

## Comparison of Ketoprofen Gum and Ketoprofen Gel for Pain Relief after Activation of Orthodontic Appliances

L. Eslamian<sup>1</sup>, F. Dehghani<sup>2</sup>✉, H. Amraie<sup>3</sup>.

<sup>1</sup> Professor, Department of Orthodontics, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup> Postgraduate Student, Department of Orthodontics, School of Dentistry, Hamadan University of Medical Sciences, Hamadan, Iran

<sup>3</sup> Postgraduate Student, Department of Prosthodontics, Dental Research Center Faculty of Dentistry, Hamadan University of Medical Sciences, Hamadan, Iran

### Abstract

**Background and Aim:** Pain control is important for both patients and clinicians in orthodontics. The researchers have used different modalities for this purpose, each having its own advantages and disadvantages. The aim of this study was to compare the efficacy of ketoprofen gum and gel for pain relief after activation of fixed orthodontic appliances.

**Materials and Methods:** In this double-blind controlled randomized clinical trial, 115 patients between 14-29 years who had pain in previous sessions, were randomly divided into three experimental groups of ketoprofen chewing gum, ketoprofen gel and placebo chewing gum. All patients were instructed to use the gum and gel three times daily for three days after activation of fixed orthodontic appliances. Patients recorded their level of pain at two, six and 24 hours and two, three and seven days using a 5-score visual analogue scale (VAS). Two-way and repeated measures ANOVA were used to compare differences in the pain scores among the three groups.

**Results:** Eighty-seven patients (54 women, 33 men) completed the questionnaires. The mean pain score decreased over time in both males and females in all groups ( $P < 0.05$ ). However, repeated measures ANOVA showed significantly lower mean pain score in females ( $P < 0.001$ ). The mean pain score was also slightly (but not significantly) lower in ketoprofen chewing gum group compared to gel and placebo groups ( $P > 0.05$ ).

**Conclusion:** Although ketoprofen chewing gum was more effective for pain relief, this difference did not reach statistical significance. The highest pain score was observed after six hours, and decreased thereafter.

**Key Words:** Orthodontic Appliances, Pain, Ketoprofen, Ketoprofen topical gel, Chewing Gum

✉ Corresponding author:  
F. Dehghani, Postgraduate  
Student, Department of  
Orthodontics, School of  
Dentistry, Hamadan University  
of Medical Sciences, Hamadan,  
Iran

dehghanfateme65@yahoo.com

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### Introduction

Orthodontic patients often experience varying degrees of pain following activation of orthodontic appliances and placement of interdental separators [1]. Pain caused by orthodontic treatment is one of the main reasons for patients discontinuing

treatment [2]. Pain control by orthodontists increases the patient cooperation during orthodontic treatment [3]. No consensus has reached on a standard pain relief protocol for orthodontic patients [2].

Several methods have been recommended for pain

relief including oral administration of non-steroidal anti-inflammatory drugs (NSAIDs), topical use of anesthetic gels, chewing gums or bite wafers, laser therapy and vibratory stimulation [4-7]. However, use of these medications by patients with a history or at risk of cardiovascular disease may have side effects. Also, they may interfere with the anticoagulant activity of aspirin. Elevated liver enzymes have also been reported after taking these medications, since they may cause liver toxicity [8].

Research results in use of anesthetic gels suggest that this method is useful to control pain after orthodontic procedures such as banding, cementation, arch wire ligation and band and bracket removal. Gel application is easy since it is topically applied to the gingival crevice [3]. To increase patient satisfaction, new methods of drug delivery have been introduced such as the use of medicated chewing gums, which is convenient for patients. This method is also suitable for patients with deglutition problem, the children and the elderly [9].

Medicated gums have gained increasing popularity in dentistry. Gums containing potassium chloride are used to treat tooth hyper-sensitivity [10]. Krillaz gum is used to prevent gingivitis and plaque inflammation [11] and gums containing *Salvadora persica* extract [12] and gums containing *Eucalyptus* extract [13] are used for gingival and periodontal health. Due to optimal efficacy, medicated chewing gums have been introduced as an oral hygiene aid along with toothpastes and mouthwashes.

Pain relief may vary depending on the origin. If the origin of pain is ischemia, the pressure must be released to allow blood flow into the compressed area such as the periodontal ligament (PDL). In case of application of light force, repeated chewing of sugar-free gums, plastic wafers located between the teeth or anything similar during the first eight hours after activation of orthodontic appliance may reduce the pain experienced. This method enhances the blood flow to the area under compression and eliminates the metabolic products that stimulate pain receptors [14].

A number of NSAIDs such as ketoprofen have been introduced for pain relief. These drugs have analgesic, antipyretic and anti-inflammatory

effects due to inhibition of prostaglandin synthesis from arachidonic acid. Ketoprofen with the brand names Orudis and Oruvail is one of the NSAIDs that inhibits the formation of leukotrienes and prostaglandins and is highly effective for reducing inflammatory reactions.

Its formulation is 2- (3-Benzophile) propionic acid. It is excreted in the urine with a rate of 60% within 24 hours. Ketoprofen is rapidly absorbed from the gastrointestinal tract and due to rapid absorption, short half-life and rapid removal, the risk of toxic reactions is low [15]. Also, its efficacy for relieving mild to moderate pain has been confirmed [16, 17]. According to a study on the efficacy of single dose ketoprofen for acute pain relief after dental, orthopedic, gynecological and general surgical procedures in adults, ketoprofen is an effective painkiller for acute moderate to severe pain after surgery and the number-needed-to-treat (NNT) of it was calculated to be similar to that of commonly used NSAIDs such as ibuprofen and diclofenac [18].

Considering the increasing demand for orthodontic treatment among patients and high pain complaint following placement of orthodontic appliances, finding an efficient pain reliever is of high clinical significance for orthodontists. In this context, the present study compared the efficacy of ketoprofen gum and ketoprofen gel for reducing pain after the activation of orthodontic appliances.

## Materials and Methods

This study was conducted after obtaining approval from the Ethics Committee of Shahid Beheshti University and registered in the Iranian registry of clinical trials (IRCT2016121916466N5). In this randomized double-blind controlled clinical trial, sample size was calculated to be 85 using the Power and Sample Size Calculation software version 2.1.31 considering  $\alpha=0.05$  and power=80%. Considering the possible dropouts, 115 patients with fixed orthodontic appliances presenting to the Orthodontics Department of Shahid Beheshti University, School of Dentistry and a private clinic in Tehran were evaluated. Patients were selected randomly with an age range of 15-25 years, using a table of random numbers. Patients were randomly divided into three groups (ketoprofen gel, ketoprofen gum and placebo

gum). The inclusion criteria were as follows:

- Reported pain in their previous visits after orthodontic treatment.
- No pain in the teeth and gums at baseline.
- No analgesic intake at baseline and during the study.
- No liver or kidney disease or any other contraindications for using the afore-mentioned drugs.
- Patients at the leveling phase of orthodontic treatment.

Patients who did not complete the questionnaire at any time and those using analgesics other than what was recommended during the study were excluded. Carbomer P 940 (thickening agent), preservative (methyl paraben and propylparaben), glycerin, pH regulators and ketoprofen were used to make ketoprofen gel. It was then loaded into 30g containers and was ready to use. Ketoprofen chewing gum (at a dose of 100 mg ketoprofen per gum) was produced in the laboratory of Research and Development Unit of Mino Company under the supervision of a consulting pharmacist. The chewing gum contained basic gum compounds, sorbitol, xylitol, maltitol, aspartame, acesulfame potassium, mint essence and ketoprofen (Switzerland). The placebo gum had the same flavor and form of packaging as the medicated chewing gum. Patients and researchers who administered the gums among patients were unaware of the type of gum. The statistician who analyzed the data was also unaware of the group allocation of subjects. Patients were randomly divided into three groups receiving ketoprofen gel, ketoprofen gum and placebo gum and were instructed on how to use the gums or apply the gel (every eight hours, for three days). They were asked not to use any other analgesic. Informed consent was obtained from all patients. The study questionnaire included a visual analog scale (VAS) for pain. The patients were asked to fill out the questionnaire at two, six and 24 hours and two, three and seven days (10 a.m. and 6 p.m.) after their visit. Chi square test was used to compare the pain score between males and females. The mean and standard deviation of pain evaluated at different time points were calculated and compared using one-way and repeated measures ANOVA. In order to compare the mean pain score based on

gender, independent sample t-test and repeated measures ANOVA were used).

## Results

The results showed that the mean pain score in ketoprofen gum, ketoprofen gel and placebo gum groups was 0.82, 1.15 and 1.15, respectively (Table 1). However, the mean pain in ketoprofen gum group was lower compared to the other two groups by nearly 50%; this difference was clinically significant; however, repeated measures ANOVA did not show a significant difference. Comparison of pain score at different time points by gender showed that although females initially reported higher pain score, the mean pain was generally lower in females compared to males (0.97 in females and 1.14 in males) (Diagram 1). This difference was statistically significant ( $P < 0.001$ ). Despite clinically significant differences in the mean pain score between ketoprofen gum group and other groups, this difference was not statistically significant ( $P > 0.05$ ).

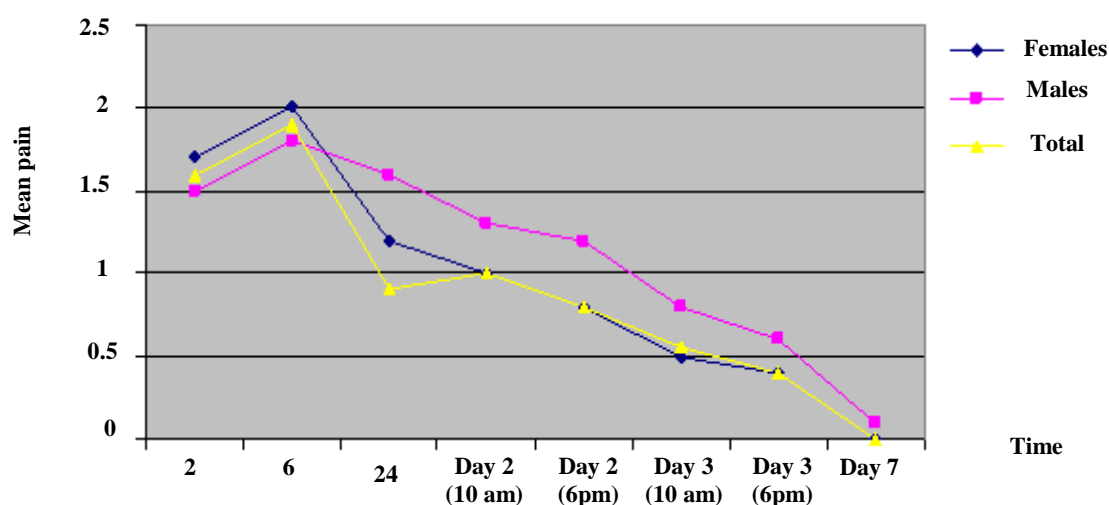
## Discussion

In a study by Eslamian et al, [17] the highest level of pain in the two groups of ketoprofen gel and control gel was noted two hours after applying the gel and its severity decreased over time. When using 5% benzocaine gel, pain severity was the highest during the 6 hours after activation of orthodontic appliance [17].

In a systematic review by Kapoor et al, [19] the level of cytokines after orthodontic force, maximum level of IL-1 $\beta$  released 24 hours after force application and this increase was correlated with increased pain perception. In a study conducted by Ngan et al, [20] the highest level of pain experienced was reported 24 hours after insertion of interdental separator. In the study by Salmasian et al, [21] the pain began three hours after arch wire placement and reached its highest level after 19 hours (next morning). In their study, patients in acetaminophen and ibuprofen groups had less pain than the control group but the difference was not statistically significant. In the study by Murdock and colleagues [22], the pain increased in the first 2 hours and its highest level was noted during sleep at the first day. In the

**Table 1.** Mean and standard deviation of minimum and maximum pain score reported by 87 subjects studied at 8 time points

--	Standard deviation	Mean	Maximum	Minimum
After 2 hours	1.12	1.64	4	0
After 6 hours	1.14	1.93	4	0
24 hours later	1.13	1.39	4	0
The second day 10 a.m.	1.03	1.13	4	0
The second day 6 p.m.	1.06	0.96	4	0
On the third day, 10 a.m.	0.82	0.67	3	0
On the third day, 6 p.m.	0.85	0.48	4	0
Seventh day	0.45	0.07	3	0

**Diagram 1.** Mean pain score at different time points according to gender

current study, the highest level of pain was after six hours, and then it had a descending trend and on the seventh day, most patients had no pain. Difference between the results of the afore-mentioned study and ours can be due to different methods of pain assessment and different analgesic drugs. Murdock and colleagues [22] compared over the counter analgesics and bite wafer and reported the same level of pain in both groups, although the pain score in the bite wafer group was lower than that in the over the counter analgesic group. They recommended bite wafer as an alternative to analgesics for pain control after orthodontic treatment. According to Eslamian and colleagues [17], ketoprofen gel had more analgesic

effect than the control group and benzocaine gel group. The difference with the control group was statistically significant. The highest pain was observed in the control group and the lowest pain was noted in use of ketoprofen gel. According to Patel and colleagues [23], ibuprofen was superior to placebo in reducing pain after insertion of the separator, while acetaminophen and naproxen sodium were not significantly different from the placebo.

Bruno et al. [24] investigated the effects of single dose lumiracoxib. No significant differences were observed among the three groups (drug, placebo and no intervention group); however, the pain score was lower in those who received the drug.

The results of their study did not support the use of single dose lumiracoxib [24]. Otasevic and colleagues [25] concluded that although the pain levels reported by orthodontic patients varied, higher level of pain was observed in patients treated with bite wafer than those who had less chewing activity after insertion of fixed orthodontic appliance. In their study, the highest pain level in bite wafer group was at the end of the first day. They found no statistically significant difference between males and females.

According to Polat and Karaman [26], pain began two hours after bonding and the highest level of pain was reported during sleep and 24 hours after insertion of arch wire. For all parameters except for pain while chewing, pain index score two hours after bonding was significantly less than that in the placebo group. Prescribing analgesics before the treatment successfully eliminated orthodontic pain within two hours.

Lauritano and colleagues [27] showed that ketoprofen solution had a significant effect on reducing pain caused by orthodontic treatment. Based on the VAS as well as the judgment of patients, the effectiveness of ketoprofen was significantly higher than benzocaine hydrochloride. They concluded that the analgesic effects of oral ketoprofen lysinate solution were achieved faster and were more persistent. Both analgesic drugs used in the two groups were well tolerated. Concentration of ketoprofen solution in their study was 160 mg per 100 mL, which may explain optimal analgesic efficacy of ketoprofen. In a study conducted by Hwang and colleagues [28], 55.4% of patients believed that chewing Thera bite wafer was effective for reducing orthodontic pain [28]. Eslamian and colleagues [17] concluded that ketoprofen gel had significantly better efficacy than the placebo gel, but in our study, the efficacy of ketoprofen gel was similar to the placebo gum. In our study, the pain score had a descending trend in all groups over time. Similar efficacy of control gum and

ketoprofen gel suggests that chewing gum alone without any analgesic drug can also be effective in reducing orthodontic pain. This has also been reported by Proffit [14], Hwang and colleagues [28] and Murdock et al [22].

In our study, no side effects were reported in ketoprofen gum group and only two patients were not able to use the gum due to extreme pain. Overall, patients were satisfied with the medicated chewing gum due to its convenience. In ketoprofen gel group, one patient reported that because of dry mouth after using the gel, he only used the gel for one day. Pain was relieved for a limited time in two other patients after using the gel. They had pain until they reapplied the gel. This is probably due to inefficacy or inadequate amount of gel used. In this study, we tried our best to control for the confounding variables. For this purpose, all patients were in the same stage of treatment, and the dosage of gel and gum was the same for all patients. Also, they were given necessary instructions on how to use the VAS. Use of VAS increases the accuracy of the findings and generalizability of the results. Difficulties in obtaining the ketoprofen drug and limited number of studies about ketoprofen and its application were among the limitations of the present study.

## Conclusion

According to this study, ketoprofen gum had higher analgesic effect compared to ketoprofen gel and control gum groups; these differences were clinically significant but statistically insignificant. The mean pain score in the control gum and ketoprofen gel groups was the same, which indicates that chewing gum can be an alternative to pharmaceutical therapy for orthodontic pain relief. The highest level of pain in all groups was noted at six hours after the visit and use of chewing gum and gel and then the pain decreased in most patients and reached zero on the seventh day.

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