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Evaluation of Locally Administered 1% Metformin Gel in the Treatment of Chronic Periodontitis

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Abstract

Background: Adjunctive use of locally administered 1% Metformin gel with scaling and root planing (SRP) has been found to be beneficial in the treatment of Periodontitis.

Aims & Objective: To evaluate the effect of locally administered 1% metformin gel on clinical parameters namely Gingival index, Probing Pocket Depth and Clinical Attachment level.

Materials & Method: A total of 60 patients with probing pocket depth of 5-6mm in chronic generalized periodontitis were randomly divided into two groups; SRP followed by 1% metformin gel as test site and SRP only as control site. The clinical parameters including Gingival index, Probing pocket depth and Clinical attachment level (CAL) were recorded at baseline, 3 month and 6 month. The results were statistically analysed using ANOVA test and independent t-test.

Result: Both the groups (test & control) showed improvement in all the recorded parameters (GI, PPD, CAL) while the test group showed statistically significant reduction in all the clinical parameters compared to control group ($p < 0.05$).

Conclusion: 1% Metformin gel can be effectively used as an adjunct to SRP in non-surgical management of chronic periodontitis.

Keywords: Adjunctive use, Metformin gel, Local drug delivery, Nonsurgical periodontal treatment.

Introduction

Periodontal disease is a chronic inflammatory disease characterized by inflamed gingiva, bleeding on probing, resorption of alveolar bone, and attachment loss between the tooth and its surrounding alveolar bone. In the past decade, periodontal disease has been recognized as not merely a local infectious disease but also as a chronic, subclinical, inflammatory disease for the host. [1]

Progression of the inflammatory condition leads to increase in probing depth which makes non-surgical therapy such as scaling and root planning (SRP) less effective. Due to this reason various authors have evaluated the potential benefit of local drug delivery in deeper pocket sites. [2]

Diabetes mellitus is a clinically and genetically heterogeneous group of metabolic disorders manifested by abnormally high levels of glucose in the blood. Metformin is one of the most commonly used oral antihyperglycemic agents for the treatment of type II diabetes mellitus. The mechanism of action is mainly at the hepatocyte mitochondria in which metformin interferes with intracellular handling of calcium, decreasing gluconeogenesis and increasing the expression of glucose transporters. The United

Kingdom Prospective Diabetes Study showed that treatment with metformin reduces the risk of lifethreatening macrovascular complications compared to other antihyperglycemic agents. [1]

Sites of action have been proposed for MF, including decreased hepatic glucose output, increased peripheral glucose uptake, and improved insulin secretion (Bailey and Turner, 1996). MF was shown to inhibit cytosolic and mitochondrial reactive oxygen species production induced by advanced glycation end products in endothelial and smooth muscle cells (Bellin et al., 2006). The U.K. Prospective Diabetes Study showed that MF treatment reduces the risk of life-threatening macrovascular complications compared to other antihyperglycemic agents[3].Studies have also shown favourable effect of Metformin on bone formation. There are two mechanisms of action that have been suggested for the osteogenic effect of Metformin: increased proliferation of osteoblasts and reduction of osteoclast activity. It was observed that exposure to Metformin led to a decrease of osteoclast and bone formation. Metformin down-regulates the production of receptor activator of nuclear factor kappa B ligand (RANKL) and up-regulates the production of osteoprotegerin (OPG) from osteoblasts. This decreased RANKL/OPG ratio in turn decreases the osteoclast activity, thereby inducing bone formation and inhibiting bone resorption. The general clinical benefits observed in therapy with metformin seem to be greater than expected. They induce osteoblast cells to promote early bone formation through AMP kinase (AMPK) activity. Moreover, in a recent in vitro study, metformin facilitated in the proliferation of MG63 osteoblast like cells. Thus, their action in stimulating bone formation has justified their use in the treatment of periodontal bone defects in chronic periodontitis. [4, 5]

Among these compounds, locally delivered metformin have recently been introduced for the treatment of periodontal bone defects in chronic periodontitis. Further, different concentrations of MF (0.5%, 1% and 1.5%) used locally in the treatment of Chronic Periodontitis proved 1% concentration to be most effective, both clinically and radiographically. [6]

These recent studies support the concept that the local application of these agents significantly improves clinical parameters and leads to defect depth reduction. Therefore, the aim of the study was to investigate the effectiveness of metformin gel as an adjunct to scaling and root planing in the treatment of periodontitis. [1]

Materials And Methods

A total of 60 (28 males and 32 females) systemically healthy subjects aged 25-55 years suffering from chronic generalized periodontitis were selected from the outpatient department of Periodontia, Government Dental College , Ahmedabad. A brief case history was recorded from all the patients who were taking part in the study. The purpose of the study was explained to the patients and written informed consent was obtained and ethical approval was obtained from the institutional ethical committee.

Inclusion Criteria:

1. Systemically healthy patients with age group between 25-55 years.
2. Patients with sites showing PD ≥5 mm and clinical attachment loss ≥4 mm in chronic periodontitis patients.
3. Patients with no history of periodontal therapy in the past 6 months.
4. Patients without any antibiotic treatment in last six months.
5. Patients with established willingness and ability to perform adequate oral hygiene.

Exclusion Criteria

1. Systemic illness known to affect the outcomes of periodontal therapy such as diabetes mellitus, cardiac disease and immunocompromised conditions.
2. Patients who have known allergy to metformin.
3. Patients who are on systemic metformin.
4. Alcoholics and smokers.
5. Pregnant and lactating females were not included in the study.

Treatment Procedures

A total of 60 patients were selected randomly and divided into 2 groups:

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Control group (group I): scaling and root planning was done

Study group (group II): scaling and root planning followed by 1% Metformin gel as a local drug delivery.

Proper oral hygiene instructions were given to all patients. After the recording of clinical parameters like Gingival index, Probing pocket depth and Clinical attachment level, all patients underwent full mouth oral prophylaxis using ultra sonic scaler (Woodpecker UDS P LED) and hand instruments. After the completion of scaling, sites with PPD of 5mm or more were selected for local drug delivery.1% METFORMIN was injected into the pocket of 5mm or more using a syringe with a blunt cannula in Group II(Figure 3).Periodontal dressing was applied after delivery of the drug. After placement of the gel, patients instructed to refrain from chewing hard or sticky foods, brushing near the treated areas for 1 week.

Formulation Of MF Gel

The Metformin gel was prepared at Mediont Pharma company at Surat, Gujarat. All the required ingredients were weighed accurately.Dry gellan gum powder was dispersed in 50ml of distilled water maintained at 95°C for 20 minutes using a magnetic stirrer (Remi magnetic stirrer 2MHLH , Mumbai, India) 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. Metformin was added with stirring. Finally, required amount of sodium citrate was dissolved in 10ml of distilled water and added to the mixture. The weight of the gel was monitored continuously during manufacturing and finally it was adjusted to 100gm with distilled water. The mixture containing gellan gum and metformin was allowed to cool to room temperature to form gel (Figure 1).

Statistical Analysis

The Statistical Analysis Software (SPSS version 16) was used for data processing and analysis. The differences in means of the parameters at the baseline between test and control groups were evaluated using an independent t-test. The changes in parameters over time within intragroup were evaluated using a ANOVA for each group separately, $p < 0.05$ was considered statistically significant.

Result

All the sixty patients completed the study. No adverse effects and allergic responses of the drugs were noticed. On intergroup comparison of GI at specific time intervals using independent sample T test, the means were comparable at BL, the means at 3 month and 6 months were statistically significant; indicating more reduction in GI scores for test group. (Table 1).Similarly, on intergroup comparison of PPD, CAL at specific time, the means were comparable at BL, the means at 3 month and 6 months were statistically significant; indicating more reduction in PPD, CAL scores for test group.(Table 2, Table 3).

Figure 1: 1% Metformin gel

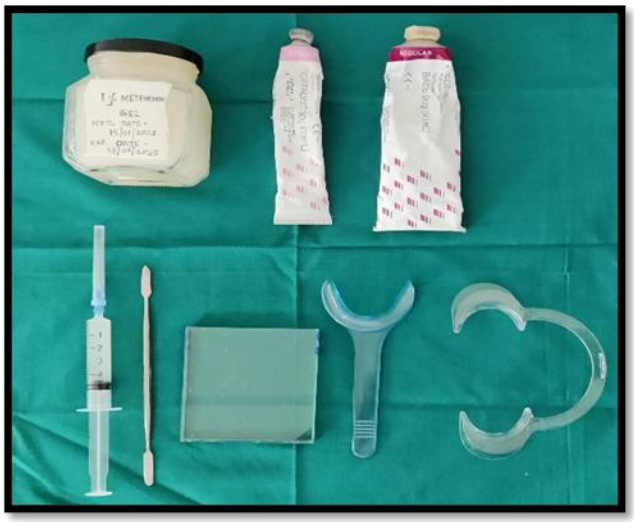

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Figure 2: Pre treatment pocket depth

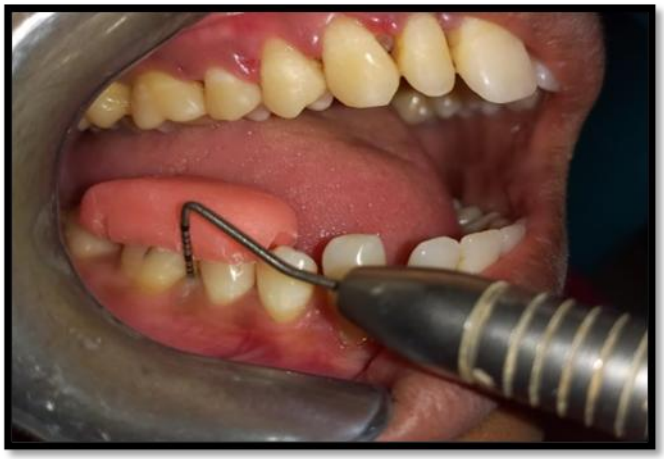

Figure 3 : 1% Metformin gel drug delivery in periodontal pocket

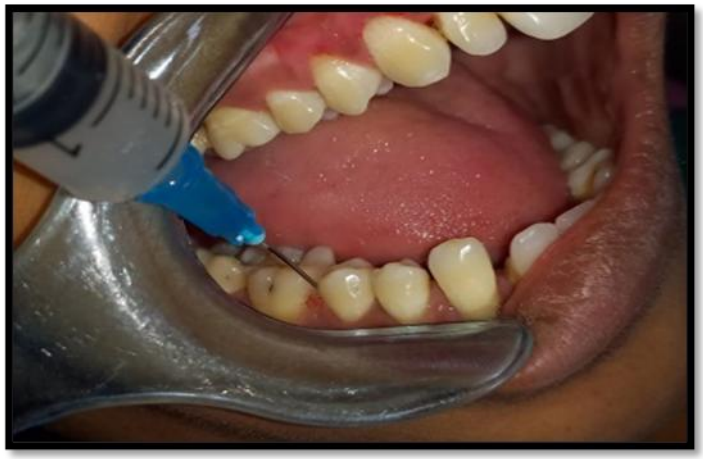

Figure 4: Placement of periodontal dressing

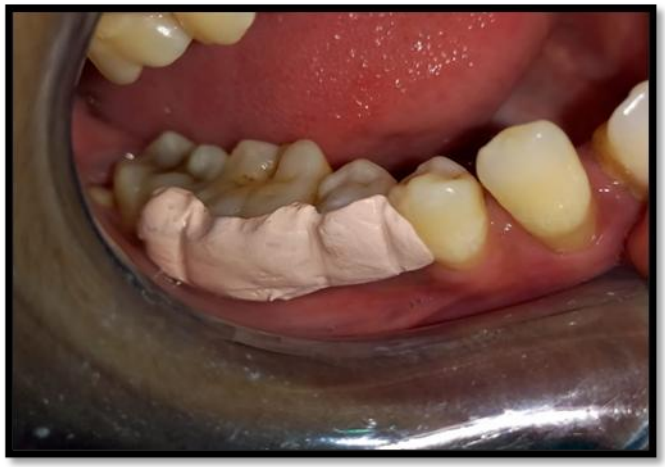

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Figure 5 : Post-treatment pocket depth

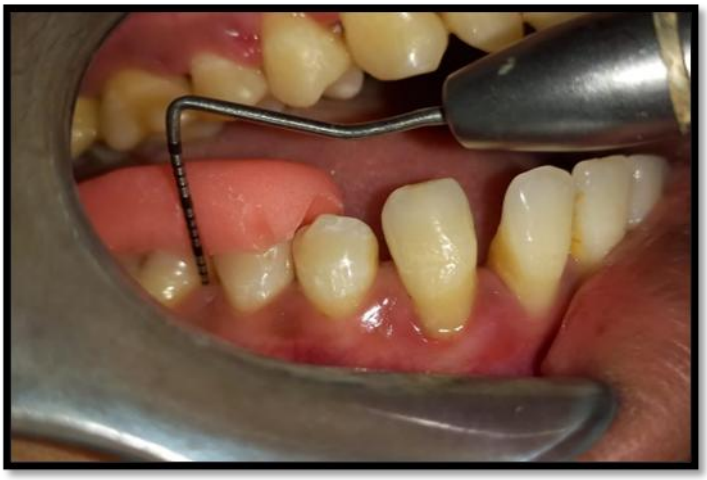

Table 1: Comparison of Gingival Index (GI) scores at different time interval

GI	Groups	Mean	P value (Independent sample t test)
Baseline	SRP	1.7033	0.003
	SRP+MF GEL	1.8900	
3 months	SRP	1.2767	0.042
	SRP+MF GEL	1.1200	
6 months	SRP	0.9833	0.002
	SRP+MF GEL	0.8033	

Table 2: Comparison of Probing Pocket Depth (PPD) scores at different time interval

PPD	Groups	Mean	P value (Independent sample t test)
Baseline	SRP	3.2500	0.120

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	SRP+MF GEL	**3.0667**	
3 month	**SRP**	**2.7767**	**0.000**
	SRP+MF GEL	**2.0267**	
6 months	**SRP**	**2.4600**	**0.000**
	SRP+MF GEL	**1.3133**	

Table 3: Comparison of Clinical Attachment Level (CAL) scores at different time interval

CAL	Groups	Mean	P value (Independent sample t test)
BL	**SRP**	**7.2967**	**0.001**
	SRP+MF GEL	**7.8967**	
3 month	**SRP**	**6.5467**	**0.000**
	SRP+MF GEL	**5.8913**	
6 months	**SRP**	**6.0000**	**0.000**
	SRP+MF GEL	**4.7367**	

S-Significant (P<0.05); NS – Non-significant (P>0.05) ; HS – Highly significant (P<0.001)

Discussion

Chronic periodontitis is a highly prevalent oral disorder, which is associated with several periopathogenic microorganisms, one of which is Porphyromonas gingivalis that contains lipopolysaccharide (LPS), which is the key inflammatory mediator. A recent study investigated the role of metformin on the LPS-influenced inflammatory response and showed that metformin exerts anti-inflammatory effects on various LPS-induced periodontal cells. [5]

Adjunctive chemotherapies can be used to try to enhance results normally achieved with mechanical instrumentation or to improve outcomes at sites not responsive to conventional periodontal therapy. [7] LDD system is considered as one the effective method used in periodontal therapy.[8] Its advantages are attaining a high intrasulcular drug concentrations, site specific, less systemic adverse effects and better patient compliance.[8,9]

MF, first developed in 1957, is one of the most commonly used oral antihyperglycemic agents for the treatment of type II diabetes mellitus.[10] It is currently recommended as first-line therapy in overweight or obese patients with this condition.[11] However, it does not only effectively lowers blood glucose but also protects bone tissue in patients with diabetes. Previous experiments have been performed on biologic transport of MF in osteoblasts to verify the feasibility of local drug delivery in vitro and found that the osteoblasts can uptake MF.[12] MF was found to significantly decrease intracellular reactive oxygen species and apoptosis and also had a direct osteogenic effect on osteoblasts that could be partially mediated via promotion of Runx2 and insulin-like growth factor-1 expression.[13] Thus,

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these possible bone-sparing and bone-formative effects of MF may be of considerable interest to the periodontist in managing periodontitis-induced alveolar bone loss.[3]

MF also has a stimulating effect in the ex vivo osteogenic potential of bone marrow progenitor cells BMPCs results increase in bone formation and remodelling, via enhancing BMPC osteoblastic Alkaline Phosphatase, type I collagen and osteocalcin. MF promotes mineral deposition in vitro, probably by increasing the expression of the Runx2/Cbfa1 transcription factor.[14] MF promotes osteoblastic effect on alveolar bone in periodontal disease by exerting an osteoblast differentiation action, and shows improvement in clinical and radiographic parameters when delivered subgingivally in Chronic Periodontitis patients with smoking.[15]

Vestergaard et al study on diabetic patients taking metformin, paved a path for promoting metformin as a bone regenerating factor. [16] The ability of metformin to persuade the differentiation and mineralization of osteoblasts through AMPK pathway activation and induction of endothelial nitric oxide synthase (eNOS) was demonstrated invitro by Kanazawa et al 2008. [17]

In the present study, on intergroup comparison of GI between baseline, 3 month and 6 months the difference was significant at baseline, 3 month and 6 months ($p<0.001$).This indicates that both the treatment procedures are equally effective in improving gingival health at 6 months. There was a greater improvement in Group II (SRP + 1% Metformin gel) in comparison to Group I (SRP) at the end of the study. Reduction in GI may be due to Anti – inflammatory, antioxidant, properties of Metformin and MF exerts anti-inflammatory action via restoring the endothelial function, increased Nitric Oxide synthesis via activation of AMP-activated protein kinase and decreased reactive oxygen species production through inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[18,19]

Administration of 1% Metformin gel has been studied in various studies previously by A.R Pradeep et al 2013 which reported that 1% metformin concentration brought superior results in inducing bone formation than any other concentration.[20] Furthermore, this study is in correspondence with Kurian et al. study which also showed significant reduction in GI at all intervals. Another study performed by Pankaj et al.to compare the performance of subgingival delivered 1.2% SV and 1% MF gel showed that greater reduction GI like present results of this study.[21] S. Khalifehzadeh (2019) compared 1% Metformin biofilm with plasma rich in growth factor (PRGF) for treatment of two-walled intra-bony defect showing decrease in GI at 6 months. The results obtained were better for 1% Metformin biofilm with PRGF group. [22]

Also, significant reduction in the means were noted from baseline to 6 months and the difference in mean Probing pocket depth (PPD) at the specific time intervals was found to be statistically highly significant($p<0.001$). On intergroup comparison, the difference at baseline was non-significant whereas it was significant at 3 month and 6 months. The present study that metformin is a Ca2+ antagonist, and provides a critical clue for delineating the molecular mechanisms underlying the inhibition of MMP-9 activation by metformin. Metformin is known to activate AMP-activated protein kinase (AMPK). [23]

Previous studies done by Pradeep and Rao on 1% MF in treatment of chronic periodontitis (CP) have shown favourable improvement in clinical parameters. [3,24] The results showed in the present study that 1 % MF gel was most efficacious in treatment of Chronic Periodontits in sites with baseline probing depth ≥5mm. Reduction in PPD can be justified by the study conducted by NS Rao 2013 in which it was observed that Metformin is associated with a reduction in periodontal inflammation. [25] Furthermore, study done by IG Kurian and P Dileep (2018) showed that on Metformin and Aloe vera gel delivery in treatment of intrabony defects showed a similar pattern that is decrease of PPD at 6 months. [26] Studies by IG Kurian , P Dileep on metformin use in periodontal lesion showed a decrease in PPD in patents taking Metformin along with decrease signs of inflammation , reduces edema of the soft tissues in those patients. [26]

Studies by Iqra Mushtaq et al (2018) in the efficacy of 1% Metformin gel as an adjunct to scaling and root planning showed decrease in CAL and increase in CAL gain at 6 months.[27] The effect of MF on osteoblasts in vitro was revealed previously (Cortizo

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et al., 2006; Kanazawa et al., 2008). In a study by Cortizo et al., exposing osteoblast-like cell lines to MF increased proliferation of the cells as well as higher alkaline phosphatase activity and an increased collagen-II turn over were observed (Cortizo et al., 2006). In a study by Kanazawa et al., osteoblast-like cells cultured with MF exhibited increased proliferation by the activation of AMP-activated protein kinase (AMPK) (Kanazawa et al., 2008). [28, 17] Additionally, the cells increased expressions of endothelial nitric oxide synthase (eNOS) and bone morphogenetic protein-2 (BMP-2) were detected. eNOS has a vital role in maintaining and controlling bone turnover (Chambliss and Shaul, 2002; Armour et al., 2001). BMP-2 is also known to increase osteoblast differentiation and bone formation (Govender et al., 2010).Hence, results obtained in in vitro studies indicate that MF has an osteogenic effect which is triggered by the increased proliferation of osteoblasts.[29,30,31]

A R Pradeep et al (2016) in their study of varying concentration subgingivally delivered Metformin gel showed changes in CAL with a decrease in CAL and increase in CAL gain at 3 month and 6 months. [3] Similarly, A R Pradeep 2015 and N S Rao et al (2013) showed a decrease in CAL and increase in CAL gain at 6 months in their study evaluating the efficacy of 1% Metformin gel as an adjunct in local drug delivery.[21,03]

However, in the 28-day study by Liu et al., MF had negligible effect on osteoblasts but decreased RANKL/OPG ratios and, hence, inhibited proliferation of osteoclasts (Liu et al., 2012). Hence, to date, the mode of action of MF is unclear and more long-term studies are needed to better understand the mechanism of osteogenic effect of the drug. [32]

Conclusion

In the present study the following conclusions were drawn from the results:

1. GI: The percentage of change in GI is more significant in Group II from baseline to 6 months.

2. PPD: The percentage of change in PPD index is more significant in Group II from baseline to 6 months.

3. CAL: The percentage of change in CAL is more significant in Group II from baseline to 6 months.

Metformin in adjunct with SRP is effective in reducing the clinical parameters (GI and PPD) and gain in CAL.

Thus, results of the present study favour the use of locally delivered metformin gel in the treatment of chronic periodontitis. This study indicated that clinical effect achieved with the agent may reduce the need for further advanced and surgical periodontal treatment which would limit morbidity for the subject, the time of treatment, and the cost of therapy.

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