Original Article

Efficacy of Ketoprofen and Benzocaine Chewing Gums for Reducing Orthodontic Pain

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Abstract

Background and Aim: Pain relief is important during orthodontic treatment. The aim of this study was to compare the efficacy of ketoprofen and benzocaine chewing gums for pain reduction during fixed orthodontic treatment.

Materials and Methods: Thirty patients aged 15-25 years experiencing orthodontic pain were randomly divided into 3 groups, each receiving one of the experimental chewing gums namely ketoprofen, benzocaine and the placebo. Instructions were given to the patients and they received the gums taking into account the washout period.
Patients recorded their degree of pain perception at 2, 6 and 24 hours, and 2, 3 and 7 days using the visual analog scale (0-100). Friedman and Wilcoxon tests were used to compare the mean pain scores among the 3 groups.

Results: The mean pain score decreased over time in both genders and all groups (p=0.017). The mean pain score recorded in benzocaine group was lower than that in the ketoprofen and placebo groups but a significant difference was only observed between benzocaine and the ketoprofen groups during the first two hours using Friedman and Wilcoxon tests (p=0.042). Compared to the control group, both ketoprofen and benzocaine chewing gums significantly decreased pain at all time points except for day 7.

Conclusion: Ketoprofen and benzocaine gums were both significantly effective for orthodontic pain reduction.

Key Words: Pain, Orthodontic tooth movement, Ketoprofen, Benzocaine

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Introduction

Orthodontic patients experience various degrees of pain for 2-4 days following activation of fixed orthodontic appliances. Orthodontic pain is among the most common complaints of patients receiving orthodontic treatment [1]. Pain is an important aspect of oral health-related quality of life (OHRQOL). Moreover, orthodontic pain prevents accurate plaque control by the patient during the treatment course and has a negative impact on oral hygiene maintenance. Also, it is an important reason for not showing up for dental visits [2]. Orthodontic pain negatively affects the overall patient satisfaction of the outcome of treatment [3]. By prevention and control of pain, orthodontists may be able to increase patient cooperation during the course of treatment [4]. The pain mechanism due to orthodontic tooth movement has yet to be fully understood; however, it appears that application of orthodontic forces to teeth triggers

the release of inflammatory mediators like prostaglandins and initiates proinflammatory reactions. Prostaglandins are considered as mediators of tooth movement; but they also increase the transmission of painful stimuli and cause pain [5].

Despite extensive studies on this topic, no standard protocol for use of analgesics is available for orthodontic pain control. Orthodontists often recommend patients to simply take analgesics in case of pain [2].

Chewing gums, topical analgesic gels, bite wafer, mucosal patches, transcutaneous electrical nerve stimulation, low dose laser and vibration stimulation are among the available topical pain control measures [6-10]. Chewing gums or using plastic wafer have been recommended for pain control in the first hours following activation [11]. This method often provides a high level of comfort and satisfaction for patients.

In the past decades, some new non-steroidal anti-inflammatory drugs (NSAIDs) like ketoprofen were introduced as suitable alternatives to topical analgesics. Efficacy of ketoprofen for alleviation of mild to moderate pain has been confirmed [12]. It is rapidly absorbed from the gastrointestinal tract and due to its fast absorption, short half-life and quick excretion, it has minimal toxicity [13].

Benzocaine is a topical ester analgesic [14] with topical application only. It has low potency and low systemic toxicity with an efficacy lower than that of lidocaine [15]. It is superior to NSAIDs in that it has no negative effect on orthodontic tooth movement, has no drug interference and insignificant systemic effects since its efficacy is limited to the site of pain [16]. Considering the high demand for orthodontic treatment and patient complaints of pain due to fixed orthodontic appliances, pain reduction is an important topic that needs to be addressed. This study aimed to compare the efficacy of ketoprofen and benzocaine chewing gums for orthodontic pain reduction.

Materials and Methods

In this double blind controlled clinical trial (IRCT2014041416466N3), sample size was calculated to be 27 subjects using Power and Sample Size Calculation software version 2.1.31 considering the standard deviation of 1.1 for pain reduction, $\alpha=0.05$, power=80%, $Z\alpha=1.96$ and $Z\beta=0.48$ via the formula:

$$N=3\ \frac{\delta(Z\alpha+Z\beta)^2}{(\mu_1-\mu_2)}$$

Considering possible dropouts, 30 fixed orthodontic patients presenting to the Orthodontics Department of Shahid Beheshti University, School of Dentistry and a private clinic in Tehran were evaluated. Patients were randomly selected among male and female subjects in the age range of 15-25 years and randomly received ketoprofen, benzocaine or the placebo chewing gums for three time intervals.

Thirty patients were randomly divided into three groups of 10 and each group received ketoprofen, benzocaine or the placebo chewing gums at three time intervals with consideration of washout period. Considering the crossover design of this study, all patients received all three chewing gums. Considering the subjective nature of pain, crossover design was chosen to minimize errors.

The inclusion criteria were: no pain at the onset of study, complaint of pain over 50 based on the VAS in previous sessions, 6-8mm crowding, no use of analgesics during the study period, no history of renal or river disease or any other contraindication for the use of understudy medications.

Ketoprofen chewing gums were manufactured in the laboratory of Minoo Company, Iran under the supervision of a consulting pharmacist. Chewing gum basic ingredients such as sorbitol, xylitol, maltitol, aspartame, Acesulfame potassium, and eucalyptus essence were used. Ketoprofen and benzocaine were purchased from Switzerland and added to the chewing gums. The placebo chewing gum was manufactured with the same shape and packaging as the experimental gums. Patients and those administering the gums among patients were blinded to the type of chewing gums and questionnaires were analyzed by a statistician blinded to the group allocation of patients.

Patients randomly received one of the three chewing gums and received instructions on the method and frequency of consumption (every eight hours for three days). The patients were asked not

to take any other analgesics.
The VAS questionnaire had a 0-100 scale The VAS questionnaire had a 0-100 scale as follows:
0: No pain
50: Moderate pain
100: Severe pain
Patients were asked to fill out the questionnaire at 2, 6 and 24 hours, and 2, 3 (10 a.m. and 6 p.m.) and 7 days after the visit. Written informed consents were obtained from all patients. Those not signing the consent form were excluded. Considering the washout period and the mean interval of 4 weeks between sessions, all patients received all three types of interventions. Normal distribution of data was tested using Kolmogorov Smirnov test. Due to non-normal distribution of data ($p>0.0001$), Friedman non-parametric test was used to compare pain scores among the groups. Wilcoxon Signed Rank test was used for pairwise comparison of groups. The mean and SD of pain score at different time points for the three groups were calculated and reported in a diagram. Type one error (α) was considered as 0.05 and type two error (β) ≤ 0.05 was considered statistically significant.

Results

Sample size was calculated to be 27 patients. Considering possible dropouts, 30 patients under fixed orthodontic treatment who complained of pain in the previous sessions were selected; out of which, 26 remained until the end of the study including 12 males and 14 females with a mean age of 18.07±3.19 years (range 15-25). In all groups, the mean pain score was the lowest on day 7 and the highest at 6 hours after the activation of appliance (Table 1). Over time, the mean pain score decreased in both sexes and in all three groups and this reduction was statistically significant ($p=0.017$). The mean pain score in females was higher than that in males (36.48 in females versus 31.24 in males). However, this difference according to independent sample t-test was not significant. The mean pain score at 6 hours post consumption was the highest in the two experimental groups; but decreased afterwards. The pattern of pain reduction in both genders after the first 6 hours was similar. The only difference between males and females was in level of pain within the first two hours when males experienced the highest level of pain (Diagram 1 and Table 2).
Statistical analysis of pain score according to VAS revealed that the mean pain score was 29.72 in ketoprofen group, 23.99 in benzocaine group and 47.89 in the placebo group. Although the mean pain score in benzocaine group was lower than that in the remaining two groups, this difference was only significant in the first two hours according to Friedman and Wilcoxon Signed Rank test ($p=0.042$). But, ketoprofen and benzocaine caused significantly greater analgesia than the placebo at all time points except for day 7.
Benzocaine chewing gum showed higher analgesic efficacy than ketoprofen and the placebo; but statistically, this difference between benzocaine and ketoprofen only at the first two hours was significant and both benzocaine and ketoprofen had significantly higher analgesic efficacy than the placebo at all time points except for day 7.
Moreover, the highest pain score was observed at 6 hours post activation while the lowest was reported at 7 days following activation of fixed orthodontic appliances (Diagram 2).

Discussion

This study compared the analgesic efficacy of benzocaine and ketoprofen chewing gums (manufactured by Minoo Company) following the activation of fixed orthodontic appliances using VAS at 2, 6 and 24 hours and 2, 3 (10 a.m. and 6 p.m.) and 7 days. Six-hour time intervals were selected according to previous studies by Eslamian et al, [9, 10] and also according to the recommendation of manufacturers of commercially available benzocaine sprays (Americaine, Heritage Brands Insight Pharmaceuticals Corp. USA) in order to decrease side effects and increase patient cooperation. The three-day time intervals were selected because maximum orthodontic pain had been reported in the first 2-4 days [17]. The current study results demonstrated that the mean pain score in benzocaine group was lower than that in the other two groups. However, only the difference between benzocaine and ketoprofen at the first two hours was statistically significant. Ketoprofen and benzocaine had significantly higher efficacy than the control group at all time points (except for day 7).

Comparison of pain score at different time points based on gender revealed that the mean pain score at all time points in the two groups of ketoprofen and benzocaine was higher in females compared to males. But, in the placebo group, males experienced higher level of pain than females in the first day. From day 2 on, the mean score of pain in men was lower than that in women. However, overall, the association between gender and the mean pain score was not significant. It should be noted that all patients reported a mean pain score of over 60 at the onset of study.

Table 1. The mean and SD of the highest and lowest pain scores reported by the 26 subjects in three groups at eight time points

Group	Time	Minimum	Maximum	Mean	SD
Ketoprofen	At 2 hours	0	90	51/15	31/41
	At 6 hours	0	90	52/88	24/09
	At 24 hours	0	85	43/07	23/75
	At day 2 (10 a.m.)	0	85	31/15	22/68
	At day 2 (6 p.m.)	0	85	25/96	22/62
	At day 3 (10 a.m.)	0	60	18/84	17/56
	At day 3 (6 p.m.)	0	40	11/92	12/49
	At day 7	0	35	4/03	8/1
Benzocaine	At 2 hours	0	85	38/84	27/39
	At 6 hours	5	95	45/38	26/71
	At 24 hours	0	80	36/15	20/01
	At day 2 (10 a.m.)	0	70	22/88	18/61
	At day 2 (6 p.m.)	0	65	20	19/13
	At day 3 (10 a.m.)	0	55	15/57	18/01
	At day 3 (6 p.m.)	0	45	10/96	13/85
	At day 7	0	40	5/38	11/74
Control	At 2 hours	40	100	73/84	17/22
	At 6 hours	30	100	73/07	16
	At 24 hours	30	100	62/88	18/77
	At day 2 (10 a.m.)	25	100	52/88	20/98
	At day 2 (6 p.m.)	10	100	45/38	24/93
	At day 3 (10 a.m.)	0	95	37/88	27/50
	At day 3 (6 p.m.)	0	95	28/65	25/12
	At day 7	0	70	8/84	17/16

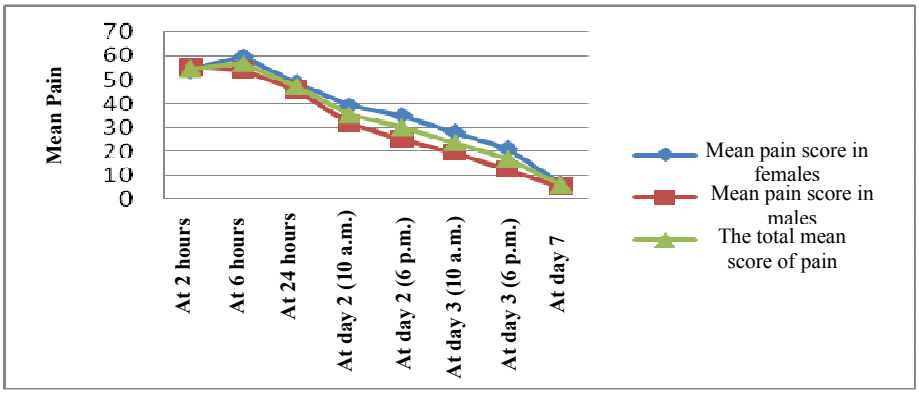

Diagram 1. The mean pain score at the understudy time points in males and females

Table 2. The mean pain score in groups and at eight time points

Group / Time	At 2 hours	At 6 hours	At 24 hours	At day 2 (10 a.m.)	At day 2 (6 p.m.)	At day 3 (10a.m.)	At day 3 (6 p.m.)	At day 7
Ketoprofen	51/22	52/62	43/04	30/92	25/68	18/60	11/67	4/02
Benzocaine	38/90	44/82	35/68	22/26	19/43	15/03	10/60	5/24
Placebo	73/93	73/30	63/10	52/89	45/09	37/68	28/27	8/87
Total	54/68	56/91	47/27	35/35	30/06	23/77	16/84	6/04

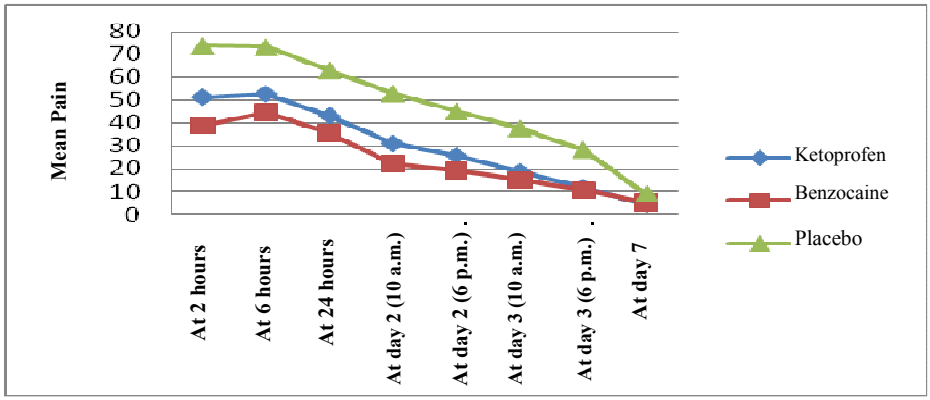

Diagram 2. The mean pain score at different time points in the three groups

Considering the pain score of 47.89 in the control group, it can be concluded that chewing per se may decrease pain; which is in accord with the results of Profit [11]. Also, the highest mean pain score was observed within the first 6 hours post activation and the lowest was reported at 7 days later. The variation in pain scores reported by patients was high in the current study. The multifactorial and subjective nature of pain can contribute to the lack of significant difference among groups.

Reports on the effects of age and gender of orthodontic patients on level of pain perception are controversial. Many studies found no significant association between gender and pain score [6]; our findings confirm this lack of correlation as well.

In our study, level of pain was the highest at 6 hours post activation and after that, the pain score decreased and reached its lowest level on day 7. This finding is in line with the result of Eslamian et al. In their study, the highest level of pain was reported at two hours after the application of placebo and ketoprofen gel; over time, level of pain decreased. In the group using 5% benzocaine gel, level of pain was the highest at 6 hours following the activation of fixed orthodontic appliance.

In contrast to the results of the current study, Murdock et al, [18] and Karaman and Polat [19] reported that pain increased at 2 hours post - bonding and reached the highest level at the first night. In the study by Salmasian et al, [20] on three study groups, pain initiated three hours after the placement of arch wire and reached its maximum level at 19 hours (next morning). Although level of pain was lower in acetaminophen and ibuprofen groups compared to controls, this difference was not statistically significant. Such difference in results may be attributed to the different method of pain assessment and type of analgesics used.

Lauritano et al [21]. Demonstrated that ketoprofen solution significantly decreased orthodontic pain. Based on VAS and patient's opinion, ketoprofen was significantly more effective than benzocaine hydrochloride. They concluded that the analgesic effect of oral ketoprofen lysinate started sooner and lasted longer than that of benzocaine. Also, both analgesics were well tolerated. Higher efficacy of ketoprofen in their study was in

contrast to our finding and may be due to its higher concentration (160 mg/100 ml) in their study.

Eslamian et al, in their study reported that ketoprofen gel had superior analgesic efficacy than the control and benzocaine gel groups. Also, ketoprofen and benzocaine gels had higher efficacy than the placebo and this difference was statistically significant; which confirms our findings. The highest pain score was observed in the control group and the lowest in ketoprofen gel group. Lower efficacy of benzocaine gel may be attributed to its low percentage (5%). The dosage of ketoprofen in their study was higher than that in the current investigation (160 mg versus 75 mg). Dosage of benzocaine in their study was lower than that in the current one (5% versus 20%). Thus, since in the study by Eslamian et al, the efficacy of ketoprofen was reported to be higher than that of benzocaine, it can be concluded that the efficacy of both drugs is dose-dependent. It should be noted that several factors play a role in perception of pain. These factors affect the results and may explain differences in the results of studies. Age, gender, duration of chewing gum, the time interval between chewing two gums, type of analgesic drug, treatments performed between the interventions, type of placebo material used, method of pain measurement and patient's psychological status can all affect the results in this regard.

Conclusion

Based on the results, benzocaine chewing gum had higher analgesic efficacy than ketoprofen and the placebo gums. However, this difference only with the ketoprofen group at the first 2 hours was statistically significant. Both ketoprofen and benzocaine showed significant differences in pain scores with the control group at all time points except for day 7. In all groups, the highest level of pain was reported at the first 6 hours following the visit and chewing gums and decreased afterwards. The pain score reached zero in most patients at day 7.

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