Original Article

Clinical efficacy of 1% metformin and alendronate intra-pocket gel in moderate localized chronic periodontitis

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Objective: To compare clinical efficacy of 1% metformin and alendronate gel in adjunct to scaling and root planning (SRP) on clinical and biochemical parameters in patients having moderate localized chronic periodontitis.

Methodology: In this randomized open label clinical trial, 60 systemically healthy, males and females aged 30-50 year, diagnosed with localized moderate chronic periodontitis were enrolled from Bahria Dental College Hospital by convenient sampling technique. Duration of study was 6 months. Participants with deepest periodontal pocket depth (PPD), clinical attachment loss (CAL), plaque index (PI) and mean sulcular bleeding index (mSBI) were included whereas those with history of periodontal therapy and mouthwashes were excluded. Patients were divided randomly into two groups each group consisting of 30 patients. Group A received Metformin 1% gel and Group B received Alendronate 1% gel, both intra-pocket with SRP at day 0. Clinical parameters were evaluated at day 0, 45 and 90. TNFα was evaluated by Eliza at day 0 and 90. Statistical analysis was done using SPSS version 23.

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

Conclusion: We found that1% Metformin gel produced more beneficial effects in adjunct to SRP on clinical and biochemical parameters in comparison to 1% Alendronate gel.

Keywords: Alendronate, chronic periodontitis, gingival crevicular fluid, metformin, TNFα.

INTRODUCTION

Chronic periodontitis (CP), an inflammatory disease of gingiva, periodontal ligament and alveolar bone, leads to irreversible bone loss. It contributes 30 – 50% to globally common diseases according to a WHO report. Recent study has documented a prevalence of 98% in Pakistan.[1] Periodontitis initiates upon exposure to bacterial lipopolysaccharide (LPS) antigen, releasing polymorphonuclear leukocytes (PMNL) mediated cytokines TNFα, IL-1 and prostaglandins leading to collagen breakdown and bone resorption.[2]

Chronic periodontitis of mild to moderate severity is managed by conservative and conventional treatment. Scaling & Root planning (SRP) occasionally fails to eradicate pathogens.[3] Generally antimicrobials are given with SRP but limits their use due to antibiotic resistance. The world has shifted paradigm towards local drug delivery systems with stipulation of anti-resorptives and anti-inflammatory at target site reducing adverse effects.[4] Metformin has been documented as anti-inflammatory and anti-resorptive via activation of Run × 2 gene and AMPK pathway for osteoblast differentiation in CP.[5]

Recent approaches to prevent bone resorption have used

Alendronate (ALN) that inhibits farnesyl pyrophosphate synthase enzyme impeding Ras, Rho, Rac signalling molecules.[6] In Pakistan, no documented study is found upon literature search for last 10 years using multiple search engines, on these drugs either alone or in comparison. This pioneer study was designed with the objective to compare the efficacy of metformin and alendronate on clinical and biochemical parameters using 1% intra-pocket gel adjunctive to SRP in localized CP.

METHODOLOGY

This randomized open label clinical trial was conducted at out-patient Department of Periodontology, Bahria Dental College Hospital, Karachi, after obtaining approval from ERC (Ref No: ERC-BUMDC-13/2019/Phar). Written informed consent was acquired prior to enrolment. It was conducted from October 2019 to March 2020 with a calculated sample size was 56 by 'Comparing Two Means' on www.Openepi.com obtained from a study with 5% margin of error and 95% Confidence interval.[5]

Healthy male and female, aged 30 – 50 years, diagnosed with localized moderate CP with PPD $\geq$ 3mm to

< 7 mm, CAL = 1 mm to < 5 mm, PI = 2, mSBI = 2 were included. Participants using antibiotics and mouthwashes prior to SRP were excluded.

Participants were divided randomly into two groups by computer allocated balloting. Group A (n = 28) was given intra-pocket 1% metformin gel and Group B (n = 28) intra-pocket 1% alendronate gel following SRP at day 0 & 45. Clinical parameters were assessed using UNC#15 probe at day 0, 45 & 90. TNF-α in GCF was evaluated at baseline and day 90.

The amount of active drug metformin to prepare a gel formulation of 100 ml (1%) was 1 gm dissolved in 50 ml distilled water. 2 gm of polaxamer 407 and 0.1 gm laponite was soaked in 1ml water for 24 hours. In a separate beaker, 0.1 gm sodium benzoate was mixed in 2.2 ml of distilled water. All the ingredients were mixed with shear mixer to prepare 100 ml with distilled water. pH was fixed between 5 – 6.[7] A weighed quantity of 2 gm carboxymethyl cellulose (2%w/w) was added to 50 ml distilled water. The mixture was gradually stirred and carboxymethyl cellulose was allowed to soak for 24h. In a separate beaker, 0.1 gm sodium benzoate was dissolved in 7.1 ml distilled water. Mix well all the ingredients with shear mixer and make up to the final volume i.e., 100ml with remaining distilled water. The pH was regulated between 5 to 6.[6]

Participants were advised fasting at least two hours prior sampling. Affected molar was isolated with cotton rolls and supra-gingival plaque was removed without disturbing the soft tissues. Tooth was gently dried and gingival crevicular fluid (GCF) was collected via absorbent paper points #30 by inserting into deepest pocket (≥ 4 mm). Paper points were left for 30 seconds to collect resting GCF. Blood contaminated paper points were discarded. Samples were transferred to sterile Eppendorf tube (2 ml) containing 150 µl phosphate-buffered saline placed under ice-packs, cold centrifuged at 10.000 rpm for 5minutes and immediately stored at -80°C. TNF-α analysis done using ELISA kit (Bioassay Technology Laboratory, E0082Hu, China). Standard curve plotted by regression analysis.[8]

Statistical Analysis: The data were analyzed using SPSS version 23. Intra-group comparison done by paired Student's t-test. Inter-group comparison done by unpaired Student's t-test. $P < 0.05$ was considered significant.

RESULTS

In present study, a total of 56 patients completed study with 28 in each group. One patient in Group A and three of Group B were lost to followup. Intra-group comparison with mean levels of PPD, PI, CAL and mSBI at day 0 and 90 showed highly significant difference in Table 1.

Inter-group comparison among PPD and CAL between two groups revealed highly significant difference whereas PI and mSBI showed non-significant difference at day 90 (Table 2). Intergroup comparison for TNFα showed significant difference at day 90, more pronounced in Group A (Table 3).

DISCUSSION

Present study revealed significant decrease in PPD and PI from day 0 to day 90[9] owing to anti-inflammatory effect of metformin but contrary to a study with non-significant reductions in PPD at 1 month probably due to short term follow up and small sample size.[10] We

Table 1: Intra-Group Comparison in Clinical Parameters, Group A &B, Day 0&90.

Variable	Group A, Metn = 28 Mean ± SD			Group B, Alenn = 28 Mean ± SD		
	Day 0	**Day 90**	**p-value**	**Day 0**	**Day 90**	**p-value**
Periodontal Pocket Depth (PPD)-mm	5.13 ± 0.69	2.17 ± 0.38	< 0.001 **	5.44 ± **0.57**	2.62 ± 0.49	< 0.001 **
Plaque Index (PI)	2.24 ± 0.36	0.17 ± 0.24	< 0.001 **	2.27 ± 0.40	0.25 ± 0.25	< 0.001 **
Clinical Attachment Loss (CAL)-mm	4.03 ± 0.99	2.03 ± 0.18	< 0.001 **	4.45 ± 0.55	2.86 ± 0.40	< 0.001 **
M. Sulcular Bleeding Index (mSBI)	2.0 ± 0.0	0.58 ± 0.50	< 0.001 **	2.0 ± 0.0	0.48 ± 0.50	< 0.001 **

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

Table 2: Inter-group comparison of clinical parameters Group A & B, Day 0, 45 & 90.

Variable	Day	Group A	Group B	p-value
Periodontal pocket Depth	Baseline	5.13 ± 0.69	5.44 ± 0.57	0.176
	45	3.48 ± 0.63	3.77 ± 0.42	0.011*
	90	2.17± 0.38	2.62± 0.49	< 0.001**
Plaque Index	Baseline	2.24 ± 0.36	2.27 ± 0.40	0.720
	45	0.62 ± 0.34	0.70 ± 0.37	0.920
	90	0.10 ± 0.24	0.25 ± 0.25	0.723
Clinical attachment loss	Baseline	4.03 ± 0.99	4.45 ± 0.55	0.999
	45	2.45 ± 0.65	3.37 ± 0.47	< 0.001**
	90	2.03 ± 0.18	2.86 ± 0.40	< 0.001**
Mean sulcular bleeding index	Baseline	2.0 ± 0.0	2.0 ± 0.0	−
	45	1.0 ± 0.0	1.0 ± 0.0	−
	90	0.58 ± 0.50	0.48 ± 0.50	0.720

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

Table 3: Biochemical parameter, intra-group and inter-group comparison, Group A&B, Day 0 & 90.

	Intra-group comparison, Day 0 & 90					
Variable	**Group A, Met Mean ± SD ng/L**			**Group B, Alen Mean ±SD ng/L**		
TNFα	**Day 0**	**Day 90**	**p-value**	**Day 0**	**Day 90**	**p-value**
	49.38 ± 11.49	29.15 ± 11.97	0.014*	47.38 ± 11.83	33.86 ± 12.65	0.019*
	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	49.38 ± 11.49		47.38 ± 11.83		0.762 NS	
90	29.15 ± 11.97		33.86 ± 12.65		0.036*	

Group A = Metformin, Group B = Alendronate, NS = non 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

observed a significant gain in CAL and mSBI in harmony with a study but contrary to another study documenting non-significant gain in CAL at 3 months.[7,11] Our study revealed significant reduction in PPD and PI score following 1% alendronate gel adminstration[12] but contrary to a study with non-significant reductions in PPD and PI score which accounts to 2 months duration.[6]

Significant gain in CAL was observed at day 90 following 1% alendronate gel insertion but contradicts non-significant gain in CAL at 3 months owing to enrolled smokers.[13,14] Present study showed highly significant drop in mSBI from day 0 to 90 whereas a study documented no difference in mSBI being non-adherent to oral hygiene instructions.[6] Present study

showed improvement in PPD and CAL from baseline to day 90 with highly significant (p < 0.001) levels in group A in comparison to group B coherent with a study reporting more improvement in PPD and CAL following intra-pocket metformin gel insertion.[11]

Improvement in PI score was more in favour of metformin but contradictory to a study reported no difference in PI score probably due to inadequate oral hygiene measures.[10] A study documented significantly decreased mSBI score which contradicts our findings probably due to profound effects of Alendronate in comparison to placebo group.[16] Present study showed significant reduction in mean levels of TNFα in metformin group coherent with a study at day 90.[17]

CONCLUSION

We found that 1% metformin gel produced more beneficial effects on clinical and biochemical parameters in comparison to 1% alendronate gel. Multi-centric studies with large sample size may be conducted to authenticate the results of present study.

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Drafting of the article: Mamoora Arslaan.
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