Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.01.017 2019;26(3):510-6

Original Article

Clinical efficacy and acceptability of 0.25% flurbiprofen mouthwash after periodontal flap surgery: A double-blinded, parallel-group, placebo-controlled, randomized clinical trial

Sila Cagri Isler, Cise Nazim, Muge Aydogan , Memnune Dinc, Hikmat Bakhishov, Burcu Ozdemir

Gazi University Faculty of Dentistry, Department of Periodontology, Ankara, Turkey

Copyright © 2019 by authors and Annals of Medical Research Publishing Inc.

Abstract

Aim: The aim of the present study was to investigate the analgesic and anti-inflammatory efficacy of 0.25% flurbiprofen mouthwash, and to evaluate its effect on the parameters related to patient morbidity and early wound healing after periodontal flap surgery.

Material and methods: Thirty-two patients (19 females and 13 males), diagnosed with moderate periodontitis and presenting at least one quadrant scheduled for periodontal flap surgery, were randomly allocated to either the flurbiprofen group or the placebo group. The plaque index (PI), gingival index (GI), probing pocket depth (PPD), bleeding on probing (BOP) and clinical attachment level (CAL) were evaluated at baseline and PI and GI were re-evaluated at 30-day follow-up. On postoperative 1, 3, 7, 14 and 30 days, postoperative pain, discomfort, changes in patients' dietary habits, burning sensation and postoperative swelling were analyzed by using a visual analog scale (VAS). At postoperative 7 days, the early wound healing index was assessed clinically.

Results: The mean VAS scores exhibiting postoperative pain were significantly lower in flurbiprofen group compared to placebo group at days 1, 7 and 30 ($p<0.05$). Flurbiprofen group had significantly lower scores compared to the placebo group at 14-day follow-up in terms of changes in patients' dietary habits ($p<0.05$), as well as burning sensation at the first postsurgical day ($p<0.05$). At 30-day follow-up examination, the mean GI values were significantly higher for the placebo group ($p<0.05$).

Conclusion: A postsurgical protocol including rinsing with a 25% flurbiprofen mouthwash revealed better analgesic and anti-inflammatory effect and moreover, had a beneficial impact in terms of patient morbidity after periodontal flap surgery.

Keywords: Flurbiprofen; Inflammation; Postoperative Pain; Periodontal Flap Surgery.

INTRODUCTION

Periodontitis is a multi-factorial inflammatory disease that involves inflammation of the tooth supporting structures (1). This pathological condition is characterised by a bacterial challenge that can incite a destructive host response leading to periodontal attachment loss, bone destruction and moreover, tooth loss (2). Periodontal therapeutic approaches including scaling and root planing, open flap debridement surgeries and reconstructive surgical procedures, may cause a certain degree of pain and discomfort to some patients (3). However, periodontal surgical approaches have been indicated to increase patient morbidity many times greater than that found after scaling and root planing alone (4). Various topical antimicrobial and analgesic substances used as an adjunct to surgical therapies intended to treat periodontal pockets and to prevent infection of the affected wound area and create a favourable environment for the healing process (5).

Postoperative pain is one of the most common postoperative complication that disturbances the patients' quality of life, especially with the progress of inflammation and swelling in the surgical area. Tissue damage derived from surgical procedures induces the production of Cyclooxygenase-2 (COX-2), which in turn leads to the synthesis of prostaglandins (PGs) that sensitize pain fibers and promote inflammation (6). Non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used for pain prevention and relief, act by inhibition of the enzyme cyclooxygenasein arachidonic acid pathway

Received: 10.01.2019 **Accepted:** 13.02.2019 **Available online:** 22.2.2019
Corresponding Author: Sila Cagri Isler, Gazi University Faculty of Dentistry, Department of Periodontology, Gaziantep, Turkey
E-mail: silaisler@gazi.edu.tr

and as a consequence NSAIDs block the the production of PGs, prostacyclins (PGI2), and thromboxanes. The increased proinflammatory cytokines, promote a state of hyperalgesia by the sensitization of the nociceptors, leading to a reduction of the patient's pain threshold (7).

Systemic administration of NSAIDs has been reported to have serious gastrointestinal adverse events that includes nausea, dyspepsia and gastrointestinal bleeding. Several strategies are available to reduce the risk for NSAID associated with gastrointestinal adverse effects. With the purpose of minimizing the gastrointestinal adverse effects, limiting the systemic exposure to oral NSAIDs and maximizing drug levels at the site of affected area, topical medications such as gels, sprays toothpastes and mouthrinses have been suggested (8).

Flurbiprofen, a chiral NSAID of the 2-arylpropionic acid class, interferes with the formation of products of the arachidonic acid cascade by inhibiting COX-1 and COX-2 (9). Topical flurbiprofen have been demonstrated to produce analgesia comparable with systemic administration while minimizing exposure to potential targets for toxicity (10). A previous study evaluated the analgesic and anti-inflammatory effects of flurbiprofen mouthwash and 100 mg systemic administration of flurbiprofen after extraction of inferior molars combined with limb gingivectomy and osteotomy (11). In that study, the patients' pain perception was similar for both groups, however the recovery from the edema and the healing of the wound was achieved quicker with flurbiprofen mouthwash. In another previous study, topical administration of flurbiprofen at a local site of surgical wound was reported to suppress postoperative pain after removal of impacted third molars at lower doses than systemic administration (10).

The aim of the present study was to investigate the analgesic and anti-inflammatory efficacy of 0.25% flurbiprofen mouthwash, and to evaluate its effect on the parameters related to patient morbidity and early wound healing after periodontal flap surgery. The null hypothesis was that use of flurbiprofen and placebo mouthwash as an adjunct to periodontal flap surgery presented no difference in the postoperative outcome variables.

MATERIAL and METHODS

The present study was a prospective, double-blinded, parallel-group, placebo-controlled, randomized clinical trial on a total of 32 patients scheduled for periodontal flap surgery, evaluating the efficacy of a 0.25% flurbiprofen mouthwash. The study was conducted at the Dental Clinic of the Periodontology Department in Gazi University, Ankara, Turkey, between September 2017 and August 2018. The study design was reviewed and approved by the Institutional Review Board at Ankara University, Faculty of Dentistry, Ankara, Turkey (Protocol ID: 36290600/66). All patients signed a written informed consent before participation of the study.

Study population and design

Patients, diagnosed with moderate chronic periodontitis (12) and presenting at least one quadrant (three to five teeth, maxilla or mandible) scheduled for periodontal flap surgery, were considered to be eligible for the present study. The initial therapy including scaling and root planing, polishing, and occlusal adjustment as indicated and professional oral hygiene procedures was performed to each patient 3 months prior to enrolment. After 3 months following the initial therapy, indication for periodontal flap surgery was given when sites exhibiting residual probing pocket depths (PPD) of 5 to 8 mm and clinical attachment loss of 3 to 4 mm. The inclusion criteria for the present study were: age ≥18 years; non-smoker; having at least 20 teeth; no periodontal treatment the previous 6 months and no periodontal surgery on the experimental sites before; having good oral hygiene with full-mouth plaque index (FMPI) (13) <1 and having low levels of residual infection with full-mouth bleeding scores (FMBS)14 of <25%. Patients were excluded from the study if they met one or more of the following criteria: having serious systemic diseases, medications or conditions that would contraindicate for periodontal surgery and compromise wound healing (cardiac, hepatic or renal insufficiency, uncontrolled diabetes mellitus, gastric ulcer, malignancies, psychiatric diseases); hypersensitivity to flurbiprofen; history of allergy to NSAIDs; treated with systemic antibiotics 6 months prior to enrolment; there is a need of reconstructive periodontal surgery involving regenerative materials; and pregnancy or lactation.

Following patient selection, the patients were randomly designated to either a commercially available flurbiprofen mouthwash (Majezik 0.25%, Sanovel Pharmaceuticals INC, Istanbul, Turkey) (flurbiprofen group) or placebo mouthwash (placebo group) using a computer-generated randomisation scheme by the statistician. Allocation concealment was achieved using sealed-coded opaque envelopes that contained the assigned intervention. Each envelope was assigned a number identifying a patient to receive the respective treatment, which was only revealed immediately after the surgical procedure was completed. A study examiner (H.B.) who was not involved in the surgical procedures and postoperative examinations, opened the envelopes and recorded which patient to given flurbiprofen or placebo mouthwash. Furthermore, the patients were unaware of the type of mouthwash used.

The primary endpoint was to assess changing in postoperative pain scores by using a visual analogue scale (VAS) questionnaire and to compare the amount of systemic analgesic consumption. The secondary endpoints included to evaluate plaque index (PI), gingival index (GI), (15) the early wound healing index (EHI) (13), (16) patients' discomfort, changes in patients' dietary habits, burning sensation and postoperative swelling.

Interventions

The same periodontist (S.C.I.) performed all surgical procedures and the other periodontitists (Ç.N. and M.A.)

assisted during the operations. All surgical procedures were performed after administering a local anesthesia using 0.6 ml (1/3 of capsule contents) of 4% articaine and 1:200,000 epinephrine (Maxicaine, Vem Ilaç Ltd. Şti, Tekirdağ, Turkey) to the patients. During flap surgery, root surfaces were debrided by means of hand instruments (Gracey curette, Nordent Mfg Inc., Elk Grove Village, IL). All surgical wounds were rinsed with sterile 0.9% w/v sodium chloride solutions, and surgical flaps were repositioned and closed primarily using 4-0 monofilament polypropylene (Dogsan, Trabzon, Turkey) interrupted single sutures.

Study medications and postoperative instructions

Each patient were instructed to strictly follow post-surgical maintenance protocols and had a 7-day cycle using an undiluted 10-ml dose of mouthwash for 1 minute, three times a day. Both flurbiprofen-containing and placebo mouthwashes were packaged in identical 200 mL bottles and provided by same pharmaceutical company (Sanovel Pharmaceuticals INC, Istanbul, Turkey). The commercial preparation of flurbiprofen mouthwash contains 0.50 g (25%) of flurbiprofen, sorbitol, saccharin sodium, glycerine, polyoxyl 40 hydrogenated castor oil, ethyl alcohol, menthol and sodium hydroxide. Placebo mouthwash were prepared with the same ingredients without flurbiprofen. During the period of study medication intake, patients were instructed to rinse with a 0.12% chlorhexidine gluconate solution two times a day and were warned about passing at least half an hour between rinsing with flurbiprofen/placebo and chlorhexidine mouthwash and they were advised to firstly use flurbiprofen/placebo mouthwash and then to use chlorhexidine mouthwash. The first treatment was administered in the evening of the day in which performed surgical procedures. When the postoperative pain persisted, patients were instructed to take up systemically 100 mg flurbiprofen tablets three times/day for a week. During the first 7 days after surgery, the patients were also instructed not to brush or floss the study sites. At postoperative 7 days, the sutures were removed.

Clinical assessment

Clinical assessments and the postoperative parameters in relation to patient morbidity were evaluated by the same calibrated examiner (M.D.) who was not involved in providing treatment and who was blinded to the treatment assignment. The baseline clinical parameters including PI according to Silness & Löe, (13) GI acording to Löe & Silness, (15) bleeding on probing (BOP) assessed following PPD measurements based on the presence or absence of bleeding up to 30 s, (14). PPD assessed as the distance between the gingival margin and the base of the periodontal pocket, and clinical attachment level (CAL) assessed as the distance between cemento-enamel junction and the base of the periodontal pocket were measured using a manual periodontal probe (Nordent Mfg Inc., Elk Grove Village, IL) and recorded at four sites (mesio-buccal, mid-buccal, distobuccal and palatal) per tooth. At the 1-month follow-up, the measurements of PI and GI were obtained from each patient.

The parameters in relation to patient morbidity, including postoperative pain, patient discomfort, changes in patient dietary habits and burning sensation were assessed using questionnaires showing the intensity of the given event on a VAS on days 1, 3, 7, 14 and 30. A standard VAS on which patients have been asked to mark subjectively along a 10-point scale from 0 (no pain/discomfort/changes in dietary habits/burning sensation) to 10 (highest degree of pain/ discomfort/changes in dietary habits/burning sensation) was used for the assessments. Postoperative pain was also evaluated by the amount of systemic analgesic consumption in a 7-day postoperative period reported by the patient (in milligrams). Postoperative swelling was assessed on a 4-point scale (0: absent, 1: slight, 2: moderate, 3: severe) (17). All the assessments of parameters related to patient morbidity were performed in the morning at 9 AM on the designated days.

At day 7, assessment of post-operative wound healing was performed by using EHI (16) differentiating between the following 5 degrees:

1. Complete flap closure–no fibrin line in interproximal area

2. Complete flap closure–fibrin line in interproximal area

3. Complete flap closure–fibrin clot in the interproximal area

4. Incomplete flap closure–partial necrosis of interproximal tissue

5. Incomplete flap closure–complete necrosis of the interproximal tissue (16).

Statistical analysis

The sample size was determined on a previously reported clinical trial3 using the data (80% power at an effect size of 0.20 and a 0.05 level). On the basis of these data, 16 subjects would be necessary for each group. These calculations were made using a software (G*Power Version 3.1.2, Christian-Albrechts-Universität, Kiel, Germany).

The data was analyzed using the statistics packages SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Quantitative data are expressed as mean ± standard error of the mean (SE) for repeated-measures analysis of variance analyses and for the other statistical methods, the data were expressed as as the mean ± standard deviation (SD); qualitative data are reported as number and percentage. A Kolmogorov-Smirnov test was used the compatibility of data with normal distribution. For the comparison of the quantitative variables between the groups, Student's t-test was performed if the normal distribution assumption was met; if not, Mann-Whitney U test was used. For the VAS score analyses, repeated-measures analysis of variance was used to evaluate the differences within and between groups, followed by Bonferroni post hoc tests. Chi-square test was used to examine the relation between the two qualitative variables. For all analyses, the p value was set at 0.05.

RESULTS

Thirty-two patients (19 females and 13 males; mean age, 39.93 ± 8.94 years) completed the study. In flurbiprofen group, periodontal flap surgery were performed on sixteen sites and the distributions of the periodontally involved teeth were as follows: six maxillary/seven mandibular anterior teeth, ten maxillary/eight madibular premolars, and twenty maxillary/ten mandibular molars. In placebo group, fifty five teeth in sixteen sites received periodontal flap surgery and the distributions of the periodontally involved teeth were as follows: twelve maxillary/six mandibular anterior teeth, eight maxillary/five mandibular premolars and eleven maxillary/thirteen mandibular molars. No postoperative complications were reported by the patients and no adverse reactions were observed in any individual from the flurbiprofen or placebo group. The patients' demographics as well as baseline FMPI, FMGI, FMBS, PPD and CAL values are presented in Table 1.

Table 1. Patients' Demographic Data and Baseline Clinical Periodontal Parameters

Parameters		Flurbiprofen Group	Placebo Group	p value
Age	Mean±SD	40.6±8.7	39.2±9.4	0.506[b]
	Median (Min.-Max.)	39.0 (23.0 –55.0)	38.0 (28.0 –56.0)	
Gender	Female n(%)	9 (56.25)	10 (62.5)	0.494[c]
	Male n(%)	6 (43.75)	5 (37.5)	
FMPI	Mean±SD	0.41±0.19	0.46±0.24	0.901[b]
	Median (Min.-Max.)	0.44 (0.02 – 0.67)	0.39 (0.05 –0.92)	
FMGI	Mean±SD	0.27±0.14	0.23±0.18	0.394[b]
	Median (Min.-Max.)	0.29 (0.05 –0.48)	0.23 (0.06 –0.62)	
FMBS (%)	Mean±SD	22.89±11.07	21.63±8.93	0.803[b]
	Median (Min.-Max.)	20.8 (4.1 –25.8)	18.0 (6.1–24.9)	
PPD mm	Mean±SD	2.73±0.65	2.61±0.54	0.578[a]
	Median (Min.-Max.)	2.64 (1.83 –4.30)	2.48 (2.03 - 3.77)	
CAL mm	Mean±SD	2.88±0.65	2.76±0.55	0.556[a]
	Median (Min.-Max.)	2.81 (2.03 – 4.45)	2.65 (2.12– 3.98)	

a: Student-t test, b: Mann-whitney U test, c: Chi-square test. FMPI: full-mouth plaque index, FMGI: full-mouth gingival index, FMBS: full-mouth bleeding score, PPD: probing pocket depth, CAL: clinical attachment level

All parameters did not reveal any significant difference between the flurbiprofen and placebo groups.

Regarding the mean VAS scores exhibiting postoperative pain, flurbiprofen group showed significantly lower scores compared to placebo group at days 1, 7 and 30 (p=0.045, p=0.015 and p=0.04) (Figure 1). All patients in flurbiprofen group scored as zero at 30-day follow-up periods in terms of postoperative pain. In parallel to these findings, the total amounts of systemic analgesic consumption during postoperative 7 days were significantly lower for the flurbiprofen group (p<0.001) (Figure 2). However, patient discomfort was not different between the groups at any time points (p>0.05). In terms of changes in patients' dietary habits, the only statistically significant difference was observed between the groups at 14-day follow up. The mean VAS scores were significantly lower in the flurbiprofen group compared to the placebo group at this time point (p=0.03) (Figure 1).

The mean VAS scores exhibiting burning sensation was also significantly lower in the flurbiprofen group compared to the placebo group only at the first postsurgical day (p=0.032) (Figure 1). There were no differences between the groups regarding to postoperative swelling at any follow-up periods (p>0.05).

Post-surgical maintenance protocols presented comparable wound healing profiles for the flurbiprofen and placebo groups without statistically significant differences at 7-day follow-up (p>0.05). The mean EHI values were 1.40 ± 0.63 and 1.86 ± 0.63 for the flurbiprofen and placebo group, respectively.

At 30-day follow-up examination, no significant difference was observed in terms of the mean PI values in the operated areas of the study groups (p>0.05). However, the mean GI values were significantly higher for the placebo group (p=0.036) (Table 2).

Table 2. The Mean PI and GI Values of Operated Sites at Baseline and 30-day Follow-up

Parameters		Baseline	30 Days	p Value
PI	Flurbiprofen Group	0.32±0.18	0.25±0.19	0.609[a]
	Placebo Group	0.39±0.22	0.40±0.24	0.552[a]
	p Value	0.703[c]	0.101[c]	
GI	Flurbiprofen Group	0.25±0.17	0.07±0.06	<0.01[b]
	Placebo Group	0.23±0.14	0.15±0.14	0.017[b]
	p Value	0.896[d]	0.036[d]	

a:Wilcoxon Signed Ranks Test, b:Paired-t test, c:Mann-whitney U test, d:Student-t test, PI: plaque index, GI: gingival index

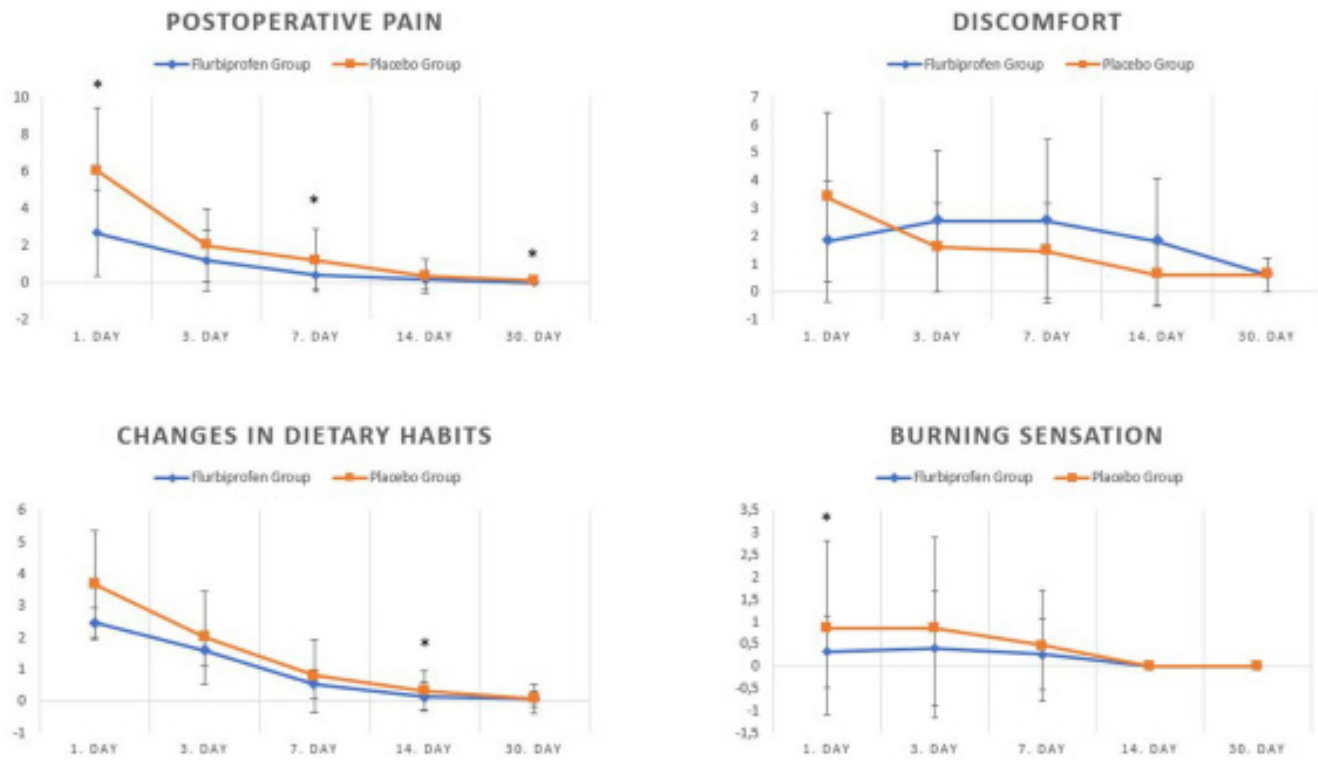

Figure 1. Intergroup comparison of the parameters regarding to postoperative pain, discomfort, changes in dietary habits and burning sensation for a 30-day postoperative follow-up. Data were expressed as the mean ± standard error of the mean (SE).*, p<0.05 considered statistically significant, repeated-measures analysis of variance test

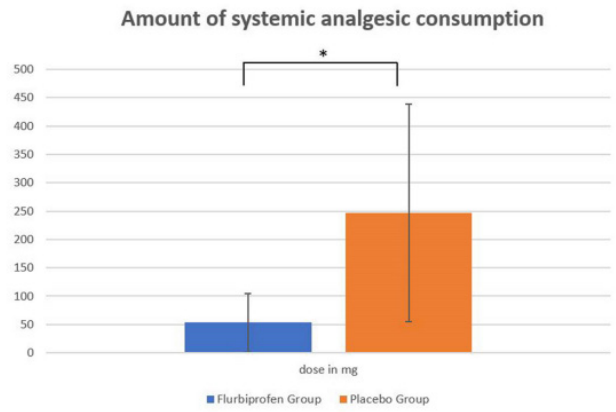

Figure 2. Comparison between flurbiprofen and placebo groups with regard to the total amount of systemic analgesic consumption in a 7-day postoperative period. Data were expressed as the mean ± standard deviation (SD). *, p<0.05 considered statistically significant, Mann-whitney U test

DISCUSSION

The postoperative complications regarding to patient morbidity such as pain and discomfort are usually expected after periodontal flap surgeries and an efficient postoperative medication protocol could minimize these undesirable effects (3,18-20). In the present randomized controlled clinical trial, a postsurgical protocol including rinsing with a 25% flurbiprofen mouthwash revealed better analgesic and anti-inflammatory effect and lower administration of systemic analgesic consumption. Moreover, it provided a positive effect on patient morbidity in terms of changes in patients' dietary habits and burning sensation.

Several studies have investigated the efficacy of different NSAIDs after periodontal flap surgery (3,18-20). In most of those studies, systemic medications were applied and their effects on postoperative pain were evaluated. However, there is little information in the current literature about the impact of topical NSAIDs agents on periodontal pain model. To our knowledge the the efficacy of analgesic and antiinflammatory of topical flurbiprofen after periodontal flap surgery has not been extensively studied to date.

Flurbiprofen is a centrally and peripherally acting NSAID that inhibits both COX-1 and COX-2 in the brain and the peripheral tissues (21). It has proven analgesic and antiinflammatory properties and efficacy in the oral surgical postoperative pain models (10,11,18,21,22). Gallardo & Rossi (18) compared the analgesic efficacy of oral flurbiprofen, acetaminophen and placebo after periodontal surgery and reported that flurbiprofen showed to possess an adequate analgesic effect superior to either placebo (p <0.005) or acetaminophen (p <0.01). Battisti (11) investigated the impacts of flurbiprofen mouthwash and oral flurbiprofen tablet after extraction of inferior molars combined with limb gingivectomy and osteotomy

and found the comparable effects on the profile of intensity of postoperative pain. Recently, our study group compared the effects of 0.075 g of flurbiprofen spray and placebo spray following free gingival graft (FGG) procedures and demonstrated that flurbiprofen spray had significantly lower the mean VAS values exhibiting postoperative pain during the study periods except for first postsurgical day ($p<0.05$) (22). In consisitent with the previous findings, 0.25% flurbiprofen mouthwash showed a statistically significant difference from placebo mouthwash in its ability to reduce pain at 1, 7 and 30 postoperative days after periodontal flap procedures ($p<0.05$). This potential advantage of topical flurbiprofen applications may be related with better penetrability of flurbiprofen into the gingival tissues due to their lipophilic nature and rapidly inhibit local gingival crevicular fluid PGE2 levels within an hour (23).

After periodontal surgery procedures, changes in patients' dietary habits have been considered an another postoperative complication that is negatively associated with daily activities and overall well-being. In a recent study, our group showed a negative impact of flurbiprofen spray on dietary habits compared to the placebo group after FGG operations (22). However, on the contrary, this study indicated that flurbiprofen mouthwash presented significantly better improvements for changes in patients' dietary habits after periodontal flap surgery. This contradictory results could be attributable with that topical flurbiprofen applications might have negative effects on epithelization of secondary wound healing although they did not show any unfavorable effects for primary wound healing (22). It is well documented that the early wound healing phase after any type of periodontal surgery decisively influences the postoperative morbidity.5 In the present study, we similarly observed no significant difference between the the groups in terms of EHI scores presenting the information about early wound healing profile.

Another interesting finding of our study was a trend toward a reduction in gingival inflammatory scores in favor of the use of flurbiprofen mouthwash. At 30-day follow-up, flurbiprofen group had significantly lower GI values compared to the placebo group. On the other hand, flurbiprofen group did not reveal a significant difference about postoperative swelling compared to placebo group at any study periods. However, 0.25% flurbiprofen mouthwash was reported to achieve the recovery from the swelling quicker than systemic administration of flurbiprofen after periodontal flap surgery (11).

CONCLUSION

Within the limitations of this placebo controlled and randomized clinical trial, the present results provided that flurbiprofen mouthwash had a significantly beneficial effect on patient morbidity regarding to the reducing postoperative pain, changes in patients' dietary habits and burning sensation. Moreover, an important aspect of the present study findings was a marked antiinflammatory impact of flurbiprofen mouthwash at postoperative 30 days after periodontal flap surgery.

Competing interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports
Ethical approval: The study design was reviewed and approved by the Institutional Review Board at Ankara University, Faculty of Dentistry, Ankara, Turkey (Protocol ID: 36290600/66).

Sıla Cagri Isler: ORCID:0000-0001-5419-9658
Cise Nazım: ORCID:0000-0002-2618-400X
Muge Aydogan: ORCID:0000-0003-3310-5960
Memnune Dınc: ORCID:0000-0003-0895-8777
Hikmat Bakhishov: ORCID:0000-0002-3518-2292
Burcu Ozdemir: ORCID:0000-0003-0356-7769

REFERENCES

1. Kinane DF. Causation and pathogenesis of periodontal disease. Periodontol 2000 2001;25:8-20.
2. Irfan UM, Dawson DV, Bissada NF. Epidemiology of periodontal disease: a review and clinical perspectives. J Int Acad Periodontol 2001;3:14-21.
3. Steffens JP, Santos FA, Pilatti GL. The use of etoricoxib and celecoxib for pain prevention after periodontal surgery: a double-masked, parallel-group, placebo-controlled, randomized clinical trial. J Periodontol 2011;82:1238-44.
4. Matthews DC, McCulloch CA. Evaluating patient perceptions as short-term outcomes of periodontal treatment: A comparison of surgical and non-surgical therapy. J Periodontol 1993;64:990-7.
5. Laugisch O, Ramseier CA, Salvi GE, et al. Effects of two different post-surgical protocols including either 0.05% chlorhexidine herbal extract or 0.1 % chlorhexidine on post-surgical plaque control, early wound healing and patient acceptance following standard periodontal surgery and implant placement. Clin Oral Investig 2016;20:2175-83.
6. Haas DA. An update on analgesics for the management of acutepostoperative dental pain. J Can Dent Assoc 2002;68:476-82.
7. Czock D, Keller F, Rasche FM, et al. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet 2005;44:61-98.
8. Mishra A, Amalakara J, Avula H, et al. Effect of diclofenac mouthwash on postoperative pain after periodontal surgery. J Clin Diagn Res 2017;11:ZC24-26.
9. Richy F, Rabenda V, Mawet A, et al. Flurbiprofen in the symptomatic management of rheumatoid arthritis: a valuable alternative. Int J Clin Prac 2007;61:1396-406.
10. Dionne RA, Haynes D, Brahim JS, et al. Analgesic effect of sustained-release flurbiprofen administered at the site of tissue injury in the oral surgery model. J Clin Pharmacol 2004;44:1418-24.
11. Battisti N. The evaluation of the analgesic and anti-inflammatory effects of flurbiprofen mouthwash and 100-mg tablets in oral medicine. Minerva Stomatol 1994;43:141-4.
12. Armitage GC. Development of a classification system for periodontal diseases and conditions. Ann Periodontol 1999;4:1-6.
13. Silness J, Löe H. Periodontal disease in pregnancy II. Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964;22:121-35.
14. Ainamo J, Bay I. Problems and proposals for recording gingivitis and plaque. Int Dent J 1975;25:229-35.
15. Löe H, Silness J. Periodontal disease in pregnancy I. Prevalence and severity. Acta Odontol Scand 1963;21:533-51.

16. Wachtel H, Schenk G, Böhm S, et al. Microsurgical access flap and enamel matrix derivate for the treatment of periodontal intrabony defects: a controlled clinical study. J Clin Periodontol 2003;30:496-504.
17. Curtis JW Jr, McLain JB, Hutchinson RA. The incidence and severity of complications and pain following periodontal surgery. J Periodontol 1985;56:597-601.
18. Gallardo F, Rossi E. Analgesic efficacy of flurbiprofen as compared to acetaminophen and placebo after periodontal surgery. J Periodontol 1990;61:224-7.
19. Pilatti GL, Andre´ dos Santos F, Bianchi A, et al. The use of celecoxib and dexamethasone for the prevention and control of postoperative pain after periodontal surgery. J Periodontol 2006;77:1809-14.
20. Rashwan WA. The efficacy of acetaminophen caffeine compared to Ibuprofen in the control of postoperative pain after periodontal surgery: A crossover pilot study. J Periodontol 2009;80:945-52.
21. Cooper SA, Kupperman A. The analgesic efficacy of flurbiprofen compared to acetaminophen with codeine. J Clin Dent 1991;2:70-4.
22. Isler SC, Eraydin N, Akkale H, et al. Oral flurbiprofen spray for mucosal graft harvesting at the palatal area: A randomized placebo-controlled study. J Periodontol 2018;89:1174-83.
23. Williams RC, Jeffcoat MK, Howell TH, et al. Topical flurbiprofen treatment of periodontitis in beagles. J Periodontal Res 1988;23:166-9.