Original Article

Clinical Efficacy of 1% Metformin gel and Systemic Doxycyline in Chronic Periodontitis: A Randomized Clinical Trial

Mamoora Mirza, Nasim Karim, Wahab Baksh Kadri, Shama Asghar

ABSTRACT

OBJECTIVE: To compare and evaluate the clinical efficacy of 1% Metformin gel and oral Doxycycline in adjunct to SRP on clinical and biochemical parameters in patients having localized moderate chronic periodontitis.

METHODOLOGY: This randomized open-label clinical trial was held at Bahria Dental College Hospital by convenient sampling technique from October 2019 to March 2020. Sixty systemically healthy, males and females aged 30-50 years, diagnosed with localized moderate chronic periodontitis were enrolled. Molars with deepest PPD, CAL, PI, and mSBI were included. Patients with a history of periodontal therapy and mouthwashes were excluded. Patients were divided randomly into two groups with 30 in each. Group A had SRP and Doxycycline and Group B received Metformin 1% gel intra-pocket with SRP at day 0. Clinical parameters were evaluated on days 0, 45, and 90. TNFα was evaluated on days 0 and 90. Results were statistically analyzed using SPSS software version 23.

RESULTS: Group B showed a significant reduction in PPD and CAL compared to group A while PI and mSBI were found non-significant. TNFα was significantly reduced in group B on day 90.

CONCLUSION: 1% Metformin intra-pocket gel has produced more beneficial effects on clinical and biochemical parameters in comparison to conventional Doxycycline in adjunct to SRP in localized moderate chronic periodontitis.

KEYWORDS: Chronic periodontitis, Doxycycline, Efficacy, Local delivery, Metformin gel, TNFα.

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INTRODUCTION

Periodontitis is characterized by gum inflammation accompanied by loss of tooth-supporting tissues. This leads to irreversible loss of attachment of gums and adjacent alveolar bone[1].

According to a WHO report, 20-50 % of chronic diseases include periodontitis that ultimately forms a component of globally common ailments. The higher prevalence among Asian countries has been documented exhibiting 85% among Indian population whereas National oral health survey in Pakistan has documented prevalence up to 98%[2].

Inadequate oral hygiene measures lead to the predisposition of dental plaque later calculus deposition. Also, systemic diseases, age, socioeconomic, genetics, general habits predispose to periodontal disease[3].

Periodontitis is commenced upon chemotaxis of polymorphonuclear leukocytes (PMN) against bacterial lipopolysaccharide (LPS) antigen. Pro-inflammatory cytokines, namely TNFα, IL1, and prostaglandins are secreted by PMN gives rise to fibroblasts and osteoclast differentiation resulting in detachment of gingiva and resorption of alveolar bone[4].

Chronic periodontitis of mild to moderate severity is managed by conservative and conventional treatment. Scaling & Root Planning (SRP) is a conventional treatment but occasionally fails to achieve complete eradication of pathogens at the site of infection. An adjunctive pharmacological treatment is employed to improve clinical parameters and prevent further bone loss[5]. Since, progression of the disease is based on three main pillars namely microbe involvement, inflammation, and bone resorption, therefore, specifically targeting these sites can minimize the disease progression.

Generally in our clinical setups, Doxycycline, a protein synthesis inhibitor, has been the drug of choice for treating periodontal diseases for since long. It exhibits anti- collagenase activity and targets Matrix metalloproteinases released by macrophages and tissue fibroblasts[6].

The world is now shifting paradigm towards local drug delivery system to ensure effective management of disease with the provision of the drug in situ with the advantage of avoiding systemic effects. Novel researchers have documented the use of anabolics and anti-resorptive through local drug delivery systems, that has replaced the traditional anti-inflammatory and anti-microbial agents[7].

Metformin, an oral hypoglycaemic drug, has been documented to inhibit alveolar bone resorption and reduce inflammation. It improves bone healing by activating the Runx-2 and AMPK pathway required for osteoblast differentiation of progenitor cells[8].

Comparative studies on the clinical efficacy of 1% Metformin intra-pocket gel and systemic Doxycycline have not been documented yet. In Pakistan, no documented study is found upon a literature search for the last 10 years using multiple search engines, on these drugs either alone or in comparison. This pioneering study was designed to evaluate and compare the efficacy of Metformin on clinical and biochemical parameters by using it in the form of 1% intra-pocket gel in adjunct to scaling and root planning in comparison to systemic Doxycycline, owing to the hypothesis that there is a difference between the clinical efficacy of 1% Metformin gel and oral doxycycline in the treatment of localized chronic periodontitis of moderate severity.

METHODOLOGY

This randomized open-label clinical trial was conducted at the out-patient Department of Periodontology, Bahria Dental Hospital Karachi, after obtaining approval from Ethical Review Committee (ERC) reference No: ERC-BUMDC-13/2019/Phar-007 -18/2020. The present study was conducted from October 2019 to March 2020. The calculated sample size was 56 calculated by 'Comparing Two Means' on www.Openepi.com with the mean and standard deviation of mSBI in 1% Metformin and placebo gel group obtained from a study with 5% margin of error and 95% Confidence interval[17]. Written informed consent was acquired from all participants before enrolment.

Systemically healthy individuals, both male and female, aged 30-50 years, diagnosed with localized moderate chronic periodontitis with sites showing PD≥ 3mm to <7 mm, CAL =1mm to <5mm, PI=2, mSBI=2 with no scaling in past 6 months were included in the study. Participants using anti-biotic therapy and mouthwashes during the study were excluded.

Participants have divided randomly into two groups by computer allocated balloting. Group A(n=28) advised Scaling & Root planning with Doxycycline capsule 200mg stat, 100mg OD for 14 days. Group B (n=28) SRP with intra-pocket 1% Metformin gel, day 0. At baseline, day 45 and 90 clinical evaluations were carried out using UNC#15 probe to assess periodontal pocket depth(PPD), clinical attachment loss(CAL), plaque index(PI), and mean sulcus bleeding index (mSBI). Biochemical analysis of TNF-α was evaluated at baseline and day 90.

PREPARATION OF 1% METFORMIN GEL

The amount of active drug MF to prepare a gel formulation of 100 ml (1%) was 1gm dissolved in 50 ml distilled water. 2gm of poloxamer 407 and 0.1gm laponite was soaked in 1ml water for 24 hours. In a separate beaker, 0.1 gm sodium benzoate was dissolved in 2.2 ml of distilled water. All the ingredients were mixed with the help of a shear mixer and makeup to the final volume that is 100 ml with distilled water. The pH was adjusted between 5-6. [9]

Gingival crevicular fluid (GCF) sample collection and TNF-α assay

Selected affected molar tooth with deep PP and CAL as per inclusion criteria was isolated with cotton rolls and a supra-gingival plaque was removed without disturbing soft tissues. The tooth was dried with a gentle stream of air for 5seconds. GCF was collected from the affected tooth by absorbent paper point #30 for 30sec (**Figure: Ia**). Contaminated paper points were discarded. Samples were transferred to a sterile Eppendorf tube (2 ml) containing 150 µl phosphate-buffered saline (**Figure: Ib**) stored under ice-packs, cold centrifuged at 4^0C at 10.000 rpm for 5minutes and immediately stored at -80^o C.[10] Analysis of TNF-α was performed by using enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory, E0082Hu, China) as per manufacturer's instructions.

Figure Ia: GCF collection via Paper point

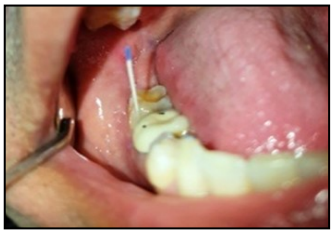
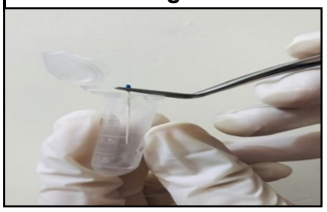


Figure Ib: Transfer to Eppendorf tube containing PBS for storage



PROCEDURE

Following SRP 1% metformin gel was applied intra-pocket in group B using a 24 gauge needle assuring the tip reaches the deepest point of the pocket. The needle was gradually withdrawn from the pocket when Metformin gel appeared along the gingival margin. Data analysis was performed by statistical software package SPSS version 23. Mean was computed for quantitative variables including age whereas gender was analysed using percentage. The intra-group comparison was done by paired Student's t-test. Inter-group comparison analysis was done by unpaired Student's t-test. P-value < 0.05 was considered to be significant.

RESULTS

In the present study, the calculated sample size was 56 patients whereas 60 patients diagnosed with localized moderate chronic periodontitis were enrolled with 30 equally age matching patients in each group (**Table I**). A total of 56 patients completed the study with 28 in each group. 2 patients in Group A (Doxycycline) and 2 of Group B (Metformin) were lost to follow up. Intra-group comparison with a mean level of clinical parameters, PPD, PI, CAL, and mSBI at days 0 and 90 showed a highly significant difference (**Table II**). Inter-group comparison among clinical parameters PPD and CAL between two groups

revealed highly significant differences whereas PI and mSBI showed non-significant differences at day 90 (**Table III**). A significant reduction in TNFα concentration was seen in group B on day 90. Intergroup comparison showed a significant difference at day 90 (**Table IV**)

TABLE I: AGE AND GENDER OF STUDY PARTICIPANTS (n = 56)

Parameter	Group A = Dox Mean±SD n=28	Group B = Met Mean±SD n=28
Age (yrs)	35.79±2.78	35.24±3.69
Gender		
(Male)	16(57.1%)	15(51.7%)
(Female)	12(42.9%)	14(48.3%)

Group A=Doxycyline, Group B=Metformin

DISCUSSION

The clinical parameters periodontal pocket depth (PPD), plaque index(PI), and clinical attachment loss (CAL) of our study during intra-group comparison showed highly significant(*P*< 0.001) results from baseline to day 90, which coincides with a study due to anti-collagenolytic activity of Doxycycline[11]. The present study showed highly significant results (*P*< 0.001) regarding PI in the doxycycline group probably due to oral hygiene instructions advised to patients along with treatment but contradicts another study that observed non-significant changes in PI at 3 months[12]. The present study showed a highly significant (*P*< 0.001) difference in mSBI score at day 90 which is in coherence with a study but contradicts another study with non-significant difference[13] due to enrolment of diabetic patients.

Novel researches by Rao and colleagues, Iqra and colleagues, and Pradeep and colleagues employed intra-pocket administration of 1% Metformin gel and derived effective results in clinical parameters. The present study revealed a statistically significant decrease in PPD from day 0 to day 90 coherent with a study[14] but contrary to other study reported non-significant reductions in the periodontal pocket depth at 1 month[15] probably due to short term follow up and small sample size of 16 subjects. PI was significantly reduced from day 0 to 90 in harmony with the results of a study[16] but contradicts a study on smokers non-adherent to oral hygiene measures.

The present study showed highly significant reductions in PPD and CAL at the end of 3 months following SRP with 1% Metformin intra-pocket gel insertion whereas a non-significant difference in PI[17] but contradicts a clinical trial with a significant reduction in clinical parameters at the end of 6 months[15]. The present study coincides with the results of a study reporting a non-significant difference in mSBI but a more reduced score in favor of Doxycycline in between the groups at day 90[18]. Our study contradicts greater improvement in mSBI score

TABLE II: INTRA-GROUP COMPARISON IN CLINICAL PARAMETERS, GROUP A & B, DAY 0 & 90

Variable	Group A Dox (n=28) Mean±SD			Group B Met (n=28) Mean±SD		
	Day 0	Day 90	p-value	Day 0	Day 90	p-value
Periodontal Pocket Depth(PPD)-mm	5.10±0.62	3.32±0.61	<0.001**	5.13±0.69	2.17±0.38	<0.001**
Plaque Index (PI)	2.32±0.41	0.21±0.25	<0.001**	2.24±0.36	0.17±0.24	<0.001**
Clinical Attachment Loss(CAL)-mm	4.46±0.32	3.77±0.45	<0.001**	4.03±0.99	2.03±0.18	<0.001**
Mean Sulcus Bleeding Index(mSBI)	2.0±0.0	0.46±0.50	<0.001**	2.0±0.0	0.58±0.50	<0.001**

*Group A=Doxycycline , Group B=Metformin, P value <0.05: significant, NS = non-significant, *:statistically significant <0.05, **: highly significant <0.001, Test applied: Paired t-test*

TABLE III: INTER-GROUP COMPARISON- CLINICAL PARAMETERS GROUP A & B, DAY 0, 45 & 90

Variables	Day	Group A	Group B	p-value
Periodontal pocket Depth	Baseline	5.10±0.62	5.13±0.69	0.982
	45	3.60±0.56	3.48±0.63	0.011*
	90	3.32±0.61	2.17±0.38	<0.001**
Plaque Index	Baseline	2.32±0.41	2.24±0.36	0.797
	45	0.62±0.3	0.62±0.34	0.815
	90	0.21±0.25	0.10±0.24	0.984
Clinical attachment loss	Baseline	4.46±0.32	4.03±0.99	0.890
	45	3.77±0.45	2.45±0.65	<0.001**
	90	3.77±0.45	2.03±0.18	<0.001**
Mean Sulcus Bleeding index	Baseline	2.0±0.0	2.0±0.0	---
	45	1.0±0.0	1.0±0.0	---
	90	0.46±0.50	0.58±0.50	0.636

*Group A=Doxycycline ,Group B=Metformin, P value <0.05: significant, NS = non-significant, *: statistically significant <0.05, **: highly significant <0.001, Test applied: unpaired t-test*

TABLE IV: BIOCHEMICAL PARAMETER, INTRA-GROUP, AND INTER-GROUP COMPARISON, GROUP A&B, DAY 0 & 90

INTRA-GROUP COMPARISON, DAY 0 & 90						
Variable	**Group A Dox Mean±SD ng/L**			**Group B Met Mean±SD ng/L**		
	Day 0	**Day 90**	**p-value**	**Day 0**	**Day 90**	**p-value**
TNFα	46.67±8.27	41.57±10.80	0.510 NS	49.38±11.49	29.15±11.97	0.014*

INTER –GROUP COMPARISON, GROUP A& B, DAY 0 & 90			
DAY			
	Group A Mean±SD ng/L	**Group B Mean±SD ng/L**	**p-value**
0	46.67±8.27	49.38±11.49	0.603 NS
90	41.57±10.80	29.15±11.97	0.009*

Group A=Doxycyline, Group B= Metformin, NS= no significant, P value <0.05: significant,: statistically significant ,**: highly significant level <0.001, Test applied: Paired t -test to assess intra-group & Unpaired t -test to assess inter group comparison.*

in the Doxycycline group in comparison to control group[19]. Hence overall more pronounced effect is produced by Metformin in clinical parameters.

The TNF-α levels in the present study reported a reduction of 20.13ng/L from day 0 to 90 in the Metformin group which accounts for a promising drug and local drug delivery strategy, targeting directly the inflamed sites by exerting inhibitory effects on TNFα through activation of AMP-protein kinase pathway. However, only a 5.10ng/L drop in levels was seen in the Doxycycline group at day 90 which concludes profound effects of 1% Metformin gel over systemic doxycycline[20]. In biochemical parameters also the more pronounced effect is produced by Metformin. Intra-pocket gel administration is found to be safe for use, as none of the patients have reported any adverse effect, in comparison to doxycycline where two patients complained of diarrhea. This was a single centric, short-duration study in which analysis of GCF-TNF α was carried out at baseline and day 90 only due to budget constraints.

CONCLUSION

1% Metformin intra-pocket gel has produced more beneficial effects on clinical and biochemical parameters in comparison to oral Doxycycline in adjunct to SRP in localized chronic periodontitis. Multi-centric studies with a large sample size may be conducted to authenticate the results of the present study.

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AUTHOR CONTRIBUTIONS

Mirza M: Conducted the study and did the write up
Karim N: Supervised the study, helped in write up & proof reading
Kadri WB: Supervised the clinical aspect of the study
Asghar S: Provided clinical help and expertise

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