The effect of benzocaine and ketoprofen gels on pain during fixed orthodontic appliance treatment: a randomised, double-blind, crossover trial

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Aims: To compare the analgesic effect of topical benzocaine (5%) and ketoprofen (1.60 mg/mL) after 2 mm activation of 7 mm long delta loops used for maxillary en-masse orthodontic space closure.

Subjects and methods: Twenty patients (seven males, 13 females, 15–25 years of age, mean age of 19.5 years) participated in a randomised crossover, double-blind trial. After appliance activation, participants were instructed to use analgesic gels and record pain perception at 2, 6, 24 hours and 2, 3 and 7 days (at 18.00 hrs), using a visual analogue scale ruler (VAS, 0–4). Each patient received all three gels (benzocaine, ketoprofen, and a control (placebo)) randomly, but at three different appliance activation visits following a wash-over gap of one month. After the first day, the patients were instructed to repeat gel application twice a day at 10:00 and 18:00 hrs for three days. The recorded pain scores were subjected to non-parametric analysis.

Results: The highest pain was recorded at 2 and 6 hours. Pain scores were significantly different between the three groups (Kruskal–Wallis test, \( p < 0.01 \)). The overall mean (SD) pain scores for the benzocaine 5%, ketoprofen, and control (placebo) groups were 0.89 (0.41), 0.68 (0.34), and 1.15 (0.81), respectively. The pain scores were significantly different between the ketoprofen and control groups (mean difference = 0.47, \( p = 0.005 \)). All groups demonstrated significant differences in pain scores at the six different time intervals (\( p < 0.05 \)) and there was no gender difference (\( p > 0.05 \)).

Conclusion: A significant pain reduction was observed following the use of ketoprofen when tested against a control gel (placebo). The highest pain scores were experienced in patients administered the placebo and the lowest scores in patients who applied ketoprofen gel. Benzocaine had an effect mid-way between ketoprofen and the placebo. The highest pain scores were recorded 2 hours following force application, which decreased to the lowest scores after 7 days.

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Introduction

Following the activation of orthodontic appliances, patients may experience pain and discomfort. Pain is the most frequent complaint of orthodontic patients\(^1\) and considered as the contributory factor to a patient’s refusal to accept orthodontic treatment.\(^1\) Many studies have found that pain following separator or archwire placement starts within four hours, continues until at least 24 hours, and dissipates by day seven.\(^1,7\) The disruption of the
periodontal tissues following the application of an orthodontic force leads to the initiation of a cascade of events involving the release of inflammatory mediators into the local environment and pain perception. However, the exact mechanism of pain related to orthodontic treatment is not clearly understood.

A number of strategies have been proposed to reduce orthodontic pain, including the oral administration of non-steroidal anti-inflammatory drugs (NSAIDs), chewing gum or a bite wafer and topical anaesthesia gel application.

Topical anaesthesia is commonly used in clinical dentistry to reduce the discomfort of local anaesthetic administration and for minor intra-oral operative procedures such as periodontal scaling and root planning, gingival manipulation, biopsy, dentinal/pulpal anaesthesia, as well as extractions, the reduction of patient anxiety or, recently, for the placement of orthodontic TADs. Benzocaine has also been used to relieve oral mucosal pain caused by orthodontic appliances. So far, other orthodontic pain reduction methods such as transcutaneous electrical nerve stimulation, low-level laser therapy and vibratory stimulation have not gained clinical popularity.

Although oral NSAIDs are effective in the treatment of acute and chronic pain conditions, their use may be associated with systemic side effects, particularly gastrointestinal disorders. In order to minimise the incidence of related systemic events, topical NSAIDs have been developed. Topical NSAIDs are applied as gels, creams or sprays that penetrate the skin, subcutaneous fatty tissue and muscle in amounts that are sufficient to exert a therapeutic effect on peripheral and central mechanisms in the absence of high plasma concentrations. Data indicate that, for instance, topical Ketoprofen is effective at relieving pain in a number of acute and chronic pain situations.

Ketoprofen is a non-steroidal anti-inflammatory drug and a derivative of propionic acid which inhibits aspects of the prostaglandin/leukotriene pathway to reduce inflammatory reactions. The rapid absorption, short plasma half-life, and equally rapid elimination of ketoprofen reduce the toxic build-up of the drug. The efficacy of ketoprofen has been approved for mild to moderate pain.

A literature search revealed few studies that investigated the effect of orthodontic pain. The use of benzocaine for orthodontic patients is limited to the assessment of pain caused by orthodontic separators or the use of benzocaine wax at relatively high doses (20%). Furthermore, most orthodontic studies have assessed pain levels at the start or after the placement of orthodontic separators. The aim of this prospective, randomised, double-blind study with a crossover design was therefore to assess the pain experienced during fixed appliance treatment in a control group compared with patients treated with topical ketoprofen or benzocaine (5%) gels. The pain was generated by the activation of stainless steel looped archwires used for the retraction of anterior maxillary teeth or space closure as part of an orthodontic treatment program.

**Null hypothesis**

The tested hypothesis was that there was no difference in the recorded orthodontic pain perceptions of a control group, a group treated with topical anaesthetic gel (benzocaine) and a group treated with an anti-inflammatory gel (ketoprofen).

**Subjects and methods**

**Sample size calculation**

In order to detect a mean pain score difference of 1 point between any two groups, with a standard deviation of 1.1, \( \alpha = 0.05 \), and power \( (1 - \beta) = 80\% \), \( Z_{\alpha} = 1.96 \), \( Z_{\beta} = 0.84 \), an approximate sample size was calculated to be 30 subjects.

**Study sample**

After approval by the ethics committee of the Shahid Beheshti University of Medical Sciences, Faculty of Dentistry, 30 patients were enrolled in this randomised double-blind, crossover trial. Patients underwent fixed orthodontic therapy but 10 were ultimately excluded due to miscellaneous protocol violations or unwillingness to participate. Of the remaining 20 participants, 13 were females and 7 were males. The age range of the patients was 15–25 years (mean age = 19.5 years). All patients had their first maxillary premolars extracted and were in the stage of en-masse anterior retraction with a 0.018 \( \times \) 0.025” stainless steel, looped archwire in a 0.022”– slot edgewise system. Identical stainless steel, looped...
archwires with a 7 mm long delta loop designed for the en-masse anterior retraction were prepared for use. The study recruitment protocol is shown in a CONSORT style diagram (Figure 1).47 Participants also met the following criteria:

- An absence of pain in the oral cavity (tooth or gingiva) at the time of inclusion in the study.
- No consumption of analgesics before the procedure, which could potentially interfere with the medications.
- No consumption of medications with contraindications related to the drugs used.
- All individuals had a positive history of pain or discomfort after orthodontic appliance activation.

**Study design and assessment of pain perception**

The current prospective, randomised study used a crossover design during which each patient received the three gels at different time periods. By the use of a random number table, each patient was prescribed one of the three gels for the next three appointments. On the initial visit, informed consent was obtained and the patients were provided with a tube containing ketoprofen, benzocaine or a control (placebo) gel, plus a visual analogue questionnaire. After a 2 mm activation of the 0.018 × 0.025” looped archwire, the patients were instructed by a trained dental nurse on gel application to the gingiva (buccally and palatally) and the coronal aspect of the teeth and to subsequently complete a questionnaire. The same nurse conducted the crossover under the supervision of the clinician, who was unaware of the content of the gel tubes.

**Assessment of Pain**

The study questionnaire comprised a visual analogue scale (VAS) horizontally graded from 0–4.48 The patients were instructed to evaluate their orthodontic pain and choose an appropriate number at two, six, and 24 hours after archwire placement. After the first day, the patients were instructed to repeat the

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**Figures 1.** CONSORT type diagram showing the flow of subjects through the trial.
application of the gel twice a day at 10:00 and 18:00 hours for three days. The pain was again recorded at 18:00 hours on days two, three and seven using the VAS ruler.

At subsequent visits (two more visits with a one month wash-over interval), the 0.018 × 0.025” looped archwire was activated by a further 2 mm. The patients received a new tube of gel (of different prescription, but with the same instructions for use) and the VAS questionnaire. The content of the gel tubes provided to the patients at each appointment was different from those received previously and governed by the randomisation. The colour and odour of all gels were identical and the tubes were not labelled, to make them indistinguishable to the patients and clinician. The patients were advised not to use other pain-relieving medication apart from the provided gel tubes. If the pain was too severe, patients were given the option of leaving the study and employing alternative medications. Ten patients failed to complete the questionnaire or adhere to instructions and were therefore excluded from the investigation.

**Preparation of the materials used in the study**

The ketoprofen (1.60 mg/mL), benzocaine (5%), and control (placebo) gels were manufactured in the laboratory of the Pharmacy School of Shahid Beheshti University of Medical Sciences. The gels contained the following ingredients: Gel maker material of 934 (Carbomer 934P) (50 g) as the gelling agent, methylparaben (5 g) and propylparaben (1 g) as the preservatives, glycerine as a humectant (400 mL), sodium hydroxide as the pH adjusting agent (pH = 6), ketoprofen (250 g) or benzocaine (200 g), and enough ethanol as the co-solvent, as well as distilled water to reach the desired concentration of ketoprofen (1.60 mg/mL) or benzocaine (5%). As gel samples had an alcoholic odour due to the inclusion of ethanol, orange essence was added as a flavouring agent to mask the smell and improve the taste. After manufacture, the gels were filled in 90 identical tubes of 20 g each (30 tubes for each gel, Razak Company, Tehran, Iran).

**Statistical analysis**

The mean, standard deviation (SD) of the pain severity scores as well as the mean pain rank were measured for each gel and for all observations at the six time intervals. The mean pain rank (VAS scores) was evaluated using the nonparametric tests for overall differences between the three gels and for each gel to compare pain perception at the six time intervals. Similarly, the 95% confidence interval of mean VAS pain ranks at the six time intervals, as well as post-hoc test was used for paired comparisons between the control gel and the experimental gels. A $p < 0.05$ level was considered as statistically significant.

**Results**

**VAS pain scores for all groups**

There was no significant gender differences in the recorded VAS pain scores ($p > 0.05$). No harmful or unintended effects were noted. The assessment of recorded pain VAS scores showed statistically significant differences (Kruskal-Wallis, Chi-square = 12.684, df = 2, $p = 0.002$) between ketoprofen, benzocaine and the control (placebo) gels. The mean pain rank for benzocaine 5%, ketoprofen and the control (placebo) gels was 182.19, 157.50, and 201.8, respectively. The corresponding mean (SD) values of pain scores were 0.89 (0.41), 0.68 (0.34), and 1.15 (0.81). The post-hoc multiple comparison tests indicated significant differences between ketoprofen and the control (placebo) gels only (mean VAS pain difference = 0.47, $p = 0.005$). Therefore, the null hypothesis for this study was partially rejected. Overall, there were statistically significant differences (Chi-square = 117.741, df = 5, $p = 0.0001$) in the VAS pain scores for all gels at the six time intervals of the experiment. The mean pain rank for two, six and 24 hours and two, three, and seven days were 251.63, 236.01, 211.56, 149.44, 127.43 and 106.63, respectively. The mean (SD) values of the recorded pain scores were 1.75 (0.67), 1.55 (0.51), 1.2 (0.47), 0.5 (0.31), 0.32 (0.21) and 0.13 (0.1) at two, six, and 24 hours, and on two, three and seven days, respectively. Overall, there was a steady reduction in recorded pain intensity over the seven day evaluation period.

**The comparison between ketoprofen, benzocaine and control (placebo) gels**

Significant differences (Chi-square = 47.638, df = 5, $p = 0.0001$) were noted in the VAS pain scores at the six time intervals for the group that used benzocaine gel. Similar findings were observed for ketoprofen (Chi-square = 45.623, df = 5, $p = 0.0001$) and the
control (placebo) groups (Chi-square = 39.726, df = 5, \( p = 0.0001 \)). Table I shows the findings of the post-hoc multiple comparisons for the three gels at the different time intervals.

A comparison of the pain scores for the three groups and six studied time periods by the Kruskal-Wallis test (Table II) revealed that significant differences were present at 24 hours (\( p = 0.01 \)) and at day two (\( p = 0.04 \)). The post-hoc tests demonstrated significant differences between the ketoprofen and benzocaine gels at 24 hours (\( p < 0.05 \)) and between the ketoprofen and control (placebo) gel on day two (\( p < 0.05 \)). No other statistically significant differences were noted.

### Table I.

The mean difference of VAS pain scores and corresponding \( p \) values of the post-hoc multiple comparison tests for three gels at different time intervals.

| Time intervals | Mean pain score diff., benzocaine | \( p \) value | Mean pain score diff., ketoprofen | \( p \) value | Mean pain score diff., placebo | \( p \) value |
|----------------|----------------------------------|--------------|----------------------------------|--------------|-------------------------------|--------------|
| 2 hrs          | 0.2                              | 1            | 0.25                             | 1            | 0.55                          | 0.94         |
| 2 hrs          | 0.05                             | 1            | 0.95                             | 0.18         | 0.64                          | 0.71         |
| 2 hrs          | 1.15                             | 0.03         | 1.35                             | 0.004        | 1.4                           | 0.003        |
| 2 hrs          | 1.35                             | 0.001        | 1.55                             | 0.001        | 1.95                          | 0.0001       |
| 6 hrs          | 0.25                             | 1            | 0.7                              | 0.62         | 0.1                           | 1            |
| 6 hrs          | 1.2                              | 0.002        | 1.1                              | 0.03         | 0.85                          | 0.27         |
| 6 hrs          | 1.35                             | 0.001        | 1.15                             | 0.02         | 1.2                           | 0.02         |
| 6 hrs          | 1.55                             | 0.0001       | 1.30                             | 0.006        | 1.4                           | 0.003        |
| 24 hrs         | 0.95                             | 0.009        | 0.4                              | 0.82         | 0.75                          | 0.25         |
| 24 hrs         | 1.1                              | 0.002        | 0.45                             | 0.67         | 1.1                           | 0.007        |
| 24 hrs         | 1.3                              | 0.0001       | 0.60                             | 0.18         | 1.3                           | 0.001        |
| Day 2          | 0.15                             | 1            | 0.05                             | 1            | 0.35                          | 0.86         |
| Day 2          | 0.35                             | 0.32         | 0.2                              | 0.86         | 0.55                          | 0.18         |
| Day 3          | 0.2                              | 0.96         | 0.15                             | 0.97         | 0.2                           | 0.97         |

### Table II.

The mean pain ranks (95% Confidence Interval) for three gels at the six studied time intervals.

| Time intervals | Benzocaine 5% | Ketoprofen | Placebo | \( df \) | Chi-square | \( p \) value |
|----------------|---------------|------------|---------|----------|------------|--------------|
| 2 hours        | 26.63 (21.05–28.54) | 28.03 (25.98–30.98) | 36.85 (33.14–39.18) | 2 | 4.316 | 0.12 |
| 6 hours        | 32.70 (28.98–34.57) | 26.80 (24.98–28.17) | 32.00 (28.19–35.17) | 2 | 1.446 | 0.49 |
| 24 hours       | 34.00 (31.25–36.78) | 21.58 (18.95–23.18) | 35.93 (32.25–38.78) | 2 | 8.652 | 0.01 |
| Day 2          | 30.08 (27.54–33.05) | 24.58 (21.74–26.55) | 36.85 (33.14–39.45) | 2 | 6.592 | 0.04 |
| Day 3          | 29.35 (27.54–32.99) | 27.58 (25.01–29.88) | 34.58 (31.45–38.18) | 2 | 3.037 | 0.22 |
| Day 7          | 29.50 (26.87–33.02) | 28.00 (25.87–31.02) | 34.00 (31.25–37.17) | 2 | 3.688 | 0.16 |

Mean and standard deviation of pain severity was measured for each gel at the six time intervals. The assessment of pain intensity by Kruskal-Wallis test indicated that statistically significant differences (\( p = 0.002 \)) were found in the VAS scores among ketoprofen, benzocaine and placebo gels. Post-hoc multiple comparison tests (Table I) were then utilised to explore the significant difference between paired groups, which indicated significant differences (\( p = 0.005 \)) between ketoprofen and placebo gels.
The mean pain intensity for the three gels at the six studied time periods is shown in Figure 2.

Discussion

The onset, duration, and intensity of orthodontic pain were assessed in the present crossover, randomised, clinical trial. Pain during orthodontic treatment is known to negatively affect compliance.1,2,7,49,50 Previous orthodontic pain studies assessed pain levels at the start or after the placement of orthodontic separators1-7 as the most severe pain can be felt following bracket bonding and archwire attachment. The design of the present study allowed the assessment of the effectiveness of topical ketoprofen and benzocaine (5%) in reducing pain produced by the activation of stainless steel looped archwires, used for the retraction of maxillary anterior teeth. Similar to previous studies which assessed pain at the start of treatment,1-7 the present study noted the highest pain level in all groups within the first two hours of appliance activation.

It was confirmed that activation of the archwire without any medicament leads to discomfort and pain.1,3,6,7,49 It was also indicated that the application of ketoprofen gel led to less pain experience following the activation of an archwire for en-masse anterior retraction than benzocaine 5% gel. It should be noted that the benzocaine concentration (5%) was considerably lower than the reported figures (20%) in previous studies,17,23,34-36 but still effective in reducing the orthodontic pain.

The evaluation of pain at the various time intervals showed that the benzocaine 5% gel was an efficient medicament for pain suppression. However, this advantage did not last long and the pain intensity recorded at six hours co-incided with that of the control (placebo) group. Ketoprofen showed a continuous downward trend from the beginning and pain intensity reduced by more than 50% within 24 hours. Benzocaine 5% showed a sharp downward trend after 24 hours. From the clinical perspective, topical anaesthetics benefit orthodontic patients only during the first day. The present sample was not equally distributed for male/female ratio and similar to a number of reports,35,36,39,41,51-53 gender did not significantly affect pain scores in the present data. However, two recent studies reported significant effect of age and sex interaction on orthodontic pain during adolescence, and 14-17 and 15-18-year-old girls experienced maximum pain.54,55 Ketoprofen is a highly potent and safe NSAID derivative of the propionic acid group and was introduced for anti-inflammatory use.56 In addition
to inhibiting the formation of prostaglandins, ketoprofen also suppresses leukotrienes and, further, limits inflammation. Ketoprofen has a short half-life, is simply metabolised, has a broad therapeutic window, and does not accumulate with multiple doses. These features contribute to a rapid onset of action, relatively strong analgesic properties, and minimal side effects.43-46,56

Most available data on ketoprofen report efficacy for systemic use, and ketoprofen is often prescribed for the relief of pain after the removal of impacted third molar teeth. Mehlisch et al.57 reported a decrease of pain scores in all studied doses of ketoprofen (25, 50, and 100 mg) compared with codeine and a control. Ketoprofen administration also had a more rapid onset (showing no dose-related differences) and longer duration of action than codeine. Cooper58 reviewed three, six-hour double-blind, single-dose, placebo-controlled studies in patients who had experienced minor dental surgery, and concluded that, in comparison with aspirin, significant differences favouring ketoprofen were found for all measures of analgesic efficacy. Ketoprofen appeared to have a more rapid onset, higher peak effect and longer duration of pain relief than codeine. In one study, ketoprofen 100 mg (compared with 25 mg), had a faster onset of action, the highest peak effect and the longest duration of action over a six-hour evaluation. Therefore, it appeared that ketoprofen compared favourably with many of the commonly used NSAIDs. While the efficacy and rapid onset of systemic ketoprofen for post-operative pain has been well documented,59-61 in the present study, the application of ketoprofen was topical and not systemic.

Recently, a tendency for the local delivery of the analgesics has emerged.43 As an example, a solubilised 200 mg liquigel formulation of ibuprofen (with a higher $\text{C}_{\text{max}}$ and an earlier $\text{T}_{\text{max}}$ than a tablet – $\text{C} = \text{concentration; T} = \text{time}$) has been shown to have a more rapid rate of absorption compared with 200 mg tablets.49 The therapeutic effect on the nervous system in the absence of high plasma concentrations is achieved by topical NASIDs (gels, creams, or sprays).43 Each can penetrate the skin, subcutaneous fatty tissue and muscles in amounts that are sufficient to exert therapeutic effects.

In consideration of these characteristics and the required repetitive nature of analgesic administration in the oral cavity following orthodontic appliance activation, a simpler alternative to oral NSAIDs would be a gel form of ketoprofen applied locally. Lauritano et al.46 measured the pain level following the application of ketoprofen gel in a patient with acute oral inflammation due to orthodontic appliances. It was revealed that ketoprofen gel was more effective in relieving pain and controlling the inflammatory processes than benzidamine hydrochloride gel. The present study also confirmed the analgesic efficacy of ketoprofen over the benzocaine gel.

Unlike parallel-randomised clinical trials, crossover trials provide each participant with two or more sequential treatments in a random order separated by a sufficient wash-over period.62,63 Subsequently, each subject is able to act as his or her own control and permit comparisons between and within groups.63-65 Crossover studies are popular for the investigation of new and developmental drugs, and most appropriate in studies in which the effects of the treatments are short-lived and reversible.63,64,66 The particular strength of the crossover design is that the interventions are evaluated within the same patient, which eliminates subject variability.63,65 However, it is important to look for a carryover effect as an earlier crossover trial can affect the outcome at a later period and generate misleading placebo data. Considering the relatively short half-life of the materials used and the one-month wash-over period, it was difficult to assess a possible carryover effect. Regarding the ‘intention-to-treat analysis’, as the present sample was limited to 20, missing data due to patient discontinuation precluded a within-individual comparison for all patients enrolled in the trial.67,68 However, it is likely that the drop-outs had a minimal effect on the final outcome as they were excluded from the outset due to the expressed unwillingness to participate. All 20 participants were provided and tested with the three gels.

In order to demonstrate that an analgesic is working, it is crucial to use a placebo68 to reveal the superiority of the medications. However, the major concern with NSAIDs is the reduction in prostaglandin production that may interfere with orthodontic tooth movement. Because of this potential effect, a worthwhile extension of the present study would be to measure the amount of tooth movement and to assess whether ketoprofen causes a reduction. The possible interference of tooth movement and a correlated analgesic effect, as well as other potential side effects, could be a valuable direction for future studies.
Conclusion
The findings of the present study indicated a significant decrease in pain following the use of ketoprofen when tested against a control (placebo) gel. The highest pain scores were experienced in patients administered the placebo gel and the lowest scores in patients who applied ketoprofen gel. Benzocaine had an effect midway between ketoprofen and the placebo. The highest pain scores were recorded two hours following force application, which decreased to the lowest scores after seven days.

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