Pharmacological Means of Pain Control during Separator Placement: A Systematic Review

Nujud A Sharawi, Ahmed Mohammed Hassan Somaili, Samar A Arishi, Raed MH Somaili, Latifah Y Ghazwani, Ali HA Sumayli, Mohammed AA Sumayli, Mohammed A Jafer, Mona S Ghoussoub, Shankargouda Patil

ABSTRACT

Aim: To assess the effectiveness of adjuvant analgesics/anesthetics in pain control after separator placement compared with no medication.

Background: Separator placement to create space for cementing bands is the first clinical procedure done in orthodontics. Pain in this stage can negatively affect patient compliance and trust in the clinician. To date, there is no universally accepted regimen for pain control.

Materials and methods: Electronic databases of PubMed, Scopus, and Web of Science were searched. One hundred and thirty-two potentially relevant studies were found. A total of eight randomized clinical trials including 642 subjects were selected. Data were extracted into customized forms, and selected studies were assessed for risk of bias using the Joanna Briggs Institute.

Results: Results showed the use of analgesics led to lower reported pain scores at almost all time intervals. NSAIDs resulted in a statistically significant reduction in pain compared to a control group.

Conclusion: According to the available literature, the use of analgesics is effective in controlling orthodontic pain due to separators. Acetaminophen and ibuprofen show a stable analgesic effect.

Clinical implication: Acetaminophen 650 mg or ibuprofen 400 mg taken 1 hour prior to separator placement can reduce pain associated with the procedure.

Keywords: Analgesics, Pain management, Separator.

The Journal of Contemporary Dental Practice (2021): 10.5005/jp-journals-10024-3010

INTRODUCTION

Pain and discomfort during orthodontic treatment are inevitable. Of the various factors that deter a patient from seeking or completing orthodontic treatment, pain ranks highest in the patient’s mind. Fixed and removable appliances apply force on the crown to bring about required tooth movement. In contrast to other dental procedures such as extraction or subgingival scaling, pain during orthodontic treatment seems to continue increasing in intensity postappointment till finally plateauing. Pain arises as a result of interconnected cascading events that begin with the application of force resulting in local ischemia, recruitment of inflammatory mediators, and changes to the periodontal ligament. The release and expression of these biochemical mediators occur over a period of hours to days, accounting for the increase in perception of pain over time. There is a great individual variation on a patient’s perception of pain based on age, gender, sex, etc. The nature of the pain differs based on the tooth movement.

The first clinical procedure carried out is the placement of elastic separators between molars to create space for seating of bands. Elastic separators apply pressure on the periodontal ligament and rapidly create space in 24 hours. An orthodontic patient experiences pain during various stages of treatment such as archwire change and activation of the appliance. Yet, the severity of pain associated with the initial procedure of separator placement is a major factor in noncompliance and dampens the patient’s resolve.

Pain control methods include pharmacological, such as the use of NSAIDs and anesthetic gels, and mechanical through the use of medicated chewable gums and transcutaneous nerve stimulation. Recently, low-level laser therapy also has emerged as another pain management technique. There are no universal policies or guidelines for pain management during orthodontic treatment. Research and consensus in this regard remain elusive. Pharmacological means using over-the-counter drugs is straightforward and presents few complications. Preoperative...
doses of acetaminophen or ibuprofen can minimize pain and improve quality of life. Each analgesic also has its own drawbacks. Pretreatment doses of NSAIDs may reduce pain and inflammation through interfering in prostaglandin synthesis. This can negatively affect the rate of tooth movement and lead to longer treatment time. NSAIDs can also have gastrointestinal side effects.

Pain is the most significant factor for adolescents and adults to eschew orthodontic treatment. The purpose of the present systematic review is to analyze data regarding various pharmacological means used for pain control during initial separator placement and provide recommendations for their use in patients undergoing orthodontic treatment.

Materials and Methods
The present systematic review was performed based on PRISMA guidelines.

Focused Question
“Does the use of adjuvant analgesics/anesthetic medication help improve pain control after placement of separators?”

Search Strategy
An electronic search of PubMed, Scopus, and Web of Science databases was done up to November 1, 2020. There were no restrictions placed on the starting date. The keywords used for the search were “separator, orthodontics, and drugs.” A single keyword was not used. Electronic search was supplemented using manual search of references of identified articles.

Inclusion Criteria
The following criteria were used in the selection of the articles:
- P—patients who are undergoing orthodontic treatment
- I—administration of analgesics/anesthetic
- C—placebo, or no analgesic administered
- O—at intervals, the patient’s pain perception is evaluated based on visual analog scale (VAS)
- S—randomized control trial

Randomized controlled trials that compared the efficacy of analgesics to placebo.
Randomized controlled trials that compared the efficacy of analgesics to control group with no analgesics given.
Randomized controlled trials that compared the efficacy of anesthetic agent to control group with no medication given.

VAS was used to report the patient’s perception of pain. Pain level measured at intervals. Participants underwent separator placement.

Exclusion Criteria
Trials concerned with pain due to orthodontic procedures other than separator placement.
Trials that used nonpharmacological means for pain control.
Trials concerned with pain due to TMD.
Trials that used nonpharmacological means for pain control.
Trials without a control/placebo group.

Study Selection and Data Extraction
Two authors independently examined titles and abstracts of all identified studies. Duplicates and studies that did not meet the eligibility criteria were discarded. In cases where title and abstract provided insufficient information to make a decision regarding eligibility, the full-text article was obtained. Complete articles of all studies included in this review were appraised.

We excluded studies that had split-mouth design and trials that did not have a placebo or a control group. Studies that had a nonpharmacological intervention were also excluded. Data were extracted independently by two researchers. Data were collected in a customized form that included the name of first author, year and country of publication, methods, study design, sample characteristics, details of pharmacological intervention, method of detection, results, and inferences. The extracted data are presented in Table 1.

Risk of Bias Assessment
Both review authors independently assessed the included studies for bias. The Joanna Briggs Institute critical appraisal tools were used to consider 13 domains.

Risk of Bias was Categorized into Three Tranches
Low risk of bias—percentage of “yes” score was more than 70%
Moderate risk of bias—percentage of “yes” score was 50 to 69%
High risk of bias—percentage of “yes” score was less than 49%
Risk of bias judgment is presented in Table 2.

Statistical Analysis
Cohen’s kappa coefficient (k) was used to evaluate observer bias. Kappa coefficient for Step 1 and Step 2 was 0.98 and 0.96, respectively.

Results
Study Selection
A search of electronic databases revealed 141 potentially relevant studies ranging from 1989 to 2020. Titles and abstracts of these studies were examined. One hundred and five studies were discarded for not meeting eligibility criteria. Thirty-six articles were selected for further scrutiny. Full-text articles of these studies were obtained. After assessment, 28 articles were excluded. Most of these studies were excluded as they did not have a clear control/placebo group. Some had interventions that were measured against nonpharmacological interventions. In the end, eight randomized controlled trials were selected for this review. The selection process is represented graphically using a flowchart in Flowchart 1.

Study Characteristics
Countries
Of the eight included trials, three were conducted in the USA, two in India, and one in Brazil, Iran, and Kuwait.

Design
Seven studies selected had the following characteristics:
- Had three arms
- Were single-center studies
- Had parallel design

One study had four parallel arms. In all eight studies, the participants had separators placed on their lower molars.

Characteristics of the Intervention
In six of the eight studies, the analgesia/anesthetic was given both preemptively and after separator placement. One study evaluated only preemptive analgesic medication. One study
Table 1: Summary of data extracted from the included studies

| Sl. No. | Author/year/country | Type of study | Sample size | Matching | Method of detection | Pain report time intervals | Results | Inference |
|---------|---------------------|---------------|-------------|----------|---------------------|---------------------------|---------|-----------|
| 1       | Ngan 1994, USA      | RCT           | Grp 1a: n = 28 pts, ibuprofen 400 mg, immediately after placement | Age/sex | VAS (1–10), Questionnaire, Discomfort Index Card | 2, 6, 24 hr, 2, 3, 7 days | Experimental group reported significantly less pain at 2, 6 hr intervals. Grp 1a reported significantly less pain than Grp 1a or control group | Ibuprofen showed better pain control than aspirin |
|         |                     |               | Grp 1b: n = 28 pts, lactose, immediately after placement |         |                     |                           |         |           |
| 2       | Steen Law 2000, USA | RCT           | Grp 1a: n = 22 pts, ibuprofen 400 mg, 1 hr before, lactose taken immediately after | Age/sex—unclear | VAS (1–10), Questionnaire | 2, 6, 24 hr, 2, 3, 7 days | Grp 1a reported significantly less pain | Administration of ibuprofen preoperatively showed better pain control |
|         |                     |               | Grp 1b: n = 19 pts, lactose placebo taken 1 hr before, ibuprofen 400 mg taken immediately after |         |                     |                           |         |           |
| 3       | Minor 2009, USA     | RCT           | Grp 1a: n = 16 pts, ibuprofen 400 mg, 1 hr before, 3 hr after, 7 hr after | Age/sex—unclear | VAS (1–10), Questionnaire | 2, 6 hr, bedtime, awakening, 24 hr | Experimental group reported significantly less pain at two intervals. p < 0.005 | Administration of ibuprofen pre- and postop showed better pain control |
|         |                     |               | Grp 1b: n = 17 pts, placebo 1 hr before, ibuprofen 400 mg 3 hr after and 7 hr after |         |                     |                           |         |           |
| 4       | Bruno 2011, Brazil  | RCT           | 17, 4 male, 13 female, 400 mg lumiracoxib 1 hr prior | Age/sex | VAS (1–10), Questionnaire | 2, 6, 24 hr, 2, 4 days | VAS values are lower in group receiving drug. Statistically significant. p ≤ 0.005 value | All groups reported pain and discomfort at all time intervals. Patients taking analgesics reported less pain |
|         |                     |               | 17, 5 male, 12 female, placebo one hour prior |         |                     |                           |         |           |
|         |                     |               | 17, 5 male, 12 female, control, no analgesic |         |                     |                           |         |           |
| 5       | Kohli 2011, India   | RCT           | Grp 1a: n = 30 pts, ibuprofen 400 mg, 1 hr prior | Age/sex | VAS (1–10), Questionnaire | 2, 6, 24 hr, 2, 3, 7 days | Experimental group reported significantly less pain at 2, 6 hr intervals. Grp 1b reported significantly less pain than Grp 1a. p < 0.05 | Piroxicam showed better pain control than ibuprofen |
|         |                     |               | Grp 1b: n = 30 pts, piroxicam 20 mg, 1 hr prior |         |                     |                           |         |           |
| 6       | Sudhakar 2014, India| RCT           | Grp 1a: n = 38, acetaminophen 650 mg, 1 hr prior, 6 hr after | Age/sex | VAS (1–10), Questionnaire | 2, 6 hr, bedtime, morning, 2, 3, 7 days | Experimental group taking aspirin reported least amount of pain felt, followed by groups taking ibuprofen and acetaminophen | Preemptive and postop administration of aspirin can effectively control pain |
|         |                     |               | Grp 1b: n = 39 pts, ibuprofen 400 mg, 1 hr prior, 6 hr after |         |                     |                           |         |           |
|         |                     |               | Grp 1c: n = 36 pts, aspirin 300 mg, 1 hr prior, 6 hr after |         |                     |                           |         |           |

Contd…
evaluated the effects of postprocedural analgesic medication. All eight studies had an experimental group, a placebo group, and/or a control group.

**NSAIDs**

Six studies compared ibuprofen 400 mg with a control group that received a placebo or no medication. One study compared the efficacy of piroxicam, an NSAID of the oxicam class, with ibuprofen and a placebo. One study compared lumiracoxib 400 mg, a COX-2 selective inhibitor, with a placebo of beta lactose and a control of no medication. Two studies compared aspirin with ibuprofen 400 mg with a placebo of beta lactose.

**Acetaminophen**

Two studies compared the efficacy of acetaminophen 650 mg with aspirin 300 mg and/or ibuprofen 400 mg and a control of no medication.

**Anesthetic**

One study compared the efficacy of chewing gum with prilocaine and lidocaine anesthetic with a placebo group who were given conventional chewing gum and a control group to whom no medication was administered.

**Control/Placebo**

Six out of the eight studies reported using a placebo. Only three studies mentioned the content of the placebo administered—beta lactose. Two studies had a control group that was not administered any medication.

**Visual Analog Scale**

All eight studies used VAS to measure pain outcomes. Registration of pain was done after placement of separators at distinct time intervals.

**Duration of Study**

Duration of the studies showed a wide variation. One study lasted only 8 hours. Three studies took pain measurements at set intervals over a period of 7 days. Four studies spanned a period of 2 to 4 days posttreatment.

**Characteristics of the Participants**

A total of 642 participants were randomized. Generally, all participants ranged in age from 14 to 21. Only one study had participants who were in the age-group of 23 to 41 years.

**Results of the Studies**

All patients who had a separator placed gave testimonies of pain and discomfort that increased over a period of time. All eight studies described an association of analgesics/anesthetic administered and lower reported pain scores; that is, the experimental group that were given medication consistently reported less pain. The pain scores recorded within the experimental group varied based on the analgesic administered. There was a correlation of preemptive administration of medication with better pain control.

**Discussion**

One of the most frequent questions an orthodontist is asked at the beginning of treatment is “Will it hurt?” Unfortunately, oftentimes, the answer is yes. Orthodontic tooth movement is a result of mechanical forces directed against the tooth. Pain and
Table 2: The Joanna Briggs Institute critical appraisal checklist for randomized controlled trials to assess the risk of bias for the included studies

| First author name/country/ year of publication/reference number | 1. Was true randomization used for the assignment of participants to treatment groups? | 2. Was allocation to treatment groups concealed? | 3. Were treatment groups similar at the baseline? | 4. Were participants blind to treatment assignments? | 5. Were those delivering treatment blind to treatment assignment? | 6. Were outcome assessors blind to treatment assignment? | 7. Were treatment groups treated identically other than the intervention of interest? | 8. Was follow-up complete, and, if not, were differences between groups in terms of their follow-up adequately described and analyzed? | 9. Were participants analyzed in the groups to which they were randomized? | 10. Were outcomes measured in the same way for treatment groups? | 11. Were outcomes measured reliably? | 12. Was appropriate statistical analysis used? | 13. Was the trial design appropriate, and any deviation from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial? | The overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ngan 1994, USA | Unclear | Unclear | No | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Moderate |
| Steen Law 2000, USA | Unclear | Unclear | Yes | Unclear | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Moderate |
| Minor 2009, USA | Unclear | Unclear | Unclear | Unclear | No | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Moderate |
| Bruno 2011, Brazil | Yes | Unclear | Yes | No | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Kohli 2011, India | Unclear | Unclear | Yes | Unclear | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Moderate |
| Sudhakar, 2014, India | Unclear | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Nik 2016, Iran | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Low |
| Al-Melh 2019, Kuwait | Unclear | Unclear | No | Unclear | Unclear | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | Yes | Yes | Moderate |

Risk of bias categorized as high when the study reached up to 49% score, yes; moderate when the study reached 50 to 69% score, yes; and low when the study reached more than 70% score, yes.
Pain Control during Separator Placement

Bruno et al. examined the efficacy of using an NSAID with less incidence of gastric side effects.16 Lumiracoxib is an NSAID that selectively inhibits the COX-2 enzyme in prostaglandin synthesis. They are thought to have fewer adverse effects and interference with tooth movement than conventional NSAIDs.24 Data regarding their cardiovascular safety are still inconclusive and thus preclude their widespread use.

Ibuprofen vs Acetaminophen

Acetaminophen is a para-amino phenol derivative that has poor anti-inflammatory action. It is a nonopioid, non-NSAID analgesic. Two studies examined the efficacy of ibuprofen and acetaminophen against a control group.18,19 Nik et al. found no difference in the analgesic efficacy of ibuprofen compared to acetaminophen. This is in agreement with previous studies by Xiaoting and Angelopoulou.27

Selection of Analgesic

Oftentimes, it is not only the analgesic effect but also the possible side effects that must be considered before prescribing a medication for pain relief. Animal studies have previously shown that NSAIDs can affect the rate of tooth movement.10 NSAIDs suppress the synthesis of prostaglandins. Prostaglandins are biochemical mediators of inflammation and bone resorption. Prostaglandin activity can alter the number of osteoclasts that are important for bone remodeling. It is hypothesized that NSAIDs that exert an anti-inflammatory action through the suppression of PG synthesis may interfere with tooth movement.28 This interference could slow down the velocity of orthodontic tooth movement and increase the duration of treatment.

Newer NSAIDs, such as piroxicam and lumiracoxib, offer no substantial advantage in preventing interference to tooth movement. Acetaminophen is a weak anti-inflammatory and does not affect PG synthesis significantly.30 In agreement with studies by Arias and Angelopoulou,27 there is moderate evidence for acetaminophen to be recommended as an analgesic to relieve minor discomfort.
Anesthetics
Both prilocaine and lidocaine are amide group anesthetics that act by a combination of receptor and receptor-independent mechanism. This topical anesthetic mix is potent and has a quick onset of action. Only one study evaluated the use of topical anesthetics. The experimental group was directed to use anesthetic chewing gum over a period of 8 hours. Subjects reported a rapid onset of the anesthetic effect. The effect diminished after half an hour. The subjects were asked to chew gum every half hour. Subjects in the experimental group had low pain scores, approaching zero. Complaints of muscle soreness and gum sticking to the separator were reported. A striking feature of this study was that it lasted for only 8 hours, whereas pain and discomfort due to a separator can increase gradually and reach peak levels at 24 hours. It may be implausible for an adult to continuously apply topical anesthetic over that period of time. When prescribing topical anesthetics, it is important to consider the potential negative effects that may result from high doses.

Preemptive Analgesic vs Postprocedure
Three studies investigated the effect of preemptive administration of anesthetics after separator placement. In all three studies, preoperative doses of NSAIDs resulted in lower reported pain scores over all time periods. NSAIDs reach peak plasma concentration about 2 hours. This could explain why subjects in the experimental groups had little discomfort even at initial time intervals. Administration of ibuprofen 400 mg 1 hour before delayed the onset of pain. This is in agreement with previous studies by Bernhardt et al.

There is moderate-quality evidence that preemptive dosing of anesthetics provided better pain control.

Further Research Required Examining
Design of future studies should include larger sample sizes to reduce risk of them being underpowered. The effect of multiple doses of anesthetics along with reports of adverse effects needs to be further investigated. Supplementary studies examining the role of nonpharmacological means for pain relief may put forth an alternative to anesthetics.

Conclusion
Based on available data, the use of adjuvant anesthetics is effective in controlling pain due to separator placement. There is moderate-quality evidence that supports the use of acetaminophen as the first choice for pain control. Ibuprofen may be an equally effective secondary choice as both show stable analgesic effect.

Implication for Clinical Practice
There is moderate-quality evidence that acetaminophen 650 mg or ibuprofen 400 mg taken 1 hour prior to separator placement can reduce pain associated with the procedure.

Compliance with Ethical Standards
Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

References
1. Bos A, Hoogstraten J, Prahl-Andersen B. Attitudes towards orthodontic treatment: A comparison of treated and untreated subjects. Eur J Orthod 2005;27(2):148–154. DOI: 10.1093/ejo/cjh071.
2. Krishnan V. Orthodontic pain: From causes to management—A review. Eur J Orthod 2007;29(2):170–179. DOI: 10.1093/ejo/cj081.
3. Alhajia ESA, Aldaiikii A, Al-Omairi MK, et al. The relationship between personality traits, pain perception and attitude toward orthodontic treatment. Angle Orthod 2010;80(6):1141–1149. DOI: 10.2319/012710-59.1.
4. Davidovitch M, Papanicolau S, Vardimon AD, et al. Duration of elastomeric separation and effect on interproximal contact point characteristics. Am J Orthod Dentofac Orthop 2008;133(3):414–422. DOI: 10.1016/j.ajodo.2006.02.036.
5. Beck VJ, Farella M, Chandler NP, et al. Factors associated with pain induced by orthodontic separators. J Oral Rehabil 2014;41(4):282–288. DOI: 10.1111/jor.12144.
6. Sergi HG, Klages U, Zentner A. Pain and discomfort during orthodontic treatment: causative factors and effects on compliance. Am J Orthod Dentofac Orthop 1998;114(6):684–691. DOI: 10.1016/s0889-5406(98)70201-x.
7. Roth PM, Thrasil JW. Effect of transcutaneous electrical nerve stimulation for controlling pain associated with orthodontic tooth movement. Am J Orthod Dentofac Orthop 1986;90(2):132–138. DOI: 10.1016/0889-5406(86)90045-4.
8. Lim HM, Lew KK, Tay DK. A clinical investigation of the efficacy of low level laser therapy in reducing orthodontic postadjustment pain. Am J Orthod Dentofac Orthop 1995;108(6):614–622. DOI: 10.1016/s0889-5406(95)70007-2.
9. Patel S, McGorray SP, Yeziarski R, et al. Effects of anesthetics on orthodontic pain. Am J Orthod Dentofac Orthop 2011;139(1):53–58. DOI: 10.1016/j.ajodo.2010.07.017.
10. Keohoe MJ, Cohen SM, Zarrinnia K, et al. The effect of acetaminophen, ibuprofen, and misoprostol on prostaglandin E2 synthesis and the degree and rate of orthodontic tooth movement. Angle Orthod 1996;66(5):339–330. DOI: 10.1043/0003-3219(1996)066<0339:TEOAIA>2.3.CO;2.
11. Rampal P, Moore N, Van Ganse E, et al. Gastrointestinal tolerability of ibuprofen compared with paracetamol and aspirin at over-the-counter doses. J Int Med Res 2002;30(3):301–308. DOI: 10.1177/14732300203000311.
12. Fang J, Li Y, Zhang K, Zhao Z, et al. Escaping the adverse impacts of NSAIDs on tooth movement during orthodontics current evidence based on a meta-analysis. Medicine (United States) 2016;95(16):1–9. DOI: 10.1097/MD.0000000000003256.
13. Ngan P, Wilson S, Shanfeld J, et al. The effect of ibuprofen on the level of discomfort inpatients undergoing orthodontic treatment. Am J Orthod Dentofac Orthop 1994;106(1):88–95. DOI: 10.1016/0889-5406(94)70025-7.
14. Steen SL, Southard KA, Alan S, et al. An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. Am J Orthod Dentofac Orthop 2000;118(6):629–635. DOI: 10.1067/mod.2000.110638.
15. Minor V, Marris CK, McGorray SP, et al. Effects of preemptive ibuprofen on pain after separator placement. Am J Orthod Dentofac Orthop 2009;136(4):510–517. DOI: 10.1016/j.ajodo.2007.09.018.
16. Bruno MB, Bruno MAD, Krymchantowski AV, et al. A double-blind, randomized clinical trial assessing the effects of a single dose of preemptive anti-inflammatory treatment in orthodontic pain. Prog Orthod 2011;12(1):2–7. DOI: 10.1007/j.jio.2011.02.002.
17. Kohli SS, Kohli VS. Effectiveness of piroxicam and ibuprofen premedication on orthodontic patients’ pain experiences: A randomized control trial. Angle Orthod 2011;81(6):1097–1102. DOI: 10.2319/022411-134.1.
18. Sudhakar V, Vinodhini TS, Mohan AM, Srivinbavan B, Rajkumar BK. The efficacy of different pre- and post-operative analgesics in the management of pain after orthodontic separator placement: A randomized clinical trial. J Pharm Bioallied Sci [Internet]. 2014 Jul;6(Suppl 1):S80–S84. doi:10.4103/0975-7406.137393.
19. Hosseinzadeh Nik T, Shahsavari N, Ghadirian H, Ostad SN. Acetaminophen Versus Liquefied Ibuprofen for Control of Pain During Separation in Orthodontic Patients: A Randomized Triple Blinded Clinical Trial. Acta Med Iran. 2016 Jul;54(7):418–421.
27. Angelopoulou M V, Vlachou V, Halazonetis DJ. Pharmacological management of pain during orthodontic treatment: A meta-analysis. Orthod Craniofacial Res 2012;15(2):71–83. DOI: 10.1111/j.1601-6343.2012.01542.x.

28. Arias OR, Marquez-Orozco MC. Aspirin, acetaminophen, and ibuprofen: Their effects on orthodontic tooth movement. Am J Orthod Dentofac Orthop 2006;130(3):364–370. DOI: 10.1016/j.ajodo.2004.12.027.

29. Krishnan V, Zahrowski JJ, Davidovitch Z. The effect of drugs and diet on orthodontic tooth movement. In: Biological mechanisms of tooth movement. second ed.; 2015. p. 173–187.

30. Salmassian R, Oesterle LJ, Shellhart WC, et al. Comparison of the efficacy of ibuprofen and acetaminophen in controlling pain after orthodontic tooth movement. Am J Orthod Dentofac Orthop 2009;135(4):516–521. DOI: 10.1016/j.ajodo.2007.05.020.

31. Kravitz ND, Graham JW, Nicozisis JL, Gill J. Computed topical anesthetics in orthodontics. J Clin Orthod. 2015 Jun;49(6):371–377 PMID: 26161833.

32. Herdevall BM, Klinge B, Persson L, et al. Plasma levels of lidocaine, o-toluidine, and prilocaine after application of 8.5 g Oraqix® in patients with generalized periodontitis: Effect on blood methemoglobin and tolerability. Acta Odontol Scand 2003;61(4):230–234. DOI: 10.1080/00016350310004106.

33. Bernhardt MK, Southard KA, Batterson KD, et al. The effect of preemptive and/or postoperative ibuprofen therapy for orthodontic pain. Am J Orthod Dentofac Orthop 2001;120(1):20–27. DOI: 10.1067/mod.2001.115616.