

Clinicomicrobiological evaluation of the efficacy of local delivery of moxifloxacin and ibuprofen gel as an adjunct to scaling and root planing in chronic periodontitis patients

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Abstract

Aims: To evaluate the clinical and microbiological effects of local drug delivery of moxifloxacin and ibuprofen gel as an adjunct to conventional periodontal therapy in chronic periodontitis patients.

Subjects and Methods: Twenty patients with moderate-to-severe chronic generalized periodontitis with probing pocket depth (PPD) of ≥ 5 mm and < 8 mm were randomly assigned to one of the following two treatment modalities: scaling and root planing (SRP) group and moxifloxacin and ibuprofen combination gel as an adjunct to SRP group. Clinical parameters include plaque index (PI), gingival index (GI), probing depths and clinical attachment level (CAL) that were recorded at baseline and 1 and 3 months after the treatment, and microbiologic assessment was done using dark-field microscopy.

Results: A statistically significant difference in mean PI and GI scores and reduction in PPD and gain in CAL were observed at different study intervals with greater difference in the test group. On microbiological examination, the percentage of cocci increased, while a statistically significant decrease in the mean percentage of bacilli and spirochetes was observed in both groups at given intervals. *In-vitro* dissolution showed controlled release of both the drugs.

Conclusions: Among the two treatment modalities, treatment with moxifloxacin and ibuprofen local delivery as an adjunct to SRP gave superior results in clinical and microbiological parameters compared to SRP group.

Keywords: Chronic periodontitis, ibuprofen, microbiology, moxifloxacin, spirochetes

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INTRODUCTION

Chronic periodontitis is an infectious bacterial disease resulting in inflammation within the supporting tissues of the teeth, which results in progressive attachment and bone loss and is characterized by pocket formation and/or recession of the gingiva.

Elimination or adequate suppression of periodontopathic microorganisms in the subgingival microbiota is necessary for periodontal healing. Reestablishment of subgingival microflora occurs in 120–140 days despite supra- and subgingival instrumentation.^[1] The main objective of systemic

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antibiotic therapy is to reinforce mechanical periodontal treatment for bacterial elimination and to support the host defense system by destroying subgingival pathogens.^[2,3] A local route of drug delivery can attain up to 100-fold higher concentrations of an antimicrobial agent in subgingival sites as compared with a systemic drug regimen. To overcome the high clearance rate of drug in gingival crevicular fluid, Goodson *et al.*^[4] first proposed the concept of controlled drug delivery in the treatment of periodontitis. Various vehicles are used to assure the therapeutic concentrations of antimicrobial agent in periodontal pocket.^[5]

Although penicillins were widely accepted drugs as the anti-infective treatment of choice, due to the high incidence of bacterial resistance, quinolones were introduced later.^[6] They represent a class of broad-spectrum antibiotics having one or more fluorine substitutions, and are called fluoroquinolones which have advantages of good penetration into tissues and antibacterial activity within the cells.^[7]

Goodson *et al.* noted that PGE2 levels in inflamed gingiva were found to be 10-fold higher than that in healthy gingiva.^[8] The major side effect of systemically administered nonsteroidal anti-inflammatory drugs (NSAIDs) is gastrointestinal tract irritation and to overcome this effect, the local delivery of these agents was proposed in periodontal treatment with successful outcome and minimal side effects. In general, topical application of NSAIDs is possible because these agents are lipophilic and are well absorbed into the gingival tissues.^[9]

In periodontal diseases, both antibacterial and NSAIDs are used simultaneously to treat infection and inflammation. A single delivery system which can deliver both drugs locally is expected to be more convenient and beneficial and improve patient compliance.^[10] Hence, the present study is conducted to evaluate the clinical and microbiological effects of local drug delivery (LDD) of moxifloxacin and ibuprofen gel as an adjunct to conventional periodontal therapy in chronic periodontitis patients.

Aims and objectives

The present study aimed to evaluate the clinical and microbiological effects of scaling and root planing (SRP) alone and LDD of moxifloxacin and ibuprofen gel as an adjunct to SRP in chronic periodontitis patients.

SUBJECTS AND METHODS

Study design

The study was a single-center, randomized, split-mouth, controlled clinical study.

Clearance from the institutional ethical committee was obtained for the study. Twenty patients were selected from the outpatient section.

Inclusion criteria

Patients above 18 years of age and diagnosed with moderate-to-severe chronic generalized periodontitis with probing pocket depth (PPD) >5 mm and <8 mm were included in the study.

Exclusion criteria

Patients with systemic disease which could influence the outcome of therapy, pregnant women and lactating mothers, those who underwent active periodontal treatment within the last 6 months, patients allergic to moxifloxacin, teeth with furcation involvement and smokers were excluded from the study.

A detailed case history was recorded in a specially prepared pro forma which included information regarding the patient's overall medical health and oral health, and an informed consent was obtained.

Randomization

After baseline examination, simple randomization by coin method was done to assign patients in a split-mouth design to one of the following two treatment modalities: SRP group (only SRP) and moxifloxacin and ibuprofen as an adjunct to SRP group (SRP + LDD).

Clinical parameters

Plaque index (PI), gingival index (GI), probing depths (PD) and clinical attachment level (CAL) were recorded at baseline and 1 and 3 months after the treatment. A custom-made acrylic stent and a Williams graduated periodontal probe were used to standardize the measurement of PD and CAL [Figure 1a and b]. Dark-field microscopic examination to assess the presence of morphologically different microorganisms was done. Subgingival plaque sample was collected from tooth with pocket depth of ≥ 5 mm with a sterile curette at baseline and at 3 months [Figure 2].

Methods

After baseline examination and recording of all clinical parameters, all patients received routine oral hygiene instructions and full-mouth SRP. For patients in SRP group, no additional treatment was provided. In SRP + LDD group, along with SRP, LDD of 0.1 ml of moxifloxacin and ibuprofen gel was injected into two sites having deep periodontal pocket using a syringe with a blunt cannula [Figure 3]. After that, the periodontal pack was placed on that area for better retention of the local drug.

Preparation of moxifloxacin and ibuprofen gel

It was prepared at the Department of Pharmaceutics, Vikas College of Pharmaceutical Sciences, Suryapet, Nalgonda district. It was prepared by using 50 mg of moxifloxacin and 50 mg of ibuprofen in 750 mg of polycaprolactone gel (biodegradable) by using 188.67 μ l of dichloromethane as solvent [Figure 4].

Sol-gel transition

Sol-gel transition occurs by two phenomena. One is due to change in temperature, and the other is due to change in pH. For this drug formulation, pH-based sol-gel transition was used, i.e., at 6.8 pH, the prepared formulation was transformed to gel form.

Statistical analysis

The data were analyzed using the SPSS software 19.00 program (SPSS Inc., Chicago, IL, USA). Comparison of plaque and GI at baseline and at 1 and 3 months was done by Wilcoxon matched-pairs test. The intragroup comparison of clinical parameters such as PD and CAL was done by using paired *t*-test at various study intervals, and intergroup comparison between SRP group and SRP + LDD group was done by using unpaired *t*-test at various study intervals. Intragroup changes in the subgingival microbiota such as percentage of cocci and bacilli and spirochetes scores were compared at various

intervals in both groups by using Wilcoxon matched-pairs test, and intergroup comparison of microbial changes between SRP group and SRP + LDD group was done by using Mann-Whitney U-test. Differences were considered statistically significant at $P < 0.05^*$.

RESULTS

The present study was designed to assess the effect of SRP (control group), SRP plus moxifloxacin and ibuprofen gel (active group) on the clinical parameters (PI, GI, PPD and CAL) and changes in subgingival microflora in periodontal pockets at various study intervals of baseline and at 1 and 3 months within and between the two groups.

Plaque index and gingival index

There was a gradual reduction in PI and GI scores over the study period. The mean PI score at baseline was 1.32 ± 0.23 , at the end of 1 month was 0.67 ± 0.09 and at the end of 3 months was 0.40 ± 0.09 . The mean GI score at baseline was 1.64 ± 0.21 , at the end of 1 month was 0.80 ± 0.18 and at the end of 3 months was 0.38 ± 0.08 . The mean PI and GI scores were statistically significant when compared from the baseline score to the end of 1 and 3 months [Table 1].

Pocket probing depth

The mean PPD (mm) difference from baseline to 1 month in SRP group was 1.20 ± 0.30 and SRP + LDD group was 1.83 ± 0.34 , and the difference from baseline to

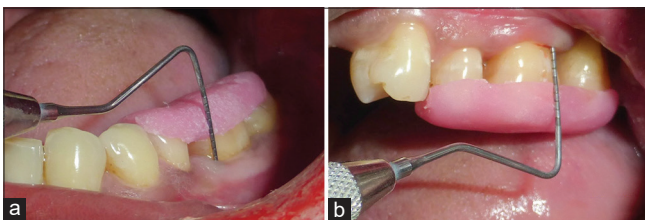


Figure 1: (a) Probing pocket depth at baseline in scaling and root planing group; (b) probing pocket depth in scaling and root planing + local drug delivery group



Figure 3: Local drug delivery of moxifloxacin and ibuprofen gel in scaling and root planing + local drug delivery group



Figure 2: Collection of plaque sample



Figure 4: Moxifloxacin and ibuprofen gel

3 months in SRP group was 1.83 ± 0.47 and SRP + LDD group was 2.85 ± 0.33 . By comparison of SRP group and SRP + LDD group, there was statistically significant difference of reduction in PPD (mm) at different study intervals with greater reduction in the test group [Table 2 and Figure 5a,b].

Clinical attachment level

The mean gain in CAL (mm) from baseline to 1 month in SRP group was 1.23 ± 0.34 and SRP + LDD group was 1.88 ± 0.28 , and the difference from baseline to 3 months in SRP group was 1.95 ± 0.22 and SRP + LDD group was 2.85 ± 0.29 . By comparison of both the groups, there was statistically significant gain in CAL (mm) at different study intervals with greater gain in the test group [Table 3].

Microbiologic assessment

The Mean cocci increased in both groups compared to baseline, with a greater increase of 67.61% and 68.12% in the test group at 1 and 3 months, respectively. This increase was statistically significant between the two groups at both time intervals. The percentage reduction of mean bacilli from baseline to different study intervals was compared, and statistically significant difference was found from baseline to 1 month and from baseline to 3 months in both the groups, with higher reduction in SRP + LDD group. The spirochetes percentage was greatly reduced in SRP + LDD group at different study intervals rather than compared with SRP group [Table 4 and Figure 6a-c].

In-vitro dissolution

The *in-vitro* dissolution results showed that there was release of drug up to 168 h, i.e., 7 days after single application of gel into the dissolution medium. At the end of 168 h, 96.34% of moxifloxacin and 95.45% of ibuprofen were released into the medium. The drug release pattern shows that both the drugs were released slowly for 168 h by following first-order kinetics. This indicates that there was a controlled release of both the drugs in *in-vitro* studies [Table 5 and Graph 1].

DISCUSSION

The primary objective of periodontal therapy for patients with chronic periodontitis is to halt disease progression and to resolve inflammation. It is aimed at reducing etiologic factors below the threshold level capable of producing periodontal tissue breakdown, thereby allowing the repair of the affected region. Very few patients can maintain periodontal health over a lifetime without the benefit of a

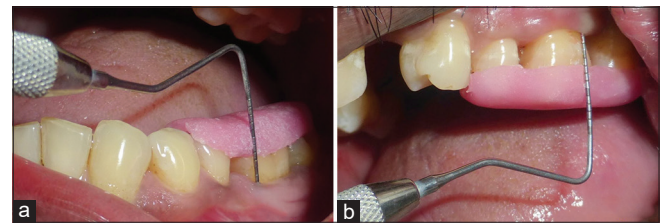


Figure 5: (a) Probing pocket depth at 3 months in scaling and root planing group; (b) probing pocket depth at 3 months in scaling and root planing + local drug delivery group

Table 1: Comparison of baseline, 1 and 3 months with respect to plaque index and gingival index scores

Parameters	Observation period	Mean value \pm SD	Comparison	Mean difference	P
PI	Baseline	1.32 \pm 0.23	-	-	-
	1 st month	0.67 \pm 0.09	Baseline versus 1 st month	0.65	0.0001*
	3 rd month	0.40 \pm 0.09	1 st month versus 3 rd month	0.27	0.0001*
	-	-	Baseline versus 3 rd month	0.92	0.0001*
GI	Baseline	1.64 \pm 0.21	-	-	-
	1 st month	0.80 \pm 0.18	Baseline versus 1 st month	0.84	0.0001*
	3 rd month	0.38 \pm 0.08	Versus 2 nd month	0.42	0.0001*
	-	-	Baseline versus 3 rd month	1.26	0.0001*

* $P < 0.05$. SD: Standard deviation, PI: Plaque index, GI: Gingival index

Table 2: Intra- and inter-group comparison of scaling and root planing and scaling and root planing + local drug delivery groups at various study intervals with respect to probing pocket depth scores

Groups	Mean \pm SD			Changes from baseline to	
	Baseline	1 month	3 months	1 month	3 months
SRP	6.08 \pm 0.57	4.88 \pm 0.56	4.25 \pm 0.57	1.20 \pm 0.30	1.83 \pm 0.47
SRP + LDD	6.03 \pm 0.62	4.20 \pm 0.57	3.18 \pm 0.57	1.83 \pm 0.34	2.85 \pm 0.33
Percentage of change in SRP				19.75 [#]	30.04 [#]
				$P=0.00001^*$	$P=0.00001^*$
Percentage of change in SRP + LDD				30.29 [#]	47.30 [#]
				$P=0.00001^*$	$P=0.00001^*$
t	0.2665	3.7769	5.9540	-6.2194	-8.0326
P	0.7913	0.0005*	0.00001*	0.00001*	0.00001*

* $P < 0.05$, [#]Applied paired t-test. LDD: Local drug delivery, SRP: Scaling and root planing, SD: Standard deviation

Table 3: Intra- and inter-group comparison of scaling and root planing and scaling and root planing + local drug delivery groups at various study intervals with respect to clinical attachment level scores

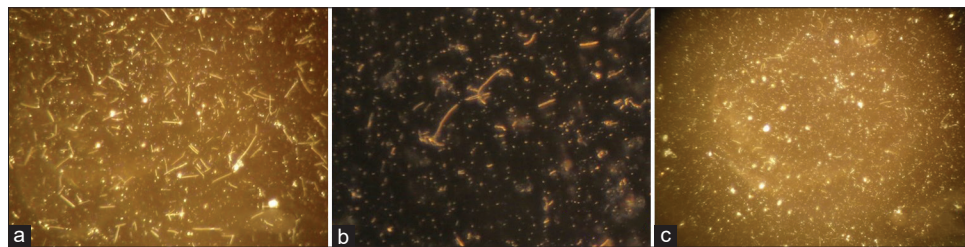
Groups	Mean±SD				
	Baseline	1 month	3 months	Changes from baseline to	
				1 month	3 months
SRP	4.65±0.65	3.43±0.59	2.70±0.70	1.23±0.34	1.95±0.22
SRP + LDD	4.65±0.65	2.78±0.75	1.80±0.73	1.88±0.28	2.85±0.29
Percentage of change in SRP				26.34*	41.94*
				<i>P</i> =0.00001*	<i>P</i> =0.00001*
Percentage of change in SRP + LDD				40.32*	61.29*
				<i>P</i> =0.00001*	<i>P</i> =0.00001*
<i>t</i>	0.0000	3.0398	3.9832	-6.6096	-11.0959
<i>P</i>	1.0000	0.0043*	0.0003*	0.00001*	0.00001*

**P*<0.05, #Applied paired *t*-test. LDD: Local drug delivery, SRP: Scaling and root planing, SD: Standard deviation

Table 4: Intra- and inter-group comparison of scaling and root planing and scaling and root planing + local drug delivery groups at various study intervals with respect to microbiota

Groups	Mean±SD				
	Baseline	1 month	3 months	Changes from baseline to	
				1 month	3 months
SRP	39.05±7.10	55.95±6.93	55.75±7.61	16.90±5.88	16.70±6.95
SRP + LDD	39.05±7.10	65.45±4.88	65.65±4.77	26.40±6.85	26.60±6.95
Percentage of change in SRP				43.28*	42.77*
				<i>P</i> =0.0001*	<i>P</i> =0.0001*
Percentage of change in SRP + LDD				67.61*	68.12*
				<i>P</i> =0.0001*	<i>P</i> =0.0001*
<i>t</i>	0.0000	-4.0169	-4.1522	-3.9628	-3.7870
<i>P</i>	1.0000	0.0001*	0.00001*	0.0001*	0.0002*

**P*<0.05, #Applied Wilcoxon matched pairs test. SD: Standard deviation, SRP: Scaling and root planing, LDD: Local drug delivery

**Figure 6:** (a) Microbiologic assessment at baseline; (b) microbiologic assessment at 3 months in scaling and root planing group; (c) microbiologic assessment at 3 months in scaling and root planing + local drug delivery group

regular dental care which consists primarily of oral hygiene instructions and nonsurgical periodontal therapy (NSPT).^[11] A novel approach is the local application of antimicrobial agents that are effective against periodontopathogens and can reduce pocket depth. This approach consists of the administration of local biodegradable sustained or controlled release antimicrobial agents in periodontal pockets. Several biodegradable local delivery systems containing different antimicrobial agents have been developed and introduced as an adjunctive measure to mechanical therapy.^[12,13] The benefits of subgingival application of drugs include:

- Better patient compliance
- Enhanced or improved pharmacokinetic response
- Greater access and ability to position the drug adjacent to the tissue

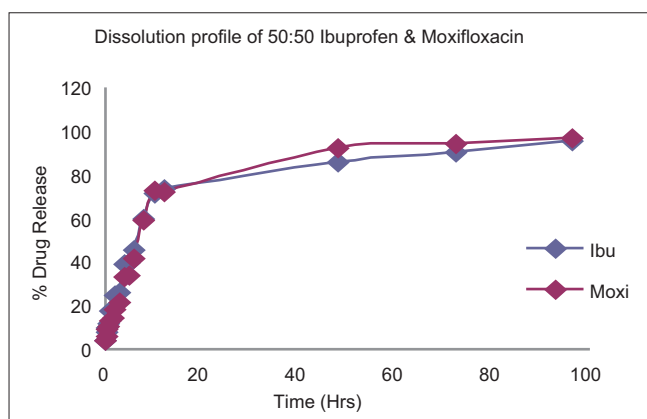
- The ability to deliver a lower total dosage of the drug at a more controlled concentration.

Moxifloxacin alone has been used earlier as LDD in the treatment of chronic periodontitis,^[7] whereas ibuprofen has been used earlier systemically in patients with chronic periodontitis.^[14] To our knowledge, the present combination of the drugs has not been investigated before, which prompted us to explore further to find their efficacy.

The present study showed significant reduction in the PI and GI scores over the study period after NSPT. Flemmig *et al.*^[7] reported significant reduction in gingival and PI scores following NSPT, which were in accordance with the present study.

Table 5: In-vitro release of drug formulation

Time (h)	F ₅	
	Percentage drug release of Moxifloxacin	Percentage drug release of Ibuprofen
0.083	3.57	3.24
0.166	9.83	15.55
0.333	9.64	16.93
0.5	20.34	32.55
1	22.36	34.21
1.5	32.33	47.021
2	40.77	57.42
3	56.18	75.38
4	70.37	65.95
5	58.29	68.25
6	62.38	70.94
8	72.69	67.28
10	83.54	76.01
12	82.05	75.14
24	86.56	72.96
48	76.13	74.36
96	92.21	85.74
144	93.90	89.95
168	96.34	95.45

**Graph 1: In-vitro drug release of moxifloxacin and ibuprofen (pH 6.8)**

The mean reduction of PPD (2.85 mm) and gain in CAL (2.56 mm) observed at the end of the study period in the SRP + LDD group of the present study was greater than that observed in the studies of Azmak *et al.*^[15] and Timmerman *et al.*^[16] which could be attributed to different antimicrobial agents used as adjunct to SRP in the abovementioned studies, i.e., chlorhexidine (CHX) chips and 2% minocycline gel, respectively. The better reduction in PPD and gain in CAL in the present study could be due to the greater efficacy of moxifloxacin as a local delivery agent and the synergistic effect of ibuprofen which acts as an inhibitor of further alveolar bone loss.

The reduction in PPD (2.85 mm) and gain in CAL (2.56 mm) in the present study were significantly more in comparison with a study using only antimicrobials in different LDD forms (tetracycline fibers, metronidazole gel, minocycline gel, minocycline microspheres, CHX chips and doxycycline

polymer) by Greenstein.^[17] The reduction in PPD ranged from 0.93 to 2.5 mm, whereas the gain in CAL ranged from 0.76 to 1.5 mm for the abovementioned antimicrobials. The significant results of the present study may be attributed to the addition of NSAID to antimicrobial agent which contributed to the improved clinical outcome of treatment when compared to antimicrobial agents alone.

Both the groups showed statistically significant increase in the number of cocci and decrease in motile rods and spirochetes when compared to baseline, which was statistically significant. The increase in cocci and decrease in motile rods and spirochetes were greater in the SRP + LDD group than in the SRP group at all-time intervals, and the difference was found to be statistically significant ($P < 0.05$). The results of the present study were in accordance with the studies of Okuda *et al.*^[18] and Pradeep *et al.*^[19] where they used minocycline and azithromycin as LDD, respectively. There was a statistically significant change in the percentage of microorganisms from baseline to 1 and 3 months in both the groups, but when compared between 1st-month and 3rd-month intervals, the change was not statistically significant. This could be due to “rebound” return, i.e., a rapid reduction followed by a slow return to pretreatment levels, which was seen for the total subgingival cell counts, which is in accordance with the studies of Listgarten and Levin^[20] and Slots *et al.*^[21]

According to our knowledge, this is the first indigenously prepared LDD formulation containing a broad-spectrum antimicrobial agent, i.e., moxifloxacin and an anti-inflammatory agent, i.e., ibuprofen that proved to be a better LDD formulation in terms of pharmacokinetic profile and clinical and microbiological effects as compared to other formulations in the treatment of chronic periodontitis patients. The strengths of the present study could be the nature of the vehicle, split-mouth design used, ease of application and better retention of drug in the periodontal pocket due to sol-gel conversion. Apart from the above significant results, this combination of drugs did not result in any adverse events and thus can be used safely as LDD in the treatment of chronic periodontitis.

CONCLUSION

Among the two treatment modalities, treatment with moxifloxacin and ibuprofen local delivery as an adjunct to SRP gave superior results in clinical and microbiological parameters compared to SRP group with statistically significant results. However, long-term studies with

greater sample size need to be carried out to confirm the observations seen in the present study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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