Original Research Article

Comparative evaluation of efficacy of 10% povidone iodine gel with 2% metronidazole and 1% ornidazole with 0.25% chlorhexidine gel as local drug delivery system in adjunt to nonsurgical periodontal therapy in chronic periodontitis: A randomized, single blind, split-mouth study

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Abstract

Background: Periodontitis is a multi-factorial chronic inflammatory disease of attachment apparatus of teeth with microorganisms playing a major role. To address periodontal disease various strategies have been adopted to target these periodonto-pathogens. Various antimicrobial drugs (systemic as well as local) are effectively used to control the disease. However due to various side effects of

systemic administration of the drugs like gastro intestinal disturbances, development of resistant organisms, high dosage of the drug required, local delivery of the drug is a better option as the drug is directly delivered at the site of infection with minimum dosage and maximum response achieved thus eliminating all the undesired effects of the drug.

Aim: To evaluate the efficacy of 10% povidone iodine with 2% metronidazole and 1% ornidazole with 0.25% chlorhexidine gel as local delivery systems for the reduction in the pocket depth, changes in CAL, gingival inflammation.

Materials and methods: A total of 20 patients diagnosed with mild- moderate chronic periodontitis were divided into two groups in a split-mouth study design - Group I and Group II with each group containing 20 sites with probing depth of >5 mm, CAL ≥3 mm. In Group I, 10% povidine-iodine gel with 2% metronidazole was delivered inside the pocket and Group II, 1% ornidazole with 0.25% chlorhexidine was used as a local delivery system in adjunct to scaling and root planning. In both groups, medications were delivered at weekly interval for a period of 4 weeks. Baseline and 4 weeks measurements were done and compared for probing pocket depth (PPD), clinical attachment levels (CAL) and gingival inflammation.

Results: The results obtained were statistically analyzed. Both groups showed statistically significant improvements in terms of clinical parameters. However, there was statistically insignificant difference when compared between the two groups. The results clearly demonstrate that both povidone iodine with metronidazole and ornidazole with chlorhexidine are also useful in controlling the acute phase of the periodontal disease in adjunct to scaling and root planning (SRP).

Conclusion: Both drugs when used as an adjunct to scaling and root planning enhances probing pocket depth reduction, change in clinical attachment levels and gingival inflammation in mild-moderate chronic periodontitis cases.

Key words

Periodontitis, Local Drug Delivery (LDD), Povidone Iodine, Metronidazole, Chlorhexidine, Ornidazole.

Introduction

Periodontitis is a common inflammatory disease characterized by progressive loss of tooth-supporting structures, i.e. connective tissue and bone with bacteria colonizing the root surfaces considered as the primary etiologic factor [1, 2]. To address periodontal disease, various treatment strategies are followed which include mechanical therapy, use of pharmacological agents and surgical intervention depending upon the stage of disease progression. Non-surgical periodontal therapy includes maintenance of oral hygiene through mechanical and chemical plaque control measures by the patient and scaling and root planing (SRP) by the clinician, which includes removal of plaque, calculus and stains from the crown and root surfaces of teeth [3]. Scaling and root planing-a "gold standard" non surgical periodontal therapy has been shown to be effective in the treatment of periodontal diseases over the years [4, 5, 6]. Scaling and root planing has been effective in immediately decreasing the microbial load but alone is insufficient to eliminate bacteria from the deep periodontal pocket (more than 5 mm), inaccessible areas (furcation areas). Antibiotics (both systemic and local) have been used as adjunctive agents in the management of periodontal disease for many years. Systemic administration has been useful in treating periodontal pockets, but it involves a relatively high dose with repeated intake over a prolonged period of time to achieve the required inhibitory concentrations in the sulcular fluid, increased chances of development of bacterial resistance, alteration of commensal flora and of increased potential for adverse effects like

allergic/ anaphylactic reaction, gastric disturbances, superinfection, nausea, vomiting, etc. [7, 8]. Since periodontitis is a localized disease, local treatment is preferred over systemic therapy to avoid the complications associated with systemic administration of antibiotics. The key to success for periodontal therapy depends on the selection of an appropriate antimicrobial agent with appropriate route of drug administration. New approaches involve the use of local drug delivery systems which enable the introduction of antimicrobial agents or other drugs directly in the periodontal pocket with the prolonged release of constant concentrations of these agents for a better control of infections, minimal side effects to local drug delivery (LDD) and good patient adherence as compared to the systemic therapy [9, 10, 11]. Various studies have revealed that LDD into the periodontal pockets can provide higher therapeutic concentrations of the antibiotic compared to the systemic administration [12, 13, 14]. Local antibiotics including, tetracycline (TET), doxycycline (DOX), minocycline (MIN), metronidazole (MTZ), ornidazole, chlorhexidine (CHX), polyvinyl pyrrolidone-iodine (PVP-I), clarithromycin (CLM), azithromycin (AZM), moxifloxacin (MXF), clindamycin (CLI), and satranidazole (SZ) are presently being used in various drug delivery systems such as irrigations, fibres, films, injectable, gels, strips, compacts, vesicular liposomes, microparticles, and nanoparticle systems in the management of periodontal disease [15-17]. Chlorhexidine (CHX) is one of the most effective topical agents, which has long been used as an effective antimicrobial agent [18] The first sustained release dosage form of chlorhexidine diacetate for topical use was developed by Friedman and Golomb [19]. It has shown effectiveness in reducing the periodontal probing depth, clinical attachment loss, and bleeding on probing [20]. The use of polyvinyl pyrrolidone-iodine (PVP-iodine or povidone-iodine) has shown favorable results in several studies [21, 22]. The advantages of PVP-iodine include broad disinfection spectrum, low cost, low risk for sensitization, and bacterial lack of resistance against the agent [23]. The group nitroimidazole (metronidazole, ornidazole, etc.) is an anti-anaerobic group, specifically targets anaerobic microorganisms believed to be the predominant causative factor in periodontitis. Thus, with this background, a study was conducted to evaluate the effect of these gels as LDD in adjunct to conventional phase I periodontal therapy so that chances of recurrence of periodontal pockets and re-infection can be reduced.

Aim

- To compare the efficacy of 10% povidine-iodine gel with 2% metronidazole and 1% ornidazole with 0.25% chlorhexidine as a local drug delivery system.

Objectives

- To evaluate the efficacy of 10% povidone iodine with 2% metronidazole administered in periodontal pockets as local delivery systems for the reduction in the pocket depth, changes in CAL, gingival inflammation.
- To evaluate the efficacy of 1% ornidazole with 0.25% chlorhexidine administered in periodontal pockets as local delivery systems for the reduction in the pocket depth, changes in CAL, gingival inflammation.
- To compare the efficacy of 10% povidine-iodine gel with 2% metronidazole and 1% ornidazole with 0.25% chlorhexidine as a local delivery system for the reduction in the pocket depth, changes in CAL, gingival inflammation.

Materials and methods

The present prospective study was a single blind, randomized clinical trial of split-mouth design. The study was conducted in the Department of

Periodontics and Oral Implantology, Government Dental College and Hospital Srinagar. Before the commencement of study an ethical clearance was obtained from institutional Ethical Committee. All patients visiting the OPD, Department of Periodontics and Oral Implantology, were evaluated for chronic periodontitis using parameters like periodontal probing depth and measurements of CAL with UNC-15 probe, gingival index of Loe and Silness, plaque index of Silness and Loe. After complete clinical examination a total of 20 patients diagnosed with mild-moderate chronic periodontitis were informed about the clinical trial. Only those willing to participate in the study were given written informed consent and enrolled in the study based on the inclusion and exclusion criteria.

Inclusion criteria

- Subjects within the age group of 35-60 years.
- Subjects with at least two non-adjacent sites each with probing PD ≥ 5 mm, CAL ≥3 mm.
- Systemically healthy individuals.

Exclusion criteria

- Smokers.
- Pregnant patients, nursing mothers.
- Subjects sensitive to iodine, metronidazole, ornidazole, chlorhexidine or any component of the trial medication, those receiving treatment with systemic corticosteroids or anticoagulants.
- Subjects who have taken antibiotic prophylaxis that could affect the progression of periodontal disease, periodontal treatment during the last 6 months prior to the study.

The present randomized, single blind clinical trial of split-mouth design was performed on 20 patients (40 sites) where the mouth was divided and randomly assigned to two experimental groups, each group containing 20 sites with probing depth of >5 mm, CAL ≥3 mm. The patients were randomly divided into two groups by flip of coin with Group I (10% povidine-iodine gel with 2% metronidazole) and Group II (1% ornidazole with 0.25% chlorhexidine) as a local delivery system. All examination was carried by a single examiner in the department of Periodontics and Oral Implantology. Initially, all subjects received supragingival and subgingival scaling with piezoelectric scaler and root planning with Hufreidygracey curettes. At the experiment site, teeth with probing pocket depth of >5 mm were irrigated with normal saline, isolated with cotton rolls, dried and the respective drug was delivered locally with a 2 ml disposable syringe with a blunt needle bent at its shank to prevent any tissue trauma by sharp needle tip. Then periodontal dressing was placed. The subjects were instructed to use regular toothpaste and not to use any oral antiseptic solution during the study period. In addition, the participants were offered soft and single-tuft interdental toothbrushes. The patients were recalled after 1 week, 14 days and 21 days for removal of the periodontal dressing and replacement of drug inside the periodontal pocket. 4 weeks post-procedure patients were recalled for re-evaluation. Periodontal dressing was completely removed and measurements were repeated for various parameters like PPD, CAL, gingival inflammation and changes were recorded accordingly.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Results on continuous measurement were presented as Mean and SD, Median. Inferential statistics for quantitative variables included the Mann-Whitney U test used to compare between two groups and the Wilcoxon Signed Rank test to compare within a group. Categorical variables were compared using the Chi-square test/Fisher Exact test. $p<0.05$ was considered statistically significant.

Results

In this study, a total of 20 patients (40 sites) were enrolled and analysed for probing pocket depth (PPD), clinical attachment level (CAL) and gingival inflammation. The clinical parameters were comparable at baseline and 4 weeks for both the groups (**Table – 1**, **Table - 2**). A statistically significant reduction was observed for PPD, CAL and Gingival Inflammation from baseline to 04 weeks for Group I and Group II (**Table – 3, Table - 4, Graph – I, Graph - II**). However, no significant differences were observed for PPD, CAL and gingival inflammation when compared between the two treatment groups (**Table - 5**). Neither discomfort nor any of adverse reactions were reported in any patients to any of the components used in the study.

Discussion

Periodontitis is a common disease of the oral cavity consisting of inflammation of the tooth supporting tissues, primarily caused by accumulation of complex polymicrobial dental plaque/ biofilm. It is initiated by Gram-negative microbial biofilms that elicit a host response, resulting in progressive, irreversible bone and soft tissue destruction (periodontal pocket formation, gingival recession or both), tooth mobility and exfoliation [9]. The management of periodontal diseases has traditionally focused on the use of mechanical procedures (scaling and root planning-SRP) to eliminate infectious agents and to hinder disease progression. However, it carries a greater risk of recurrence when used alone, specifically in cases with systemic co-morbidities [10, 24, 25]. Since scaling and root planing alone is insufficient to eliminate bacteria from the deep periodontal pocket, especially in inaccessible areas, antibiotics (both systemic and local) have been used as adjunctive agents in the management of periodontal disease for many years [10]. Also Periodontitis is a localized disease, local treatment is preferred over systemic therapy to avoid the complications associated with systematic administration of antibiotics.

LDD is one such treatment modalities that were introduced by Dr. Max Goodson in 1979 utilizing the concept of local delivery of therapeutic agents into the periodontal pocket with prolonged availability of the drug resulting in its sustainability and thereby attaining 100 folds of higher concentrations in the subgingival site.

Table - 1: Clinical Parameters at Baseline and at 4weeks in Group I (povidine-iodine gel with metronidazole).

	Parameters	**Range**	**Mean±SD**	**Median (IQR)**
Baseline	PPD	6.0-12.0	7.75±1.92	7.0(6.0-9.75)
	CAL	4.0-10.0	7.05±1.67	8.0(6.0-8.0)
04 weeks	PPD	3.0-7.0	5.05±1.32	5.0(4.0-6.0)
	CAL	0-7.0	4.45±1.57	5.0(3.0-5.0)

Table - 2: Clinical Parameters at Baseline and at 4 weeks in Group II (ornidazole with chlorhexidine).

Group II	**Parameters**	**Range**	**Mean±SD**	**Median (IQR)**
Baseline	PPD	6.0-12.0	7.65±1.78	7.0(6.0-9.0)
	CAL	4.0-10.0	7.05±1.67	8.0(6.0-8.0)
04 weeks	PPD	3.0-7.0	4.80±1.24	5.0(4.0-6.0)
	CAL	1.0-7.0	4.25±1.52	5.0(3.0-5.0)

Table - 3: Comparison within Group I from baseline to 04 weeks.

Group I	**Baseline**	**04 weeks**	**P value**
PPD	7.75±1.92	5.05±1.32	0.001*
CAL	7.05±1.67	4.45±1.57	0.001*
Gingival Inflammation			
Mild	04(20)	09(45)	0.001*
Moderate	12(60)	02(10)	
Severe	04(20)	0	
Nil	0	09(45)	

*Statistically significant ($p<0.05$)

Table - 4: Comparison within Group II from baseline to 04 weeks.

Group II	**Baseline**	**04 weeks**	**P value**
PPD	7.65±1.78	4.80±1.24	0.001*
CAL	7.05±1.67	4.25±1.52	0.001*
Gingival Inflammation			
Mild	04(20)	10(50)	0.001*
Moderate	12(60)	01(05)	
Severe	04(20)	0	
Nil	0	09(45)	

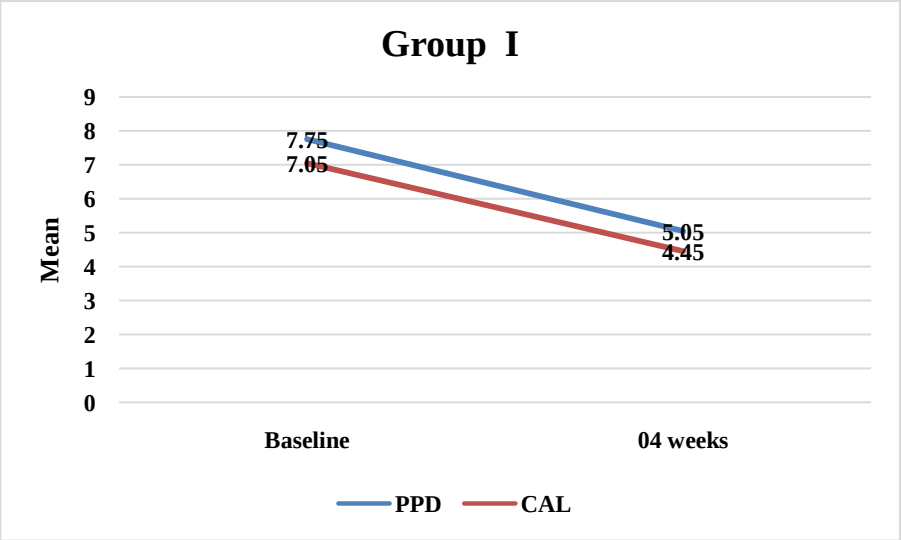
*Statistically significant ($p<0.05$)

Table - 5: Comparison between Group I and Group II at baseline and 04 weeks.

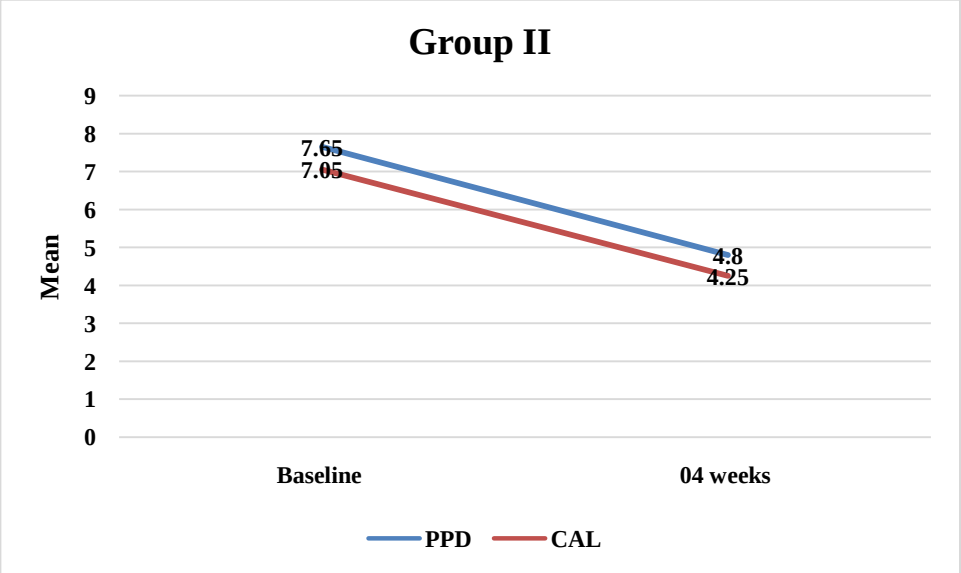
	Parameters	**Group I**	**Group II**	**P value**
Baseline	PPD	7.75±1.92	7.65±1.78	0.91
	CAL	7.05±1.67	7.05±1.67	0.99
	Gingival Inflammation			
	Mild	04(20)	04(20)	0.99
	Moderate	12(60)	12(60)	
	Severe	04(20)	04(20)	
04 weeks	PPD	5.05±1.32	4.80±1.24	0.56
	CAL	4.45±1.57	4.25±1.52	0.56
	Gingival Inflammation			
	Mild	09(45)	10(50)	0.94
	Moderate	02(10)	01(05)	
	Severe	0	0	
	Nil	09(45)	09(45)	

The present study aimed at comparing the clinical efficacy of two local drug delivery systems in gel forms: Group I-containing 1% povidone iodine gel with 2% metronidazole and Group II - containing 1% ornidazole with 0.25% chlorhexidine gel in chronic periodontitis patients. The gel formulation of drug has an advantage over other forms like mouth rinse, irrigation etc, due to its semi-solid nature it is retained in the pocket and prevented from being flushed out of the pocket by the GCF flow.

Graph - I: Changes within Group I from baseline to 04 weeks with respect to Probing Pocket Depth (PPD) and Clinical Attachment Level (CAL).



Graph - II: Changes within Group II from baseline to 04 weeks with respect to Probing Pocket Depth (PPD) and Clinical Attachment Level (CAL).



In the present study, there was a significant reduction in PPD, change in CAL and gingival inflammation in both groups at 4 weeks follow-up. A statistically significant reduction in clinical parameters in group I was found which was in accordance with the results of Mauriac J, et al. [26] and Kurian Sabu [27], Sahrmann, et al. [28]. This can be explained by the fact that Metronidazole kills most of the periodontal anaerobic micro-organisms by damaging their DNA and Povidone iodine being an effective antiseptic agent causes a transient or permanent pore formation in microbial cells resulting in loss of cytoplasmic material, deactivation of enzymes due to direct contact with iodine and coagulation of nuclear material without rupturing cell wall bonds of unsaturated fatty acids in cell walls and organelle membranes. Although Povidone iodine has been approved for external use only, use of PVP-I subgingivally is actually employing a labeled drug (approved) for an unlabeled indication. This does not signify that it is wrong,

but rather denotes that the drug manufacturer did not provide data to the U.S. Food and Drug Administration with regards to this use. Employment of a labeled drug for an unlabeled indication is common in medicine; however, clinicians must assess the risks and benefits of such utilizations [29].

Similarly a significant reduction in clinical parameters in group II can be attributed to the combined effect of ornidazole& chlorhexidine. The combination shows prolonged antiplaque action, substantivity, and its ability to adsorb and desorb, thereby providing in effect, a timed release of the antimicrobial agent [29-31]. Our results were similar with the study by Penmetsa GS, et al. [32].

Therefore, it is foreseen that using these drug formulations especially povidone iodine as local drug delivery system in adjunct to non-surgical periodontal therapy in mild to moderate chronic periodontitis patients can be of great advantage in treating the disease especially, in patients with recurring periodontal diseases and systemic co-morbidities.

Conclusion

Within the scope of this study, it can be concluded that there was a significant improvement in clinical parameters in both the groups after using respective gels in adjunct to phase I periodontal therapy (SRP). However, needs further studies with large sample size, microbial evaluation and longer follow-up periods especially with regard to the use of povidone-iodine gel as local drug delivery to validate the findings of this study.

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