Randomized, controlled clinical study to evaluate efficacy of novel indigenously designed controlled release flurbiprofen gel system for management of periodontal diseases

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Abstract

Background: This randomized, controlled clinical study was planned to evaluate the use of anti-inflammatory drug flurbiprofen in the form of locally delivered controlled release gel in the treatment of periodontal disease. **Materials and Methods:** The flurbiprofen gel was indigenously prepared in the concentration of 0.3%. The 30 patients with localized periodontal pockets measuring ≥5 mm were randomly divided into three groups. The groups received flurbiprofen gel, flurbiprofen gel after prophylaxis, and placebo gel after oral prophylaxis, respectively. The clinical parameters for plaque and gingival inflammation were evaluated at baseline, 7th day, and 14th day. **Results:** The results of the study suggested the statistically significant ($P < 0.05$) improvement in the gingival status of the patients with the use of flurbiprofen gel as an adjunct to scaling and root planing as compared to oral prophylaxis or gel alone. **Conclusion:** The data demonstrated that the additional use of local drug delivery of flurbiprofen through gel media enhances the positive effects of scaling and root planing and helps in faster resolution of the inflammation.

Keywords: Biodegradable gel system, flurbiprofen, host modulation, local drug delivery, non-steroidal anti-inflammatory drugs, periodontal disease

Introduction

Periodontal diseases are basically inflammatory in nature caused by the microbial accumulations on the tooth surfaces. The severity and clinical manifestations depend on host-related environmental factors. One of the decisive factors is the immune-inflammatory reaction manifested by host defense mechanism.

Among the inflammatory mediators, eicosanoids comprise a group of biochemical substances that are derived principally from the metabolism of arachidonic acid. They include prostaglandins, leukotrienes, hydroxyeicosatetraenoic acid, thromboxanes, etc. These mediators have a significant role in regulation of inflammation by increasing vasodilatation, vascular permeability, and edema.[1]

There is increasing interest in how these host responses, particularly pathways of destruction can be modulated or blocked to alter the progression of periodontal diseases. The ability of the non-steroidal anti-inflammatory drugs (NSAIDS) to block cyclooxygenase pathway and reduce the prostaglandin synthesis led to series of studies demonstrating inhibition of periodontal disease progression.[2,3]

Although relatively low-dose systemic NSAIDS have been successfully used in periodontics, it is not without side-effects. The major among these was gastrointestinal tract irritation. It is therefore desirable to formulate an agent that will deliver an effective dose of NSAID into periodontal tissues with minimum side-effects and maximum local effects.

This study was undertaken to evaluate the efficacy of a novel indigenously designed flurbiprofen controlled release biodegradable gel system in the management of periodontal diseases.

Materials and Methods

Source of data

This single-center, randomized, controlled, investigator blind, clinical study was conducted at the department of periodontics, Manipal College of Dental Sciences, Manipal, India.

The 51 patients with localized periodontal pockets were selected from the outpatient section of the department.

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Access this article online	
Quick Response Code:	Website: www.contempclindent.org
	DOI: 10.4103/0976-237X.111591

Informed consent was obtained from the patients and the ethical committee of the institute approved this clinical trial. These patients were scrutinized for the inclusion and exclusion criteria.

Selection criteria

The systemically healthy patients with isolated localized periodontal pocket measuring ≥5 mm and presence of bleeding on probing were selected for the study. The patients with history of scaling and root planing (SRP) for 12 months prior to baseline were excluded from the study. The medically compromised patients, pregnant or lactating mothers, and patients with history of antibiotic or anti-inflammatory therapy in last 6 months were excluded from the study. All the current smokers and the patients who have quit smoking in less than 1 year from baseline were not included in the study.

After scrutinizing, 17 patients were excluded from the study and two patients refused to participate in the study due to personal reason. To get uniformity in sample, the sample size at the baseline, two more patients were excluded to have a sample size of 30 patients.

These patients were randomly divided into three groups using the block randomization method. The first group of the patients received the placement of the gel only (GO). The second group received SRP at the baseline followed by gel placement (GOP), whereas the third group received the oral prophylaxis with placebo gel placement (OPP).

The SRP in all the subjects was performed by a single professional until the root surface was considered smooth and clean by the operator. The calibrated examiner for recording all the data in the study groups was completely blinded of the different groups in the study. The statistician performing the analysis was also blinded of the details of the group and the data were provided only as Groups A, B, and C.

The clinical parameters recorded were Silness and Loe plaque index (PI),[4] Loe and Silness gingival index (GI),[5] and Mombelli's bleeding index (BI)[6] at baseline, 7th day, and 14th day.

Formulation of 0.3% flurbiprofen *in situ* gel

The 0.3% flurbiprofen in the Poly (lactide)-co-glycolide copolymer (75:25 ratio) was used as the locally delivered controlled release delivery system. The gel was indigenously prepared at the College of Pharmaceutical Sciences, Manipal, India. The *in vitro* analysis of the drug delivery system was done to study the cumulative drug release in simulated *in vivo* conditions using Ultraviolet-visible (UV) spectrophotometer. It was found that the 85% of total drug was released by 15th day; hence the final evaluation was done on 14th day.

Placement of the *in situ* gel

The 0.2 ml of the gel was carefully injected in the dried, well-isolated periodontal pocket. The gel transformed to a solid state as soon as it came in contact with *in vivo* aqueous environment releasing the loaded drug over the prolonged period of time. The patients were advised to refrain from the use of any chemotherapeutic agents during the course of the study.

Statistical analysis

All the data were analyzed using a software program (SPSS Version 10, SPSS, Chicago, IL, USA). The statistical analysis was performed using the Mann–Whitney "*U*" test and the Wilcoxon Signed ranks test at the significance level of $P < 0.05$.

Results

This study was designed to evaluate the efficacy of flurbiprofen controlled release gel when used alone as well as when used as an adjunct to SRP. Thirty patients in the age group of 28-56 years were enrolled in the study and were randomly divided into three groups.

No statistically significant difference in the baseline values was observed between the groups ($P > 0.05$). All the three groups showed statistically reduction in all the clinical parameters ($P < 0.05$) from baseline to 14th day.

Compared to OPP and GO groups, the GOP group showed a statistically significant ($P < 0.05$) improvement in all the clinical parameters. However, there was no significant difference in OPP and GO groups in the parameters assessed.

Plaque scores

The plaque scores measured using Silness and Loe PI shown statistically significant ($P < 0.01$) reduction on days 7 and 14 as compared to baseline in OPP as well as GOP groups, whereas in GO group, the results were not statistically significant ($P > 0.01$) [Tables 1 and 2].

GI scores

The GI showed highly significant ($P < 0.001$) reduction in gingival inflammation in all the three groups on day 7 as well as on day 14. There was highly statistically reduction in the inflammation in GO group with mean GI of 2.900 ± 0.316 at baseline reduced to 1.500 ± 0.527 on day 7 and 1.000 ± 0.471 on day 14. No oral prophylaxis was performed in this group [Tables 1 and 2]. The comparison of OPP with GOP on day 14 also showed the statistically significant differences in GI ($P < 0.01$). The other intergroup comparisons of GI on days 7 and 14 were not statistically significant ($P > 0.05$) [Tables 3 and 4].

BI scores

The bleeding on probing also showed the highly significant reduction ($P < 0.001$) in bleeding from baseline to 14th day in all the three groups [Tables 1 and 2].

The intergroup analysis for all the clinical parameters was not statistically significant ($P > 0.05$) among the given three

Table 1: Clinical parameters at baseline and 7th day

Groups	Clinical parameters	Mean	Standard deviation	*P* value
Gel	Plaque index			
	Baseline	2.3	0.674	1
	7 days	2.3	0.674	
	Gingival index			
	Baseline	2.9	0.316	0.004
	7 days	1.5	0.527	
	Bleeding index			
	Baseline	2.9	0.316	0.004
	7 days	1.5	0.527	
Gel+OP	Plaque index			
	Baseline	2.4	0.516	0.004
	7 days	0.4	0.516	
	Gingival index			
	Baseline	2.7	0.483	0.004
	7 days	0.9	0.737	
	Bleeding index			
	Baseline	2.7	0.483	0.004
	7 days	0.9	0.737	
OPP	Plaque index			
	Baseline	2.5	0.527	0.004
	7 days	0.3	0.483	
	Gingival inde			
	Baselin	2.8	0.421	0.004
	7 days	1.4	0.699	
	Bleeding index			
	Baseline	2.8	0.421	0.004
	7 days	1.4	0.699	

OP: Oral prophylaxis; OPP: Oral prophylaxis with placebo gel placement

Table 2: Clinical parameters at baseline and 14th day

Groups	Clinical parameters	Mean	Standard deviation	*P* value
Gel	Plaque index			
	Baseline	2.3	0.674	0.08
	7 days	2.0	0.816	
	Gingival index			
	Baseline	2.9	0.316	0.002
	7 days	1.0	0.471	
	Bleeding index			
	Baseline	2.9	0.316	0.003
	7 days	1.1	0.567	
Gel+OP	Plaque index			
	Baseline	2.4	0.516	0.003
	7 days	0.2	0.421	
	Gingival index			
	Baseline	2.7	0.483	0.004
	7 days	0.2	0.421	
	Bleeding index			
	Baseline	2.7	0.483	0.004
	7 days	0.2	0.421	
OPP	Plaque index			
	Baseline	2.5	0.527	0.004
	7 days	0.7	0.483	
	Gingival index			
	Baseline	2.8	0.421	0.004
	7 days	0.9	0.875	
	Bleeding index			
	Baseline	2.8	0.421	0.004
	7 days	1.3	0.674	

OP: Oral prophylaxis; OPP: Oral prophylaxis with placebo gel placement

groups on day 7 as well as on day 14, except for the GOP group which showed highly significant ($P < 0.001$) reduction in BI as compared to OPP group [Tables 3 and 4].

Discussion

The development of most of the periodontal diseases is a consequence of the inflammatory and immunological reactions of the host to the bacterial plaque on the tooth surface. An essential goal of periodontal therapy is to control the inflammatory lesion in such a way that progressive destruction of the periodontium is arrested.

Various host modulatory therapies (HMT) have been developed or proposed to block the pathways responsible for all tissue breakdowns. The matrix metalloproteinases (MMP) are released by infiltrate cells like neutrophils and recordent cells like fibroblasts, osteoclasts. These MMPs play an important role in degradation of the extracellular matrix and resorption of alveolar bone. Synthetic MMP-inhibitors and other HMT are being studied in clinical trials. They include tetracycline,[7] chemically modified tetracyclines,[8] subantimicrobial dose doxycycline,[9] Alandronate,[10] and other NSAIDs.[11-13]

Various NSAIDs have been evaluated systemically or locally as an adjunctive to non-surgical and surgical periodontal therapy. Local delivery systems of NSAIDs have been evaluated in the paste, gel, and mouth rinse form.[14] Heasman *et al*., (1989)[12] and Yewey *et al*., (1991)[13] studied the controlled delivery system in animal experiments and revealed that further research is required in this aspect.

Among NSAIDs agents such as aspirin, ketoprofen, ibuprofen, piroxicam, indomethacin, and flurbiprofen have been tried as host modulating agents in treatment of periodontitis, locally or systemically.[15-17]

In this study, agent flurbiprofen was selected to evaluate its host modulation effect in localized periodontitis. Various studies show that flurbiprofen is utilized locally in the

Table 3: Comparison of clinical parameters between the study groups on 7th day

Group	Clinical parameters	Mean	Standard deviation	*P* value
Gel versus OPP				
	Reduction in plaque scores			
	Gel	2.3	0.674	0.0001
	OPP	0.3	0.483	
	Reduction in gingival inflammation			
	Gel	1.5	0.527	0.831
	OPP	1.4	0.699	
	Reduction in bleeding scores			
	Gel	1.5	0.527	0.831
	OPP	1.4	0.699	
Gel+OP versus OPP				
	Reduction in plaque scores			
	Gel+OP	0.4	0.516	0.647
	OPP	0.3	0.483	
	Reduction in gingival inflammation			
	Gel+OP	0.9	0.737	0.131
	OPP	1.4	0.699	
	Reduction in bleeding scores			
	Gel+OP	0.9	0.737	0.131
	OPP	1.4	0.699	
Gel versus Gel+OP				
	Reduction in plaque scores			
	Gel	2.3	0.674	0.0001
	Gel+OP	0.4	0.516	
	Reduction in gingival inflammation			
	Gel	1.5	0.527	0.062
	Gel+OP	0.9	0.699	
	Reduction in bleeding scores			
	Gel	1.5	0.527	0.062
	Gel+OP	0.9	0.699	

OP: Oral prophylaxis; OPP: Oral prophylaxis with placebo gel placement

Table 4: Comparison of clinical parameters between the study groups on 14th day

Group	Clinical parameters	Mean	Standard deviation	*P* value
Gel versus OPP				
	Reduction in plaque scores			
	Gel	2.0	0.816	0.0001
	OPP	0.7	0.483	
	Reduction in gingival inflammation			
	Gel	1.0	0.471	0.705
	OPP	0.9	0.875	
	Reduction in bleeding scores			
	Gel	1.1	0.567	0.434
	OPP	1.3	0.674	
Gel+OP versus OPP				
	Reduction in plaque scores			
	Gel+OP	0.2	0.421	0.028
	OPP	0.7	0.483	
	Reduction in gingival inflammation			
	Gel+OP	0.2	0.421	0.047
	OPP	0.9	0.875	
	Reduction in bleeding scores			
	Gel+OP	0.2	0.421	0.001
	OPP	1.3	0.674	
Gel versus Gel+OP				
	Reduction in plaque scores			
	Gel	2.0	0.816	0.0001
	Gel+OP	0.2	0.421	
	Reduction in gingival inflammation			
	Gel	1.0	0.471	0.002
	Gel+OP	0.2	0.421	
	Reduction in bleeding scores			
	Gel	1.1	0.567	0.001
	Gel+OP	0.2	0.421	

OP: Oral prophylaxis; OPP: Oral prophylaxis with placebo gel placement

form of toothpaste, local irrigation, or in gel form.[15,18] Flurbiprofen is found to be potent anti-inflammatory agent and showed significant decrease in bone loss as compared to other agents. It has also shown to suppress

the inflammatory mediators such as thromboxane B_2 and prostaglandin E_2.[19]

Time period in this study was restricted to 2 weeks since *in vitro* evaluation of the delivery system revealed that 85% of cumulative drug release was present on 15th day. This was done using UV spectrophotometer simulating the *in vivo* conditions.

In an experimental gingivitis model of 21 days by heasman *et al*. (1993),[17,19] 50 mg of systemically administered flurbiprofen inhibited development of redness and gingivitis. The similar results were recorded in this study in the GO group where there was a decrease in GI scores without significant change in PI score.

Yewey *et al*., (1991)[13] had demonstrated in beagles that the use of biodegradable subgingival delivery system for flurbiprofen resulted in significant reduction in gingival inflammation.[5] The same was reaffirmed in our study where the use of the flurbiprofen gel as an adjunct to oral prophylaxis in humans has showed the faster response and better outcome as compared to oral prophylaxis alone.

Flurbiprofen is a potent anti-inflammatory agent used in management of periodontal diseases, but there is no documented literature showing this drug being used in the form on biodegradable controlled delivery system in humans. The outcome of this study is very important in developing flurbiprofen controlled release gel as an effective adjunct in the management of periodontal inflammation.

Conclusion

The results of this study reveal that even though gel alone improved the gingival inflammatory status, enhanced effect of the gel and oral prophylaxis are more evident. The effect of gel thus increases the results obtained by oral prophylaxis. Resolution of inflammation early, with use of flurbiprofen gel is an added benefit not only for the patient satisfaction but also for the operator to carry out further treatment.

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How to cite this article: Deshpande NC, Bhat KM, Bhat GS, Deshpande AN. Randomized, controlled clinical study to evaluate efficacy of novel indigenously designed controlled release flurbiprofen gel system for management of periodontal diseases. Contemp Clin Dent 2013;4:32-6.

Source of Support: Nil. **Conflict of Interest:** None declared.