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COMARATIVE EVALUATION OF LOCAL DELIVARY OF 1% METFORMIN GEL AND PLACEBO GEL AS AN ADJUNCT TO PHASE 1 THERAPY IN THE INTERVENTION OF STAGE I/II WITH GRADE A/B PERIODONTITIS – A CLINICAL STUDY

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ABSTRACT:

Introduction: condition that affects the tissues supporting teeth, periodontitis is inflammatory and distinguished by a microbial challenge that triggers the human immune system, which leads to inflammation, the development of periodontal pockets and the final disintegration of the periodontal ligament and alveolar bone. Regenerating the lost periodontal tissues, including as the cementum, periodontal ligament, and alveolar bone, is ultimate objective of periodontal therapy. Numerous locally administered medication delivery strategies, including tetracycline, doxycycline, minocycline, and chlorhexidine, have been shown to be advantageous. Metformin, an antidiabetic medication, has recently been demonstrated to have osteogenic potential, which encourages the production of new bone and increases osteoblastic differentiation. Therefore, the current study's goal is to assess how well locally delivered 1% Metformin gel works in conjunction with SRP to treat stage I/II with grade A/B periodontitis.

Material and Methods: 10 patients diagnosed with stage I/II with grade A/B periodontitis were selected and divided into **Group 1/site 1(Control group):-** 10 patients got a treatment with SRP along with placement of placebo gel into gingival sulcus and **Group 2/site2 (Test group):-** 10 patients got a treatment with SRP along with placement of 1% MF Gel into gingival sulcus. Clinical parameters (PPD, CAL, PI andGI) were recorded at baseline and after 3 months. After being tallied, the clinical parameters were statistically analyzed.

Results: Both the groups revealed a significant difference from baseline to three months when comparing intragroup clinical measures (PI, GI, and PPD). The difference between the CAL at baseline and after three months was determined to be statistically non-significant. When group were compared across groups, the difference between baseline to three months was determined to statistically not significant.

Conclusion: When administered as an addition to SRP, 1% metformin gel was found to significantly enhance all the clinical measures when compared to placebo gel. When utilised as a local drug delivery method, metformin gel has the potential to be effective in treating stage I/II of grade A/B periodontitis.

Keywords: Metformin, Periodontal Regeneration, Periodontitis, LDD agent, SRP

INTRODUCTION

Inflammation in the tissues and breakdown of the tooth-supporting structures are hallmarks of periodontal disease, which ultimately results in the loss of the afflicted teeth. Understanding the progressive nature of periodontal disease and replacing the supporting structure that the illness has damaged are the two main objectives of periodontal therapy. According to World Workshop 2017, periodontitis is characterized by the progressive degradation of the tooth supporting structure and is characterized as a chronic multifactorial inflammatory condition that is associated with dysbiosis of a dental plaque.The main aim of this therapy is to eliminate pathogenic microbiota that are responsible for the causation of inflammatory responses and thereby causes tissue destruction.

It is common knowledge that pathogenic microbiota is the cause of periodontal disorders. The primary etiologic cause for the start of periodontal disease is the prolonged exposure of soft and hard tissue to anaerobic species and their endotoxins in tooth plaque generated biofilm and host immune inflammatory response to the bacterial onslaught. The most prevalent periodontal infections linked to periodontitis because of presence of periodontal pathogens which are found in periodontal pocket during the period of exacerbation (period of activity) and their elimination results in improvement in clinical parameters.[1] Periodontal pathogens with in the biofilm are well protected from the host's immunologic mechanism as well as from antibiotics used for disease treatment. To maintain the balance between host and microbiota, it is essential to treat periodontal pocket through mechanical debridement especially local etiological factors such as plaque and calculus and to disrupt the subgingival plaque biofilm itself which may act as an inhabitant for the anaerobic pathogens.

Phase I therapy is the first phase in the sequence of treatment plan of periodontal therapy and SRP is the first step of periodontal therapy. Scaling and root planing is considered as the

"gold standard" among non-surgical treatment modalities in chronic periodontitis.[2] After phase I therapy, there is a significant improvement in gingival inflammation, less bleeding, decreased PPD and increased CAL. Additionally, there were several drawbacks to systemic antibiotic therapy, including the emergence of resistance strains, the prevalence of super infections, and systemic adverse effects that prevented their widespread usage.[3.] As a result, a number of complementary therapies have been studied and applied locally in addition to SRP.

Goodson in 1979 developed and introduced the concept of various antimicrobials agents like tetracycline, doxycycline, minocycline, metronidazole, chlorhexidine and Metformin as a LDD agent as an adjunct to SRP.[4]By administering LDD directly into the periodontal pocket, there is no chance of experiencing any additional adverse effects that may come with systemic administration. This allows the active ingredient to be effectively concentrated at the diseased location.Principle behind the LDD is established on the hypothesis where microbiocidal agents delivered into the subgingival sulcus area that may further release more concentration of agent for a prolonged period of time locally without any systemic side effects.[5] It helps to reduce or eliminate the multiplication of pathogenic microflora, decreased probing depth, stabilizes attachment and diminish bleeding resulting in controlling of the disease. Therefore, local drug delivery system has been used either alone or as an adjuvant to SRP.

Metformin, a drug in the biguanide family, is frequently used to help people with type II diabetes lower their blood glucose levels. It has been observed that metformin affects bone turnover and reduces the risk of fractures in diabetic people.Six It has been demonstrated that metformin increases type 1 collagen production and osteoblast proliferation.[7]. Kanazawa and colleagues demonstrated the primary property of metformin is bone formation which may suggest that this drug may stimulate AMPK pathway, endothelial nitric oxide synthase (eNOS), and BMP-2 expression to cause proliferation and calcification of bone forming cells.[8] Osteogenic potential in metformin has been outlined by literature analysis on localised delivery

of metformin after SRP along with their application into the bony defects in Stage I/II with Grade A/B rate of progression.[9, 10]

The purpose of this research work is to examine the clinical effectiveness of locally given 1% Metformin gel in conjunction with SRP for the treatment of stage I/II patients with grade A/B periodontitis, taking into account the aforementioned facts.

Material and Methodology:

Study Population

10 patients with 20 sites diagnosed with stage I/II with grade A/B periodontitis having minimum 8 teeth with PPD of 5-7 mm were taken and divided into groups/sites.

The study was conducted in Department of Periodontics and ethical approval was taken from instituitional ethical board committee. Every patient was councelled regarding the methodology of the study.

Inclusion Criteria-

- Patients diagnosed with stage I/II with grade A/B periodontitis minimum of 8 teeth with PPD of 5-7 mm.
- Both male and females within age group 20-50 years.
- Patients had not taken any periodontal intervention since six months' time period.
- Individuals have not received any medication within the last six months.
- Those in good overall health who have demonstrated the commitment and capacity to maintain proper dental hygiene.

Exclusion Criteria-

- Patients with a history of recognised biguanide/metformin allergies.
- Patients with systemic diseases, including endocrinal disorders, cardiovascular disorders or immunosuppressed cases may affect on the success of periodontal therapy.
- Individuals receiving systemic metformin.
- Alcoholic and smoker's patients.
- Females who are pregnant or nursing.
- Individuals who have used steroids, anticoagulants, or immune suppressants for a long time period.

Formulation of Metformin gel:

For the preparation of MF gel all the necessary ingredients were precisely weighed.To help hydrate gellan gum, dry gellan gum powder was mixed with 50ml of distilled water that was kept at 95℃ for 20 minutes. The gellan gum solution was continuously stirred while the necessary amount of mannitol was added, temperature was kept above 80°C. Stirring was done, metformin,sucralose, citric acid, and preservatives (methylparaben and propylparaben) were added with stirring and in last step, sodium citrate was mixed in 10ml of distilled water.Throughout the manufacturing process, the gel's weight was continuously recorded, and distilled water was eventually added. At the room temperature both gellam gum and metformin cool down resulting in formation of gel. [11,12]

Methodology and Local drug delivery intervention:

10 patients, diagnosed with 20 sites diagnosed with stage I/II with grade A/B periodontitis, aged between 20-50 years were enrolled in this study. Complete Phase I therapy i.e., SRP was performed in all the patients.

Patients were divided into 2 groups

Group 1/site 1(Control group):- 10 patients got a treatment with SRP along with placement of placebo gel into gingival sulcus

Group 2/site2 (Test group):- 10 patients got a treatment with SRP along with placement of 1% MF Gel into gingival sulcus

Using a blunt-cannula syringe, 10 µl of produced MF gel was placed into the periodontal pockets for standardisation. The gel was injected starting at the pocket's bottom and continued until the pocket was full. Coe Pak, a periodontal dressing, was applied to the test location.

Post operative instructions:

Patienrs were instructed not to have any type of hard or sticky food. It was requested of all the patients who took part to practise good dental hygiene. After 7 days, Coe Pak was removed. Following the procedure, no prescriptions for antibiotics or/and anti-inflammatory drugs were written.

Measurements of Clinical Parameter:

Clinical parameters included PPD, CAL, PI Silness & Loe (1964) and GI Ainamo & Bay (1975) measured at baseline, 3 months.

Stent Preparation

Occlusal stents made of acrylic were made for the study models. For this, self-cured acrylic was employed. One tooth that was mesially and distally affected was the study tooth. The stent measured two to three millimetres thick. To prevent deviation, vertical grooves were constructed to guide the probe's positioning in the same plane and direction during measurements. The periodontal probe, UNC-15, was used to record the audio. Permanent marker was used to mark the stent in order to make recording easier during follow-up visits.

Statistical Analysis:

Microsoft Excel 2007 was used to enter the data for this study, and SPSS statistical software, version 20, was used for analysis. The standard deviation and mean were included in the descriptive statistics. For intra group comparision repeated measure ANOVA was used for various time intervals in order to determine the difference between each unique time interval. For this investigation, the significance level was set at five percent. The one-way ANOVA and unpaired t test were done for intragroup and intergroup assessment of mean score differences between independent groups.

Results:

Every clinical parameter was compared intragroup between 2 study groups in Table 1. At baseline, group 1/site 1 plaque index values were 1.68 ± 0.32, and three months later, they were 1.54 ± 0.27. Group 2 site 2 mean score at baseline was 1.62 ± 0.21, and after three months it was 1.40 ± 0.23. There was a statistically significant difference in the mean reduction in the plaque index scores between groups 1/site 1 and group 2/site 2 when comparing the scores at baseline to three months.

After three months, the gingival index scores in group 1/site 1 were 1.34 ± 0.11, compared to 1.50 ± 0.10 at baseline. The mean score in group 2/site 2 was 1.56 ± 0.16 at baseline and 1.36 ± 0.13 at three months. In groups 1/ site 1 and group 2/ site 2, the intragroup comparison of the mean reduction in the gingival index scores from the baseline to 3 months was determined to be statistically significant.

The PPD at the baseline in group 1/site 1 was 4.20 ± 0.83 and 2.80 ± 0.83 after 3 months. In group 2/site 2 the mean score was 4.20 ± 0.83 at the baseline and 3.40 ± 0.89 after 3 months.

The intragroup comparison of mean reduction in probing pocket depth from the baseline to 3 months was found to be statistically significant in both group 1 and group 2. The mean probing pocket depth decreased from baseline to 3 months in both group 1/site 1 and group 2/ site 2.

The clinical attachment level at the baseline in the group 1/site 1 was 4.40 ± 0.89 and 3.80 ± 0.83 after 3 months. In group 2/site 2 the mean score was 4.80 ± 0.83 at the baseline and 3.40 ± 0.89 after 3 months. The intragroup comparison of clinical attachment level from the baseline to 3 months was found to be statistically non-significant in group 1/site 1 and was found to be statistically significant in group 2/site 2. In group 2/site 2, there was a mean increase in clinical attachment level from baseline to three months.

Table 1: Intra group comparison of all clinical parameters at various time intervals at group1/ Site 1 and group 2/Site 2

	Plaque Index		**Gingival Index**		**Probing Pocket Depth**		**Clinical Attachment Level**	
	Site 1/ Group 1	**Site 2/ Group 2**	**Site 1/ Group 1**	**Site 2/ Group 2**	**Site 1/ Group 1**	**Site 2/ Group 2**	**Site 1/ Group 1**	**Site 2/ Group 2**
Baseline	1.68±0.32	1.62±0.21	1.50±0.10	1.56±0.16	4.20±0.83	4.80±0.83	4.40±0.89	4.80±0.83
3 months	1.54±0.27	1.40±0.23	1.34±0.11	1.36±0.13	2.80±0.83	3.40±0.89	3.80±0.83	3.40±0.89
P value	0.005*	0.0001*	0.005*	0.005*	0.003*	0.003*	0.208**	0.005*

*p value < 0.05 (statistically significant).

**p value > 0.05 (non-statistically significant)

Table 2 showed inter group comparison of all the clinical parameters between 2 study groups. The plaque index scores at the baseline in the group 1/site 1 was 1.68 ± 0.32 and 1.62 ± 0.21 in the group 2/site 2. After 3 months of time interval the mean plaque index score was 1.54 ± 0.27 in the group 1/site 1 and 1.40 ± 0.23 in the group 2/site 2. The intergroup comparison of plaque index scores from the baseline to 3 months was found to be statistically non-significant in between group 1/site 1 and group 2/ site 2 when analysed using un-paired t -test.

The gingival index scores at the baseline in the group 1/site 1 was 1.50 ± 0.10 and 1.56 ± 0.16 in the group 2/site 2. After 3 months of time interval the mean plaque index score was 1.34 ± 0.11 in the group 1/site 1 and 1.36 ± 0.13 in the group 2/site 2. The intergroup comparison of gingival index scores from the baseline to 3 months was found to be statistically non-significant in between group 1/site 1 and group 2/ site 2 when analysed using un-paired t -test.

The probing pocket depth at the baseline in the group 1/site 1 was 4.20 ± 0.83 and 4.80 ± 0.83 in the group 2/site 2. After 3 months of time interval the mean plaque index score was 2.80 ± 0.83 in the group 1/site 1 and 3.40 ± 0.89 in the group 2/site 2. The intergroup comparison of gingival index scores from the baseline to 3 months was found to be statistically non-significant in between group 1/site 1 and group 2/ site 2 when analysed using un-paired t -test.

The clinical attachment level at the baseline in the group 1/site 1 was 4.40 ± 0.89 and 4.80 ± 0.83 in the group 2/site 2. After 3 months of time interval the clinical attachment level was 3.80 ± 0.83 in the group 1/site 1 and 3.40 ± 0.89 in the group 2/site 2. The intergroup comparison of gingival index scores from the baseline to 3 months was found to be statistically non-significant in between group 1/site 1 and group 2/ site 2 when analysed using un-paired t -test.

Table 2: Inter group comparison of all clinical parameters at various time intervals at group1/ Site 1 and group 2/Site 2

	Plaque Index		**Gingival Index**		**Probing Pocket Depth**		**Clinical Attachment Level**	
	Site 1/ Group 1	**Site 2/ Group 2**	**Site 1/ Group 1**	**Site 2/ Group 2**	**Site 1/ Group 1**	**Site 2/ Group 2**	**Site 1/ Group 1**	**Site 2/ Group 2**
Baseline	1.68±0.32	1.62±0.21	1.50±0.10	1.56±0.16	4.20±0.83	4.80±0.83	4.40±0.89	4.80±0.83
3 months	1.54±0.27	1.40±0.23	1.34±0.11	1.36±0.13	2.80±0.83	3.40±0.89	3.80±0.83	3.40±0.89
P value	0.741**	0.416**	0.511**	0.806**	0.290**	0.305**	0.486**	0.486**

**p value > 0.05 (non-statistically significant)

DISCUSSION

Understanding aetiology and pathogenesis of periodontitis, a complex illness, has prompted researchers to focus more on pharmaceutical interventions that can be used as a supplement to SRP. The pharmacological agents can be delivered directly into the deeper periodontal tissues to supress or inhibit the growth of pathogenic microflora and modify the inflammatory response resulting in limited tissue destruction. The positive response of intervention depends upon many factors such as mode of administration of pharmacological agent, the time period of pharmacological agent into peridontium and the categorisation of pharmacological substitute to be delivered. The area-specific drug delivery an agent decreases oral microbial load in periodontal pocket, results in significantly improvement in the clinical parameter. The local delivery of pharmacological agent has an advantage of achieving a high concentration of intra sulcular drug, minimum side effects and better patient compliance.

The second generation biguanide family, which includes metformin, is the one that doctors most frequently advise using to treat type 2 diabetes. In addition to its clinical benefits,

metformin is effective in decreasing blood glucose levels and mildly reduces body weight in individuals with high BMI who have a low risk of hypoglycemia.[13] It also has the protective role on the bone tissue in patients with diabetes. A 2005 study by Vestergaard et al. on metformin-using diabetic patients cleared the way for metformin to be promoted as a bone-regenerating agent.[14] Metformin activates the AMPK system and induces endothelial nitric oxide synthase (eNOS), which can influence osteoblast development and mineralization. Metformin directly increases the number of progenitor cells in the bone marrow, which is followed by osteoblastic maturation, ALP activity, and the synthesis of type 1 collagen.[15] Metformin directly affects osteoblast cells through the reduction in the activity of ROS and where there is a any programmed cell death which also increases the production of IGF-1.Consequently, metformin have the to preserve and build bone paves the way for future study on the treatment of periodontitis.

In the present research, the effectiveness of 1% MF gel as an adjuvant with SRP for the intervention of stage I/II of grade A/B periodontitis is evaluated. All clinical parameters significantly improved when compared to placebo gel. Metformin has a 50–60% oral bioavailability. Its local use lowers dosage frequency, minimises GIT adverse effects, and lessens systemic toxicity. After three months following surgery, a decrease in the gingival and plaque indices was seen in groups 1/site 1 and 2/site 2. After three months, the mean decrease in the gingival and plaque index scores was statistically significant in both the groups.

One of the most desired results of any periodontal therapy is decrease in PPD, which is important to establish patient's need for subsequent treatment and maintenance. The current investigation revealed that statistically significant intragroup difference in terms of PPD and CAL between groups 1 and 2. Between baseline and three months after surgery, there was a decrease in PPD and an increase in the CAL. Nevertheless, it was discovered that, in both groups 1 and 2, PPD and CAL did not differ statistically between the groups. Pradeep et al.

(2017); Pankaj et al. (2018); and Mushtaq et al. (2018) demonstrated greater PPD decrease and an increase in clinical attachment level. When smokers with chronic periodontitis were treated with 1% MF gel versus placebo gel in 2013, the mean PPD decreased from 7.50 ± 0.51 mm to 5.40 ± 0.68 mm at three months and then to 4.33 ± 0.61 mm at six months, according to research by Rao et al. (2013).9

The successful combination of SRP and metformin as an adjuvant treatment for periodontitis at various phases. These investigations used locally administered MF intrabony following SRP, and the results showed improved radiographic and clinical parameters compared to control groups. Better CAL and a decrease inPPD have also been observed when metformin is used as an adjuvant with SRP treatment as opposed to placebo gel. The results of traditional periodontal therapy are enhanced by the adjuvant use of MF, according to a large body of research.

The current study's limitations include its limited sample size and the requirement for a large cross-section of participants to assess the potential advantages of using metformin gel as a LDD agent. When grading periodontitis without any underlying medical conditions, the effectiveness of metformin as a LDD agent can be compared with other medications or agents in different stages. To assess its impact on the cellular and molecular level in histology, radiography, and clinical settings, more clinical trials must be carried out.

Conclusion:

The use of 1% metformin gel as an adjuvant to SRP in terms of clinical parameters is recommended based on the findings of this study. 1% metformin gel administered subgingivally significantly improved all clinical parameters when compared to placebo gel. Research is required on various metformin concentrations and delivery systems. Metformin, a

medication that forms bones, has given researchers a new perspective on periodontal regeneration. Metformin's higher ability to regenerate bone can be used to replace lost periodontal tissue caused by periodontal disease. In order to validate the osteogenic potential of metformin in the treatment of different stages of periodontitis and associated bone abnormalities, larger sample sizes and more robust controlled studies are required.

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