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Clinical Efficacy of Subgingivally Delivered 2.5% Ibuprofen Gel in Chronic Periodontitis: A Randomized Controlled Clinical Trial

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***Abstract*:**

Background: Researchers considered the use of selective cyclooxygenase-2 inhibitors offered the prospect for reducing periodontal inflammation without the side effects, which typically were observed after long-term, non-selective, non-steroidal anti-inflammatory drug therapy. The aim of the present study is to investigate the effectiveness of ibuprofen gel as an adjunct to non-surgical periodontal treatment of chronic periodontitis.

Materials and Methods: A total of 22 individuals were randomized into two treatment groups: Scaling and root planing (SRP) plus ibuprofen and SRP plus placebo gel. Periodontal clinical parameters noted at baseline and all following (within 3 months) visits were included: Plaque index (PI), bleeding index, probing depth, and clinical attachment level (CAL).

Results: 22 patients completed the study; the outcomes revealed improvement in all clinical periodontal parameters in Group A, B which was declared within 3 months ($P < 0.05$); whereas SRP with ibuprofen gel resulted in a significant reduction of PI, bleeding on probing, probing pocket depth, and CAL parameters at 3 months as compared to baseline and placebo group.

Conclusion: Ibuprofen gel as an adjunct to SRP can provide a new direction in the management of periodontal treatment and could be used to complement the therapy to resolve the inflammatory process and clinical signs of the disease more rapidly.

Key Words: Chronic periodontitis, ibuprofen gel, non-steroidal anti-inflammatory drug therapy

Introduction

Periodontitis takes place as a result of the host immune inflammatory response to oral pathogens. Periodontal pathogens produce harmful derivatives and enzymes thus break down extracellular matrices, such as collagen, as well as host cell membranes and lead to bone resorption, creating bony defects that may cause tooth loss.[1] The importance of the host inflammatory response in periodontal pathogenesis presents the prospect for developing new treatment strategies for periodontitis using host response modulation. Host modulatory therapy is a treatment concept that aims to decrease tissue destruction and stabilize or regenerate the periodontium by modifying or downregulating critical aspects of the host response and upregulating protective or regenerative responses.[2] The basis behind this style is to aid the host in its fight against infectious causes by adding the natural inherent protection mechanisms or to adjust its response by altering the course of inflammatory systems; however, host response modulation potentially has more side-effects, is not invasive, and does not need difficult application approaches.[3] A variety of pharmacological agents has been studied for a possible character as host modulators in the management of periodontal disease. These include non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, and tetracyclines.[4] The other study described that associated prostaglandin E2 (PGE2) levels and their correlation with active periodontal disease suggesting that PGE2 could be a good biomarker of disease activity.[5] The treatment for chronic periodontitis, in contrast to other kinds of periodontitis requiring adjunct medication therapy, is traditional debridement for removing plaque.[6] However, the foundation of anti-inflammatory drugs in periodontal disease treatment is correlated to the regulator of PGE2 by the inhibition of cyclooxygenase-2 enzyme. Upper levels of PGE2 are related to increased gingival inflammation and alveolar bone loss;[7-10] Other NSAIDs, either systemically or topically administered, also have shown efficacy in treating periodontal diseases in animal models. The propionic acid derived NSAID ibuprofen has been revealed to be effective in blocking alveolar bone loss in beagles with naturally occurring periodontitis.[11] The other study has shown that topically controlled 0.1% ketorolac reduces PGE2 levels in gingival crevicular fluid (GCF) and controls the increase of PGE2 for 12 h.[12] Jeffcoat *et al.* revealed that in patients with periodontitis, twice-daily rinsing with 0.1% ketorolac was at least as effective in preserving alveolar bone as systemic flurbiprofen.[13] Studies utilizing the beagle model of periodontitis have proved that typically controlled ketoprofen, flurbiprofen can significantly decrease bone loss and slow the progress of periodontitis.[14-16] Heasman *et al.* indicated that no superior effect was observed in other clinical parameters when the topical flurbiprofen gel was used.[17] The aim of the present study is to evaluate the clinical outcome of non-surgical treatment with the adjunctive topical application of ibuprofen compared to placebo gel.

Materials and Methods

Study of the population a total of 22 patients with chronic periodontitis were selected from the outpatient division of the Department of Periodontics, Islamic Azad University, Dental School of Tehran, Iran. The clinical study matched the guideline of the Helsinki Declaration of 1975, revised in 2008. The survey design was reviewed and approved, accepted by the Ethics Commission of the Institutional Ethical Committee and Review Board of the Deputy of Research, School of Dentistry. All objects received the oral and written description of the scope of the survey and signed an informed consent after having detailed information about the purpose, the benefits, and the potential dangers associated with the trial. The study was led from November 2012 to December 2013. The clinical trial was recorded at the Iranian Registry of Clinical Trials (IRCT), (registration code: IRCT2014050517587N1).

Study design

This study was conducted as a randomized, double-blind, placebo-controlled split-mouth trial, to evaluate the effects of the 2% ibuprofen gel (Diomed Pharmaceutical Company, UK). In the Group (A), another Group (B) placebo gel (made by faculty of Islamic Azad University of Pharmaceutical Sciences) was used; in patients with chronic periodontitis were randomly assigned to receive immediate or delayed periodontal treatment. Participants were evaluated at baseline and at 3 and 6 months following randomization for multiple measures of periodontitis. Eligible participants were 28 patients with chronic periodontitis, who were selected among patients referred for periodontal treatment at the Department of Periodontology, inclusion and exclusion criteria are as a follow:

Inclusion criteria

Healthy patients; aged between 30 and 45 years; 20 natural teeth present; clinical and radiographic signs of mild, with initial moderate chronic periodontitis (clinical attachment level [CAL] of 1 to 3 mm); probing depth (PD) of >4 mm; no periodontal treatment the previous 6 months; and willingness to comply with the study protocol.

Exclusion criteria

Patients were brought away from the study if they met one or more of the following criteria: Existing systemic disease that may limit the severity or progression of periodontal disease; periodontal surgery during the previous 3 months in the area of the teeth under study; taking medications (e.g. NSAIDs or antibiotic) within the 3 months preceding the beginning of the study; concurrent orthodontic treatments; planned extensive dental restorations; using any mouthwash during the trial period; multiple dental caries; pregnancy or breastfeeding; hypersensitive to ibuprofen; smoking.

Clinical measurements

The subsequent clinical outcome changeable was noted at baseline, within 2 weeks to 3 months at the elected teeth, the evaluation of dental plaque on six sites (mesial, medial, and distal position) of facial and lingual sides, using a Silness and Loe index.[18] Bleeding on probing (BOP), through the visual inspection 30 s after probing, according Carter and Barnes including: Score 0: No bleeding or Score 1: A single discrete bleeding point appears after probing,[19] PD, and CAL; in addition, the cementoenamel junction was used as the reference point and also was made at six sites per tooth by the same calibrated examiner (four patients with periodontitis, not involved in the study, with a 1-day period, before the start of the study), although the investigator was not informed of the type of treatment rendered.

Interventions

Following patient selection by an investigator, patients were randomly designated to either the A or B group while mandibular arches are each divided into two parts: Left and right sections, with 100 sites in both groups. In the A Group, it was treated by scaling and root planing (SRP) followed by local delivery of 2% ibuprofen, whereas the B Group was treated by SRP along with placebo gel and was administered to the both groups every 15 days for 3 months. The ibuprofen gel and placebo containers were blind to the therapist and the clinical examination. After treatment, patients were given thorough oral hygiene instructions; the trial gel for local application contained ibuprofen gel in the Group (A) and another Group (B) + placebo gel was used. The individuals brushed their teeth using the techniques instructed to use the Bass brushing technique with a soft toothbrush and regular fluoride-containing toothpaste and using optimal dental floss once-daily. All pre- and post-treatment periodontal clinical parameters were noted by an investigator who was blinded to the type of treatment rendered by the objects while another clinician provided treatment for both groups.

Sample size

The sample size was determined on the basis of a former study comparing SRP with or without adjunctive NSAIDs, with a mean difference in the number of residual pockets with PD >4 mm and BOP, 3 months after therapy;[13,20] with the desired difference of 1.8 mm; using the following formula: α = 0. 05 and the power (1−β) = 80%. For the variability (σ = standard deviation [SD]), the value of 0.5 mm was used; furthermore, the number of enrolled patients to conduct this study was calculated as 14 patients per arm were included to compensate for 10% possible dropout rate.

Statistical analysis

The data were analyzed using statistical software. Means ± SD for continuous measures and frequency were calculated for the two treatment groups at baseline. The primary outcome was the difference across groups among the mean change in Pocket depth, BOP, CAL, and plaque index (PI) from baseline to the remnant of the follow-up; however, These parameters evaluated for the comparison before and frequent follow-up

meetings, holding into account the repeated measure ANOVA test as a measure of time and intervening repeated factor as between subject comparison was used and data analyzed software SPSS version 19. The average change from baseline at each visit was then calculated (baseline, 15-60 days and 3 months). Analysis of variance test was employed to measure the statistical significance in mean change from baseline in all clinical parameters within the groups while *t*-test was used to evaluate the statistical significance between the groups.

Outcomes

Primary outcome measure

The primary outcome measure of efficacy was the change in PD between baseline and follow-up examinations at the sites of four randomly selected investigations teeth in each patient showing PD of >4 mm.

Secondary outcome measures

As secondary efficacy outcome measures, changes in CAL, BOP, suppuration, and PI were measured. PI was recorded before the PD measurement, and BOP was recorded immediately after probing.

Results

About 22 of 28 individuals completed the study (Figure 1). Two patients did not report back after the first follow-up visit and four patients relocated. No adverse reaction was observed in any individual from the test group, and no patient reported any discomfort. All participants tolerated the drug well without any complications or adverse reactions to the drug. Soft tissues healed within normal limits, and no significant visual differences were noted. Both groups showed improvement in site-specific PI score, but there was statistically significant difference between the groups at 3 months; however, there was a significant difference between the groups with more improvement in the placebo group at 3 months ($P < 0.05$) (Table 1). BOP in both groups showed no difference at baseline, but it was significantly decreased in the ibuprofen group compared to the placebo group at 1 and 3 months ($P < 0.05$) (Table 2). Mean baseline data in both groups are shown in Table 3. There were no differences between groups in PD at baseline and significant PD reduction at 1 and 3 months in the ibuprofen group as compared to the placebo group at $P < 0.05$ (Table 3). The CAL gain was taken as the as secondary outcomes; the intragroup analysis for CAL for both groups was significant at all the time intervals between 1 and 3 months for both groups; however, also statistically significant difference in the ibuprofen gel group compared to the control group ($P < 0.05$) (Table 4).

Discussion

The existing concept of periodontal disease pathogenesis states that microorganisms and their products are capable of inducing inflammatory mediators, and the resulting inflammation presents as the symbol of the disease.[21] In the former reports,

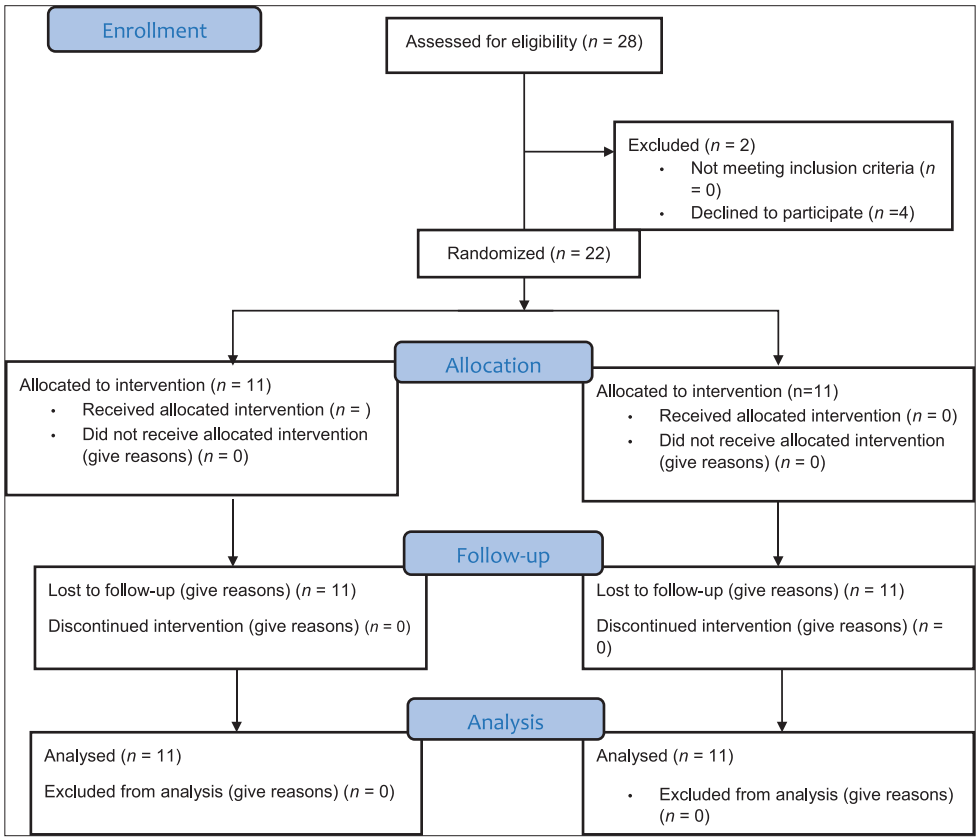

Figure 1: Flow diagram.

Table 1: Plaque index (mean±standard deviation) for Groups A: Ibuprofen gel (left side) and B: Placebo at different time intervals.

Group/time	Baseline	1 month	3 months	*P*
Ibuprofen gel	0.97±0.04	0.55±0.03	0.31±0.11	0.0365
Placebo	0.97±0.04	0.58±0.03	0.42±0.12	

Table 2: Bleeding on probing (mean±standard deviation) for Groups A: Ibuprofen gel (left side) and B: Placebo at different time intervals.

Group/time	Baseline	1 month	3 months	*P*
Ibuprofen gel	0.99±0.3	0.45±0.11	0.25±0.09	0.0382
Placebo	0.98±0.8	0.56±0.13	0.34±0.10	

Table 3: Pocket depth (mean±standard deviation) for Groups A: Ibuprofen gel and B: Placebo at different time intervals.

Group/time	Baseline	1 month	3 months	*P*
Ibuprofen gel	4.87±0.24	4.33±0.13	3.97±0.12	0.0170
Placebo	4.89±0.26	4.46±0.15	4.12±0.16	

Table 4: Clinical attachment level (mean±standard deviation) for Groups A: Ibuprofen gel and B: Placebo at different time intervals.

Group/time	Baseline	1 month	3 months	*P*
Ibuprofen gel	4.90±0.27	4.45±0.12	4.12±0.13	0.0495
Placebo	4.91±0.29	4.57±0.14	4.26±0.18	

use of NSAIDs to control inflammation and as an adjunct to conventional periodontal therapy[13,21] has confirmed advantageous in comparison with controls. The disadvantages of systemic NSAIDs can be avoided using a local drug delivery that allows the concentration of a specific drug at the desired site. Ketoprofen, a propionic acid derivative, has been found to be effective against a number of inflammatory conditions and is currently under investigation as a potential adjunct to conventional periodontal therapy;[21] beyond its capacity to block the cyclooxygenase pathway, *in vitro* statements have also indicated an anti-lipoxygenase activity,[21] and consequently, the added ability of the drug to inhibit leukotriene formation. This study is designed with the aim of assessing the efficacy of 2% ibuprofen gel as an adjunct to non-surgical periodontal therapy in the treatment of patients with chronic periodontitis compared with a placebo group. In the current study, a local drug containing 2% ibuprofen gel was used in combination with SRP to evaluate periodontal outcomes in subjects with chronic periodontitis, at 30 and 90 days following SRP and PI demonstrate that the overall oral hygiene situation displayed notable improvement. At the 3-month visits, comparison of PI seemed to favor the ibuprofen group, which could have influenced various clinical outcomes at that particular time duration; this finding was agreed with the study of Yen *et al.*[22] indicated that both groups, which the patients have taken celecoxib or placebo, showed consistent improvement in plaque control over the study period; (celecoxib: 54.5-21%; placebo: 58.7-17.5%), respectively. The considerable of difference in PI reduction between groups, after 1 month and 90 days, and the clinical improvement in the control group supports the idea that most of the clinical benefits frequently come from conventional therapy associated with an effective plaque control.[23] In addition, Srinivas *et al.*[24] demonstrate that the application a local drug delivery system containing 1.5% ketoprofen gel or a placebo was used in conjunction with SRP, a highly significant value was achieved for the PI in the ketoprofen gel group; however, Johanson *et al.*[25] determined the drug (Naprosyn) had no significant influence on PI or gingival inflammation (bleeding index). Our secondary outcome measures were BOP scorers. All position treated with SRP revealed improvement at 30 and 90 days, respectively. At 90 days, a decrease of BOP with ibuprofen gel was found to be significant in comparison with the placebo group; indicating that Group B (SRP + ibuprofen gel) revealed a significant reduction in the clinical signs of gingival inflammation. This is in conjunction with Paquette *et al.* and Srinivas *et al.* reports of reduced inflammatory components following the application of a similar ketoprofen gel;[21,26] also, Heasman *et al.* reported significantly reduced clinical gingival bleeding scores in subjects with periodontitis while on NSAID regimens, which further supports this interpretation of the BOP findings.[26] However, the improvement can be related to the comparative periodontal stability that was observed in both groups and strengthens the idea that regular periodontal maintenance with improved oral hygiene can prevent future periodontal breakdown once effective treatment has been terminated. Therefore, our data should not be explained to mean that adjunctive therapy can compensate for poor oral hygiene. In this study, although there was a significant overall gain in CAL and reduction of probing pocket depth (PPD), inter-group variations were found to be statistically significant; these changes in the investigation with Funosas *et al.*[20] had shown that administering intracrevicular 1% acetyl-salicylic acid and 2% ketoprofen gel as an adjunct to periodontal treatment in patients with chronic periodontitis can significantly reduce PD;[27] and in another study, also most PD reduction was observed in few deeper sites (>7 mm) from the SRP + loxoprofen group than in the SRP + placebo group.[20] Likewise, other studies[13,28,29] have found no differences in PD reduction between placebo and NSAID group after 28 days. Earlier published data utilizing different concentrations of a topically applied ketoprofen gel established decreased PG levels in GCF.[13] Some of the trials using anti-inflammatory medications as an adjunct to SRP have described significant differences between test and control groups with consideration to PPD, CAL, and loss of alveolar bone.[13] Srinivas *et al.*[24] exhibited that there was a highly significant overall gain in CAL and reduction of PPD, but inter-group variations were not found to be statistically significant. However, the clinical significance may be questioned and the indication of this medicament should be controlled to clinical conditions where deep pockets are present. Consequently, the prescription of ibuprofen as an adjunct for the non-surgical, mechanical therapy may have an indication on the early stages of the treatment of advanced forms of periodontal diseases. Further investigations in selected patients may clarify this potential

indication or this variation in responsiveness may be associated with discrepancies in study design in terms of duration and due to the contradictory of the kind of medicine.

Conclusion

Locally used ibuprofen gel may slightly benefit to periodontal healing following nonsurgical treatment; also can provide a new direction in the management of periodontal treatment; in addition, could be used to complement the therapy to resolve the inflammatory process and clinical signs of the disease more briskly.

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References

1. Kirkwood KL, Cirelli JA, Rogers JE, Giannobile WV. Novel host response therapeutic approaches to treat periodontal diseases. Periodontol 2000 2007;43:294-315.
2. Preshaw PM, Hefti AF, Jepsen S, Etienne D, Walker C, Bradshaw MH. Subantimicrobial dose doxycycline as adjunctive treatment for periodontitis. A review. J Clin Periodontol 2004;31(9):697-707.
3. Lawrence T, Willoughby DA, Gilroy DW. Anti-inflammatory lipid mediators and insights into the resolution of inflammation. Nat Rev Immunol 2002;2(10):787-95.
4. Llavaneras A, Ramamurthy NS, Heikkilä P, Teronen O, Salo T, Rifkin BR, *et al.* A combination of a chemically modified doxycycline and a bisphosphonate synergistically inhibits endotoxin-induced periodontal breakdown in rats. J Periodontol 2001;72(8):1069-77.
5. Salvi GE, Brown CE, Fujihashi K, Kiyono H, Smith FW, Beck JD, *et al.* Inflammatory mediators of the terminal dentition in adult and early onset periodontitis. J Periodontal Res 1998;33(4):212-25.
6. Flemmig TF. Periodontitis. Ann Periodontol 1999;4(1):32-8.
7. Noguchi K, Ishikawa I. The roles of cyclooxygenase-2 and prostaglandin E2 in periodontal disease. Periodontol 2000 2007;43:85-101.
8. Reynolds MA, Prudencio A, Aichelmann-Reidy ME, Woodward K, Uhrich KE. Non-steroidal anti-inflammatory drug (NSAID)-derived poly(anhydride-esters) in bone and periodontal regeneration. Curr Drug Deliv 2007;4(3):233-9.
9. Tipton DA, Flynn JC, Stein SH, Dabbous MK. Cyclooxygenase-2 inhibitors decrease interleukin-1beta-stimulated prostaglandin E2 and IL-6 production by human gingival fibroblasts. J Periodontol 2003;74(12):1754-63.
10. Offenbacher S, Williams RC, Jeffcoat MK, Howell TH, Odle BM, Smith MA, *et al.* Effects of NSAIDs on beagle crevicular cyclooxygenase metabolites and periodontal bone loss. J Periodontal Res 1992;27(3):207-13.
11. Williams RC, Jeffcoat MK, Howell TH, Reddy MS, Johnson HG, Hall CM, *et al.* Ibuprofen: An inhibitor of alveolar bone resorption in beagles. J Periodontal Res 1988;23(4):225-9.
12. Preshaw PM, Hefti AF, Novak MJ, Michalowicz BS, Pihlstrom BL, Schoor R, *et al.* Subantimicrobial dose doxycycline enhances the efficacy of scaling and root planing in chronic periodontitis: A multicenter trial. J Periodontol 2004;75(8):1068-76.
13. Jeffcoat MK, Reddy MS, Haigh S, Buchanan W, Doyle MJ, Meredith MP, Nelson SL, Goodale MB, Wehmeyer KR. A comparison of topical ketorolac, systemic flurbiprofen, and placebo for the inhibition of bone loss in adult periodontitis. J Periodontol. 1995 May;66(5):329-38.
14. Jeffcoat MK, Williams RC, Reddy MS, English R, Goldhaber P. Flurbiprofen treatment of human periodontitis: Effect on alveolar bone height and metabolism. J Periodontal Res 1988;23(6):381-5.
15. Howell TH, Fiorellini J, Weber HP, Williams RC. Effect of the NSAID piroxicam, topically administered, on the development of gingivitis in beagle dogs. J Periodontal Res 1991;26:180-3.
16. Paquette DW, Fiorellini JP, Martuscelli G, Oringer RJ, Howell TH, McCullough JR, *et al.* Enantiospecific inhibition of ligature-induced periodontitis in beagles with topical (S)-ketoprofen. J Clin Periodontol 1997;24(8):521-8.
17. Heasman PA, Benn DK, Kelly PJ, Seymour RA, Aitken D. The use of topical flurbiprofen as an adjunct to non-surgical management of periodontal disease. J Clin Periodontol 1993;20(6):457-64.
18. Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condtion. Acta Odontol Scand 1964;22:121-35.
19. Carter HG, Barnes GP. The gingival bleeding index. J Periodontol 1974;45(11):801-5.
20. Funosas ER, Escovich L, Maestri L. The use of topical subgingival gels of non-steroidal anti-inflammatory drugs (NSAIDs) as an adjunct to non-surgical management of chronic periodontitis. Acta Odontol Latinoam 2009;22(3):215-9.
21. Paquette DW, Lawrence HP, McCombs GB, Wilder R, Binder TA, Troullos E, *et al.* Pharmacodynamic effects of ketoprofen on crevicular fluid prostanoids in adult periodontitis. J Clin Periodontol 2000;27(8):558-66.
22. Yen CA, Damoulis PD, Stark PC, Hibberd PL, Singh M, Papas AS. The effect of a selective cyclooxygenase-2 inhibitor (celecoxib) on chronic periodontitis. J Periodontol 2008;79(1):104-13.
23. Haffajee AD, Thompson M, Torresyap G, Guerrero D, Socransky SS. Efficacy of manual and powered toothbrushes (I). Effect on clinical parameters. J Clin Periodontol 2001;28(10):937-46.
24. Srinivas M, Medaiah S, Girish S, Anil M, Pai J, Walvekar A. The effect of ketoprofen in chronic periodontitis: A clinical double-blind study. J Indian Soc Periodontol 2011;15(3):255-9.
25. Johnson RH, Armitage GC, Francisco C, Page RC.

Assessment of the efficacy of a nonsteroidal anti-inflammatory drug, Naprosyn, in the treatment of gingivitis. J Periodontal Res 1990;25(4):230-5.
26. Heasman PA, Offenbacher S, Collins JG, Edwards G, Seymour RA. Flurbiprofen in the prevention and treatment of experimental gingivitis. J Clin Periodontol 1993;20(10):732-8.
27. Pinho Mde N, Pereira LB, de Souza SL, Palioto DB, Grisi MF, Novaes AB Jr., *et al.* Short-term effect of COX-2 selective inhibitor as an adjunct for the treatment of periodontal disease: A clinical double-blind study in humans. Braz Dent J 2008;19(4):323-8.
28. Vardar S, Baylas H, Huseyinov A. Effects of selective cyclooxygenase-2 inhibition on gingival tissue levels of prostaglandin E2 and prostaglandin F2alpha and clinical parameters of chronic periodontitis. J Periodontol 2003;74(1):57-63.
29. Taiyeb Ali TB, Waite IM. The effect of systemic ibuprofen on gingival inflammation in humans. J Clin Periodontol 1993;20(10):723-8.