

Efficacy of 1.5% Metformin Gel as an Adjuvant to Scaling, Root Planing, and Curettage for the Treatment of Infrabony Defects in Chronic Periodontitis Patients

Abstract

Context: To compare and evaluate clinically and radiographically the efficacy of 1.5% metformin (MF) gel and placebo gel as an adjunct to scaling and root planing (SRP) and Curettage for the treatment of infrabony defects (IBDs) in chronic periodontitis patients. **Subjects and Methods:** The study was conducted randomly on 15 patients of both the genders. Each patient contributed two sites (total 30 sites - Split mouth design) which was randomly assigned to one of the two treatments: (i) Site A (Control Site) in which SRP was done along with curettage and intrapocket application of Placebo Gel and (ii) Site B (Test Site) in which SRP was done along with curettage and intrapocket application of 1.5% MF Gel. The Periodontal status {which included plaque index (PI), sulcus bleeding index (SBI), probing pocket depth (PPD), clinical attachment level (CAL), IBD Depth} was assessed both clinically and radiographically at baseline, 3 months, and 6 months after treatment. **Results:** It was found that there was statistically significant difference in the periodontal status (PI, SBI, PPD, CAL, IBD depth) of the two sites when compared from baseline to 6 months. **Conclusions:** Local delivery of 1.5% MF improves the clinical outcomes of traditional treatment (SRP) and curettage and should be considered particularly as an adjunct to it.

Keywords: Chronic periodontitis, metformin, periodontal diseases, periodontal pocket

Introduction

Periodontal disease is a chronic inflammatory disease characterized by bleeding on probing, inflamed gingiva, clinical attachment loss and resorption of alveolar bone. There are no conventional or surgical periodontal treatments which can regenerate lost periodontal tissue to a significant clinical level.^[1] Efforts have been made at improving various nonsurgical approaches, which are directed more specifically at the microbial nature of the periodontal disease. The use of local drug-delivery system is one such approach. There are many local drug delivery (LDD) systems such as minocycline, doxycycline, chlorhexidine, and tetracycline which have been proved to be beneficial.^[2] Recently, metformin (MF), an oral antihyperglycemic drug, has been introduced as a new LDD system which promotes bone formation and stimulates osteoblastic differentiation. Infrabony defects (IBDs) are generally

treated by periodontal flap and flap with graft procedures which are beneficial but expensive.^[3] On the other hand, MF which is cheaper and easily available, have been reported to be beneficial in the treatment of IBDs in chronic periodontitis patients. Thus, the present study was undertaken in an attempt to compare and evaluate clinically and radiographically the efficacy of 1.5% MF gel and Placebo gel as an adjunct to scaling and root planing (SRP) and curettage for the treatment of IBDs in chronic periodontitis patients.

Subjects and Methods

The study was conducted in 15 patients of both the genders from routine Out Patient Department (OPD). Thirty sites were randomly selected (split mouth design) to evaluate the efficacy of 1.5% MF gel as an adjunct to SRP and curettage for the treatment of IBDs in patients with chronic periodontitis. Each patient contributed two sites which were randomly assigned to one of the following two treatments:

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- Site A (control site): SRP + curettage + intrapocket application of placebo gel
- Site B (test site): SRP + curettage + intrapocket application of 1.5% MF gel.

The study protocol was approved by institutional ethical committee and Maharashtra University of health sciences Nashik, Maharashtra (India). The study was performed on 15 patients meeting the following inclusion criteria: (i) Patients with chronic periodontitis with at least one IBD on the contralateral side; (ii) IBD more than or equal to 3 mm, clinical attachment loss (CAL) ≥ 4 mm, probing pocket depth (PPD) ≥ 5 mm; and (iii) subjects between the ages of 25 and 60 years and presence of minimum 16 natural teeth (at least four teeth per quadrant). The exclusion criteria included patients having history of allergies to MF/biguanide group or any systemic disease, pregnant women and lactating mothers, patients using tobacco in any form or alcoholism, use of systemic MF, or any other oral anti-diabetic drug.

Formulation of 1.5% metformin gel

MF gel was prepared as described by Mohapatra *et al.*^[4] in Y. B. Chavan College of Pharmacy, Aurangabad. Briefly, all the required ingredients of the formulation were weighed accurately. Dry gellan gum powder was dispersed in distilled water maintained at 95°C. The dispersion was stirred at 95°C for 20 min using a magnetic stirrer to facilitate hydration of gellan gum. The required amount of mannitol was added to the gellan gum solution with continuous stirring, and the temperature was maintained above 80°C. A weighed amount of MF was added with stirring. Then sucralose, citric acid, and preservatives (methylparaben, propylparaben) were added with stirring. Finally, the required amount of sodium citrate was dissolved in 10 mL distilled water and added to the mixture. The mixture was allowed to cool to room temperature to form gel which was used in the present study. The drug was thus retained in the target compartment for a longer period, suggesting a controlled release of the drug till 4 weeks.

Before starting the treatment, complete procedure was explained and written informed consent was obtained from each patient. Complete case history and all clinical parameters (plaque index [PI], sulcus bleeding index [SBI], PPD, clinical attachment level [CAL], IBD depth) were recorded for all the subjects. After completing full-mouth supra and sub-gingival scaling, root planing and curettage, two sites with periodontal pockets of ≥ 5 mm were selected randomly using lottery method. Site A was isolated and dried with compressed air for the placement of Placebo gel in periodontal pockets using a syringe with 24 gauge needle [Figure 1]. Site B was isolated and dried with compressed air for the placement of 1.5% MF gel [Figure 2]. For standardization, 10 mL of prepared MF gel was injected into periodontal pockets using a syringe with 24 gauge needle. The patient was permitted

to perform normal oral hygiene procedures, but instructed not to floss for 10 days in the selected sites and adjacent sites at the same interproximal regions to avoid the possibility of dislodgement of gel from the crevice. Patients were also instructed not to use any chemotherapeutic mouth-rinse or oral irrigation devices. Periodontal status was assessed at baseline [Figure 3], 3 months [Figure 4] and 6 months [Figure 5] after treatment. Periodontal status examination involved the following measurements:

Plaque index

Turesky Gillmore Glickman modifications of Quigley Hein PI.^[5]

Sulcus Bleeding Index

Mühlemann and SonSBI.^[6]



Figure 1: Intrapocket application of placebo gel in Site A (mesial to 37)



Figure 2: Intrapocket application of 1.5% metformin gel in Site B (mesial to 47)

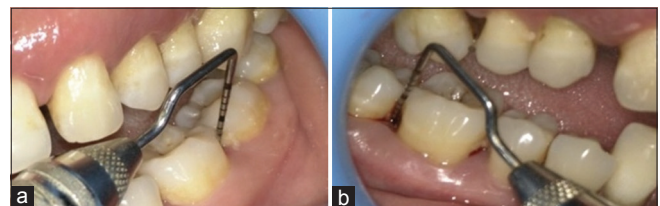


Figure 3: Probing pocket depth at baseline (a) Site A (6 mm) and (b) Site B (6 mm)

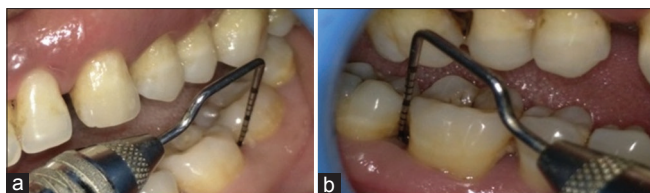


Figure 4: Probing pocket depth at 3 months (a) Site A (5 mm) and (b) Site B (4 mm)

Probing pocket depth

The measurement from gingival margin to the base of the pocket using UNC 15 probe.

Clinical attachment level

Measured as distance from Cemento-enamel junction to base of periodontal pocket using UNC 15 probe.

Infrabony defect depth

IBD depth was measured on the radiograph by measuring the vertical distance from the crest of the alveolar bone to the base of the defect using grid [Figure 6]. Individually customized bite blocks, grid and a parallel-angle intraoral radiographic technique were used to obtain radiographs as reproducibly as possible.

Infrabony defect fill

IBD fill was calculated as the difference between the values of the distance from cement-enamel junction to the base of the defect at 3 months and 6 months from baseline.

Patients were instructed to report immediately if the material is dislodged before the scheduled recall visit or if pain, swelling, or any other complication occurs. However, none of the patients reported with any such complaints.

Results

A total of 9 female and 6 male subjects were included in the study. Statistical analysis was performed with help of Epi Info (TM) 3.5.3 (Epi Info statistical software developed by Centers for Disease Control and Prevention (CDC)). EPI INFO is a trademark of the Centers for Disease Control and Prevention. Descriptive statistical analysis was performed to prepare the tables with corresponding percentages. The clinical parameters (mean PI, Mean SBI, PPD, CAL) and radiographic parameter (IBD depth and IBD fill) were compared at baseline, 3 months and 6 months after initial periodontal treatment in between two sites using independent *t*-test.

At baseline, no significant difference was found in the mean values of PI, SBI, PPD, total PPD Reduction, CAL, CAL gain, total CAL gain, radiographical comparison of mean IBD Depth, IBD Fill and total IBD Fill between the Site A and Site B in all the patients. However, the mean values of PI [Table 1], SBI [Table 2], PPD [Table 3], CAL [Table 4], and IBD Depth [Table 5] were significantly

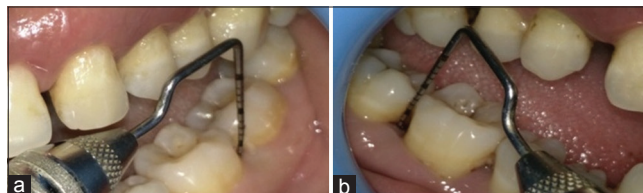


Figure 5: Probing pocket depth at 6 months (a) Site A (3 mm) and (b) Site B (2 mm)

lower in Site B than Site A, and the mean values of total PPD Reduction [Table 6], CAL gain [Table 7], total CAL gain [Table 6], IBD Fill [Table 8], and total IBD Fill [Table 6] were significantly higher in Site B than Site A in all the patients after 3 months and 6 months. All 15 patients completed the study without any adverse event presented by any subject during the study.

Discussion

Most periodontal investigators agree that bacteria are the primary etiologic agents of destructive periodontal diseases.^[7,8] Elimination or adequate suppression of putative periodontopathic microorganisms in the subgingival microbiodata is essential for periodontal healing.^[9] The main aim of any type of periodontal therapy is regeneration of periodontal tissue and alveolar bone loss caused by periodontal disease. A fundamental principle of drug therapy is that the agent must reach the site of action in adequate concentration to be effective and be maintained at that site for an adequate duration to allow the effect to occur.^[10]

Dr. Max Goodson was the one who pioneered and developed the concept of LDD systems in 1979.^[6] Drugs that need to be delivered locally are inserted into a vehicle in the form of fibers, gels, strips and compacts, actisite, films, injectable systems, vesicular liposomal systems, microparticle system, and nanoparticle system. Various drugs that have been used as LDD are tetracycline, chlorhexidine diacetate, minocycline, metronidazole, chlorhexidine gluconate, taurine, ipriflavone, ormidazole, amoxicillin and metronidazole, clindamycin, doxycycline, ofloxacin, triclosan, anti-oralis, antisense oligonucleotide.^[11,12]

A new LDD method has been reported in literature using MF which is a commonly used oral anti-diabetic drug. The use of MF has been increased recently in the field of periodontology following the results of the study by Ma *et al.*^[13] which suggested that osteoblasts can be stimulated by MF. Considering this activity of MF, the present study was undertaken to compare and evaluate the efficacy of 1.5% MF gel with placebo gel as an adjunct to SRP and curettage in the treatment of IBDs in patients with chronic periodontitis. MF has a relatively low oral bioavailability of approximately 50%–60%. The use of MF as LDD system improve its bioavailability, reduce the dosing frequency, decrease gastrointestinal side effects and toxicity



Figure 6: Intraoral periapical radiograph with grid showing infrabony defect in Site B at (a) baseline (5 mm) (b) 3 months (2 mm) (c) 6 months (1 mm)

Table 1: Mean comparison of plaque index for Sites A and B at baseline, 3 months and 6 months

Treatment	Sites	Mean	SD	P
Baseline	A	2.167	0.523	0.881
	B	2.2	0.676	
3 months	A	1.333	0.309	0.000*
	B	0.733	0.458	
6 months	A	0.7	0.316	0.000*
	B	0	0	

*Statistically significant difference found between site A and site B as compared to the baseline. SD: Standard deviation

Table 2: Mean comparison of sulcus bleeding index for sites A and B at baseline, 3 months and 6 months

Treatment	Sites	Mean	SD	P
Baseline	A	2.267	0.704	0.478
	B	2.083	0.692	
3 months	A	1.363	0.502	0.002*
	B	0.683	0.571	
6 months	A	0.667	0.294	0.002*
	B	0.00	0.00	

*Statistically significant difference found between site A and site B as compared to the baseline. SD: Standard deviation

Table 3: Mean comparison of probing pocket depth for sites A and B at baseline, 3 months and 6 months

Treatment	Sites	Mean	SD	P
Baseline	A	5.2	0.414	0.493
	B	5.33	0.617	
3 months	A	4.467	0.64	0.006*
	B	3.733	0.704	
6 months	A	3.667	0.488	0.000*
	B	2.773	0.458	

*Statistically significant difference found between site A and site B as compared to the baseline. SD: Standard deviation

Table 4: Mean comparison of clinical attachment level for sites A and B at baseline, 3 months and 6 months

Treatment	Sites	Mean	SD	P
Baseline	A	5.2	0.414	0.493
	B	5.33	0.617	
3 months	A	4.467	0.64	0.006*
	B	3.733	0.704	
6 months	A	3.667	0.488	0.000*
	B	2.773	0.458	

*Statistically significant difference found between site A and site B as compared to the baseline. SD: Standard deviation

Table 5: Mean comparison of infrabony defect depth for sites A and B at baseline, 3 months and 6 months

Treatment	Sites	Mean	SD	P
Baseline	A	3.4	0.632	0.326
	B	3.667	0.816	
3 months	A	2.667	0.617	0.016*
	B	2.133	0.516	
6 months	A	2.133	0.516	0.016*
	B	0.533	0.64	

*Statistically significant difference found between site A and site B as compared to the baseline. SD: Standard deviation

Table 6: Mean comparison of recorded parameters for sites A and B at baseline to 6 months

Parameters	Sites	Mean	SD	P
Total PPD reduction	A	1.8	1.082	0.025*
	B	2.6	0.737	
Total CAL gain	A	1.8	1.082	0.025*
	B	2.6	0.737	
Total IBD fill	A	1.2	0.414	0.000*
	B	3.133	0.834	

*Statistically significant difference found between site A and site B as compared to the baseline. PPD: Probing pocket depth; CAL: Clinical attachment Level; IBD: Infrabony defect; SD: Standard deviation

Table 7: Mean comparison of clinical attachment level gain for sites A and B at 3 months and 6 months

Treatment	Sites	Mean	SD	P
3 months	A	0.733	0.594	0.000*
	B	1.6	0.507	
6 months	A	0.8	0.676	0.417
	B	1	0.655	

*Statistically significant difference found between site A and site B as compared to the baseline. SD: Standard deviation

Table 8: Mean comparison of infrabony defect fill for sites A and B at 3 months and 6 months

Treatment	Sites	Mean	SD	P
3 months	A	0.733	0.458	0.000*
	B	1.533	0.64	
6 months	A	0.467	0.516	0.000*
	B	1.6	0.632	

*Statistically significant difference found between site A and site B as compared to the baseline. SD: Standard deviation

thus helpful for the effective use of the drug. MF includes nausea, anorexia, a metallic taste, abdominal discomfort

and diarrhea or soft bowel movements, Vitamin B12 deficiency, lactic acidosis, and hypoglycemia. However, these side effects are not encountered while using MF as LDD system.^[14]

In the present study, mean PPD in Site A was 5.2 ± 0.414 mm and in Site B was 5.33 ± 0.617 mm at baseline. After treatment, the mean PPD in Site B was reduced to 3.733 ± 0.704 mm and 2.733 ± 0.458 mm at 3 months and 6 months, respectively, whereas for Site A the value was reduced to 4.467 ± 0.64 mm at 3 months and 3.667 ± 0.488 mm at 6 months. Thus, the total PPD reduction in Site B was 2.6 ± 0.737 mm which was significantly higher than the control Site A where it was 1.8 ± 1.082 mm. Similar results were found in the study by Pradeep *et al.*,^[1] where mean PPD was reduced from 8.16 ± 0.75 mm to 5.36 ± 0.77 mm at 3 months and further reduced to 4.36 ± 0.81 mm at 6 months after using 1.5% MF gel. Rao *et al.*^[15] in his study, have compared 1% MF gel with placebo gel in smokers with chronic periodontitis patients, where the mean PPD was reduced from 7.50 ± 0.51 mm to 5.40 ± 0.68 mm at 3 months and further reduced to 4.33 ± 0.61 mm at 6 months. Similar results were obtained by Pradeep *et al.*,^[16] Pankaj *et al.*,^[17] Mushtaq *et al.*^[18] who found more PPD reduction in MF group as compared to the placebo group.

In the present study, the mean CAL in Site A was 5.2 ± 0.414 mm and in Site B was 5.33 ± 0.617 mm at baseline, which after treatment was reduced to 3.733 ± 0.704 mm and 2.733 ± 0.458 mm at 3 months and 6 months respectively in Site B. For Site A, the value was reduced to 4.467 ± 0.64 mm at 3 months and 3.667 ± 0.488 mm at 6 months. Thus, the total CAL gain of Site B was 2.6 ± 0.737 mm which was significantly higher than the control Site A where it was 1.8 ± 1.082 mm. In the study done by Pradeep *et al.*,^[1] mean CAL was reduced from 6.30 ± 0.79 mm to 3.93 ± 0.74 mm at 3 months and further reduced to 2.70 ± 0.75 mm at 6 months when 1.5% MF gel was placed in IBD. Rao *et al.*,^[15] in their study, found that the mean CAL was reduced from 6.63 ± 0.81 mm to 4.27 ± 0.64 mm at 3 months and further reduced to 3.37 ± 0.49 mm at 6 months when 1% MF gel was placed in IBD and the mean CAL was reduced from 6.43 ± 0.77 mm to 5.57 ± 0.73 mm at 3 months which further reduced to 4.97 ± 0.72 mm at 6 months when placebo gel was placed in IBD. Thus, the mean CAL gain was more in the MF group as compared to the placebo group. Similar results were obtained by Pradeep *et al.*,^[16] Pankaj *et al.*,^[17] Mushtaq *et al.*^[18] who found more CAL gain in the MF group than the placebo group.

In the present study, PI was also recorded at baseline, as well as 3 months and 6 months after treatment. After completion of SRP, all the patients exhibited low plaque levels compared to baseline at subsequent appointments indicative of good oral hygiene maintenance, successful

motivation, and adherence to oral hygiene instructions in supportive periodontal care. At baseline no significant difference was seen in both the sites but after 3 months and 6 months of treatment, PI was significantly lower in the test Site B as compared to the control Site A [Table 1]. Pradeep *et al.*^[16] and Pankaj *et al.*^[17] have found similar results in their study using 1% MF gel where the PI was reduced from baseline to 6 months in the MF group as compared to the placebo group. SBI recorded in the present study was indicative of gingival inflammation before and after the treatment. No statistically significant difference was found between Site A and B at baseline. However, significant reduction in SBI was found in the 1.5% MF group as compared to the placebo group at 3 months and 6 months, respectively [Table 2]. Similar results were obtained by Pradeep *et al.*^[16] and Pankaj *et al.*^[17] who found significant reduction in the modified SBI (mSBI) using 1% MF gel from baseline to 6 months.

At baseline, the IBD depth in Site A was 3.4 ± 0.632 mm and in Site B was 3.667 ± 0.816 mm in the present study. As MF has bone forming capacity, it leads to bone formation and hence the values were evaluated after 3 months and 6 months. The IBD depth in Site A was reduced to 2.667 ± 0.617 mm and in Site B was reduced to 2.133 ± 0.516 mm after 3 months and it was further reduced to 2.133 ± 0.516 mm in Site A and to 0.533 ± 0.640 mm in Site B after 6 months [Table 5]. Statistically significant difference was found between Site A and Site B after 3 months and 6 months ($P = 0.016$). Similar observations were made by Pradeep *et al.*^[1] who compared the IBD depth at baseline and 6 months after the placement of 1.5% MF gel where the IBD depth of 4.85 ± 0.52 mm at baseline was reduced to 3.47 ± 0.58 mm after 6 months of treatment. Rao *et al.*,^[15] Pradeep *et al.*^[16] and Pankaj *et al.*^[17] have also made similar observations in terms of IBD depth reduction in their studies using 1% MF gel. Due to the osteogenic potential of MF, more bone formation was seen in Site B. The total IBD Fill in Site A was 1.2 ± 0.414 mm and in Site B was 3.133 ± 0.834 mm from baseline to 6 months, which was statistically significant [Table 6]. Similar observations were made by Pradeep *et al.*,^[1] Rao *et al.*,^[15] Pradeep *et al.*^[16] and Pankaj *et al.*^[17] in the MF gel in terms of IBD Fill.

The effect of MF on the cellular level is studied in the literature and suggested that it significantly decreases intracellular reactive oxygen species and apoptosis and also has a direct osteogenic effect on osteoblasts that could be partially mediated via promotion of Runx2 and insulin-like growth factor-1 expression.^[19] Thus, these possible bone-sparing and bone-formative effects of MF may be of considerable interest to periodontist in managing periodontitis-induced alveolar bone loss. The mechanism of action is supposed to be mainly at the hepatocyte mitochondria where MF interferes with intracellular handling of calcium, thus decreasing gluconeogenesis and increasing the expression of glucose transporters. MF

was shown to inhibit cytosolic and mitochondrial reactive oxygen species production induced by advanced glycation end products in endothelial and smooth muscle cells.^[18]

A recent *in vitro* study have evaluated the effect of MF (25–500 mM) on osteoblast-like cells which showed that MF for 24 h had a dose-dependent increase in cell proliferation, promoted osteoblastic differentiation, increased type I collagen production, and stimulated alkaline phosphatase activity in MC3T3E1 osteoblasts.^[20] In the present study, the effect of MF gel was compared with placebo gel. Reason for the effectiveness of placebo gel on clinical and radiographic parameters has not been mentioned in literature. In such cases, improvement in clinical and radiographic parameter could be due to SRP alone.^[21]

The present study did not find any major patient-centered undesirable effects of 1.5% MF gel and Placebo gel. The lack of significant adverse events is probably due to the nonirritating nature of the medications and delivery vehicles employed. In addition, one of the advantages of LDD systems for periodontal therapy is that the total amount of drug used is quite small. As compared to systemic administration of drugs, the total body dose of drug delivered with locally sustained-release systems is miniscule. Therefore, side effects are less likely to occur when LDD systems are used.

Conclusions

The results of the present study have proved that the local delivery of 1.5% MF improves the clinical outcomes of traditional treatment (SRP) and curettage in patients with chronic periodontitis and hence should be considered as an adjunct to it. The bone-formative effects of the common oral anti hyperglycemic agent MF thus can provide a new direction in the field of periodontal regeneration.

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Conflicts of interest

There are no conflicts of interest.

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