity, gel strength, spreadability, microbiological studies, and in vitro release. These results demonstrated that this system is an option to conventional drug delivery systems, provides good patient compliance, and is economical.

In the present study, the formulation of moxifloxacin containing a polymer concentration of 0.6% w/v was considered the best formulation because drug release was sustained. Furthermore, the antibacterial activity of this best formulation was compared with the reference standard (pure drug). It was found that the zone of inhibition of this formulation was equal to that of the reference standard.

This randomized clinical trial evaluated the effects of an adjunctive antibiotic on clinical outcomes in participants with severe periodontitis. The results indicated that the greatest clinical benefits (PI, PBI, PPD, and CAL) were achieved if SRP was combined with LDD using chemotherapeutic agents. Significantly greater PPD reductions and CAL gains were observed in participants treated with adjunctive moxifloxacin compared with the control group and compared with participants treated with chlorhexidine. This is in accordance with study results by Listgarten et al. Similar reductions in PPD and gains in CAL were described in 2008 by Guentsch et al. evaluated the impact of adjunctive systemic moxifloxacin along with SRP.

A study by Milazzo et al. investigated the antibacterial activity of moxifloxacin against periodontal anaerobic pathogens involved in systemic infections. Moxifloxacin produced a bactericidal effect at 8 h. The results showed that moxifloxacin had good antibacterial activity against periodontal pathogens comparable with that of cefoxitin and amoxicillin with clavulanate and better than that of clindamycin, metronidazole, and penicillin.

To the authors’ knowledge, there are no clinical studies evaluating the use of moxifloxacin in situ gel for LDD in the treatment of periodontitis. In the present study, moxifloxacin has shown excellent bioavailability and tolerability, a long half-life, and good tissue penetration. All treatment groups in the current trial were evaluated microbiologically for Gram-positive cocci and bacilli and Gram-negative cocci and bacilli (spirochetes). The moxifloxacin group showed statistically significant reductions in the density and proportion of microorganisms compared with the other two groups. These findings are concordant with results reported by Lindhe et al., 1979. Cugini et al. found that SRP effectively reduced the number of P. gingivalis, T. forsythia, and T. denticola, but none of the species was completely eliminated from any of the 32 participants monitored at 9 and 12 months. We found similar poor results in our control group of SRP alone. The present experiment also showed that in situ gels had sustained and prolonged release of moxifloxacin and chlorhexidine, making the in situ gel dosage forms very reliable. In the present study, moxifloxacin was more effective than chlorhexidine because there was a significant improvement in all clinical parameters and all the investigated periodontal pathogens decreased after treatment with moxifloxacin.

Within the limitation of this study, use of moxifloxacin as an adjuvant to SRP showed promising results. In situ gel is an excellent vehicle to deliver the drugs in the treatment of chronic periodontitis.

CONCLUSIONS

LDD of both moxifloxacin and chlorhexidine in the form of in situ gel was well tolerated, safe and easy to deliver, and effective for patients with periodontitis along with SRP. However, moxifloxacin provided better results compared with chlorhexidine for LDD. These findings are the promising and alternative tool in the treatment of periodontal pockets.

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Conflicts of interest

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