*Original Article*

# Influence of ibuprofen combined with corticotomy on tooth movement and alveolar bone remodeling in rats

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**ABSTRACT**

**Objectives:** To investigate the effects of corticotomy-assisted orthodontic tooth movement and administration of ibuprofen on tooth movement rate and alveolar bone response.

**Materials and Methods:** A total of 78 adult male Wistar rats were randomly assigned to five groups: one baseline group (no treatment) and four experimental groups including orthodontic tooth movement only (OTM), orthodontic tooth movement with ibuprofen (OTMI), corticotomy-assisted orthodontic tooth movement (COTM), and corticotomy-assisted orthodontic tooth movement with ibuprofen (COTMI). Corticotomy was performed on a maxillary molar unilaterally. Nickel-titanium closed-coil springs generated a 10-gram force for maxillary first molar movement. The experimental drug groups received 15 mg/kg of ibuprofen, and the other groups received reverse osmosis water. Tooth movement and bone volume fraction were evaluated by micro–computed tomography on days 0, 7, 14, and 21.

**Results:** The corticotomy groups had statistically significantly higher tooth movement and lower bone volume fraction than the orthodontic groups ($P < .05$). The amount and rate of tooth movement were statistically significantly different between the OTM and OTMI groups, but not statistically significantly different in bone volume fraction. However, statistically significant differences were not observed in any measurements between the COTM and COTMI groups.

**Conclusions:** Ibuprofen during orthodontic tooth movement inhibited tooth movement and alveolar bone remodeling but had no effect on corticotomy-assisted orthodontic treatment. (*Angle Orthod.* 2022;92:773–779.)

**KEY WORDS:** Ibuprofen; Corticotomy; Micro-CT

## INTRODUCTION

Corticotomy-assisted orthodontic treatment can accelerate orthodontic tooth movement by activating bone metabolism, which is based on reducing the resistance of the surrounding cortical bone and allowing the tooth to move the entire alveolar cortical segment connected with the cancellous bone.[1] The effect of corticotomy on accelerating tooth movement is explained by the regional acceleratory phenomenon (RAP) that increases osteoclast and osteoblast activity and accelerates bone turnover in the injury site as a result of increased remodeling capacity. RAP is initiated in a couple of days after injury and continues for 1 to 2 months for maximum effect before dissipating after 6 months.[2] Corticotomy reduces bone density and enhances bone remodeling by activating the healing process of injured tissues.[3] The corticotomy procedure is associated with moderate degrees of pain and discomfort[4] because soft tissue and bone injury stimulate cytokine expression of prostaglandin E2 ($PGE_2$). $PGE_2$ is one of the most important inflammatory mediators to induce the inflammatory response, promoting pain sensations by acting on sensory endings.[5] In addition, $PGE_2$ stimulates osteoblasts by increasing the receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibiting osteoprotegerin, which subsequently allows more RANKL to bind to

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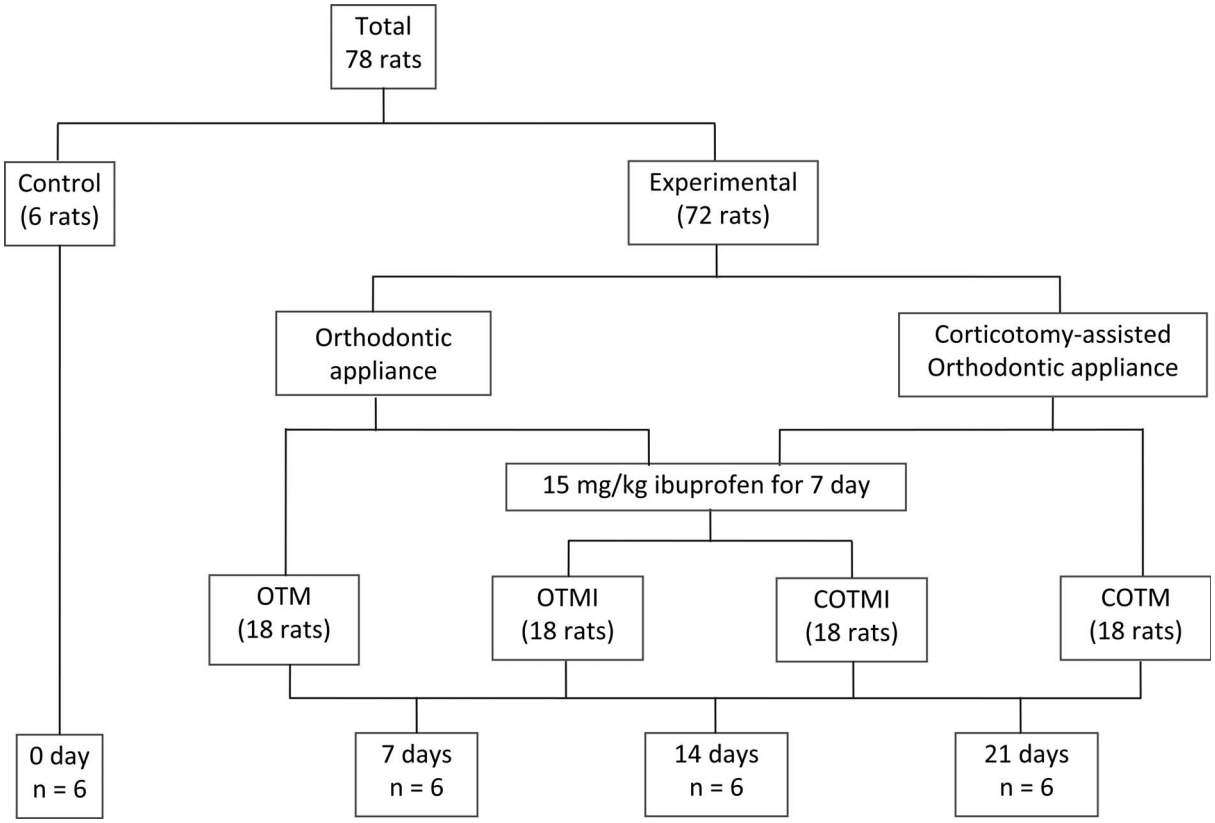


**Figure 1.** Flowchart showing the animal study design.

the receptor activator of nuclear factor kappa-B and leads to osteoclastogenesis.[6]

Pain control approaches have been introduced to alleviate unpleasant sensations. However, analgesics are the main therapeutic method to alleviate pain.[7] Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic, and anti-inflammatory properties.[8] The mechanism of ibuprofen is the inhibition of cyclooxygenase activity from converting arachidonic acid into prostaglandins and thromboxanes, which are important enzymes for the production of prostanoids.[9] In addition, ibuprofen has a stable analgesic effect for controlling pain[10]; 400 to 800 mg of ibuprofen every 4 to 6 hours is the first step in managing postoperative dental pain,[11] which biologically decreases $PGE_2$ production.[12,13] However, ibuprofen also decreases osteoclast formation, leading to a delay in tooth movement.[12,14] Therefore, patients undergoing orthodontic treatment should avoid taking these drugs.

This study aimed to investigate the effects of ibuprofen and corticotomy on the amount and rate of tooth movement and bone volume fraction in rats undergoing orthodontic tooth movement.

## MATERIALS AND METHODS

A total of 78 male Wistar rats aged 12 to 16 weeks with weights from 350 to 400 grams were used in this study. Permission to conduct this study was approved by the Animal Ethics Committee, Prince of Songkla University (Institutional Animal Care and Use Committee [IACUC] 2563-03-037). All animals were housed in an acclimatized environment at least 1 week prior to beginning the experiment. The animals were allocated into four experimental subgroups and a baseline control group (day 0) using a randomized allocation technique. The experimental groups were divided into orthodontic groups (orthodontic force only [OTM] and orthodontic tooth movement with ibuprofen [OTMI]) and surgery groups (corticotomy-assisted orthodontic tooth movement [COTM] and corticotomy-assisted orthodontic tooth movement with ibuprofen [COTMI]). The control group included six rats without intervention, and each experimental group included 18 rats assigned to three observation periods at random (days 7, 14, and 21) for a total of 78 rats (Figure 1).

General anesthesia was used in all experimental groups. The animals were weighed to determine the anesthetic doses. Initially the rats were anesthetized

with 3% isoflurane inhalation (AErrane, Baxter Healthcare Corporation, Deerfield, Ill, USA) before receiving an intraperitoneal injection mixture of 90 mg/kg ketamine hydrochloride (Ketajex, Baxter Pharmaceuticals India Private Ltd, Gujarat, India) and 10 mg/kg xylazine hydrochloride (X-Lazine, L.B.S. Laboratory Ltd, Bangkok, Thailand). All operations were done by the same operator. Tooth movement and bone volume fraction were measured on days 0, 7, 14, and 21.

### Surgical Procedures

One side of the maxilla was randomly selected in all experimental groups. The surgical procedure started with a sulcular incision at the mesial line angle of the maxillary second molar and continued along the sulcus of the maxillary first molar in a mesial direction extending 5 mm to the edentulous ridge. A full-thickness periosteal flap was elevated on the buccal and palatal aspects of the maxillary alveolar ridge adjacent to the maxillary first molar. Decortication to a depth of 0.25 mm and a width of 0.5 mm was performed at two points on the buccal side and two points on the palatal side using a slow-speed handpiece with a 0.5-mm diameter carbide round bur and sterile water irrigation.[15] The periosteal flaps were sutured using a simple interrupted technique with 5-0 resorbable sutures.

### Orthodontic Applications

The orthodontic appliance was attached from the maxillary first molar to the left and right maxillary central incisors to move the maxillary first molar in the mesial direction. The protraction forces were generated by ultra-light nickel-titanium closed-coil springs (Dentos, Daegu, Korea), 8 mm in length and 1.5 mm in depth, with an activated force of 10 grams. The spring was then ligated with 0.008-inch ligature wires and covered with flowable composite resin (Figure 2). A force gauge was used to ensure 10 grams of constant force on day 7 and day 14.

### Drug Administration

The OTMI and COTMI groups received 0.6 mL of 15 mg/kg of oral suspension ibuprofen (Nurofen syrup, Reckitt Benckiser, Bangkok, Thailand), whereas the OTM and COTM groups received 0.6 mL of reverse osmosis filtered water. Each rat was weighed before a single dose of solution administered through a gastric tube for 7 days.

### Micro–Computed Tomography Analysis

At each time point, the animals were euthanized with a high dose of anesthetic drug, and the maxilla was removed and fixed immediately in 10% neutral buffered formalin for 7 days. The Scanco μCT system and analysis software (μCT 35, Scanco Medical, Bassersdorf, Switzerland) were used to scan the maxilla with 70 kVp, 114 μA, 256-millisecond exposure time, and 10-μm voxel size. The scanning plane was set parallel to the occlusal surfaces of the maxillary second and third molars, and the scanned data were reconstructed using the built-in software. The analysis software evaluated tooth movement and bone volume fraction for the structural parameters.

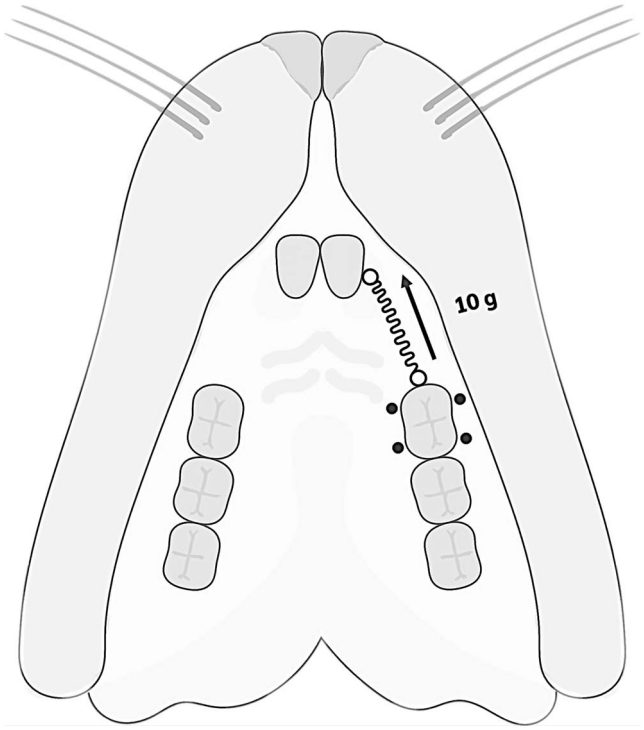


**Figure 2.** Schematic figure of orthodontic tooth movement and the decortication area.

*Measurement of Tooth Movement*. Tooth movement was measured using two-dimensional micro–computed tomography (micro-CT) imaging in transverse section. The distance between the most distal point of the first maxillary molar crown and the most mesial point of the second maxillary molar crown was measured (Figure 3A). Tooth movement rate was calculated by dividing tooth movement by the number of weeks at each time point.

*Bone Volume Fraction Measurement*. Bone volume fraction was determined from the ratio of mineralized alveolar bone volume (BV) to the total volume surrounded by the contours (TV) defined by the region of interest (ROI). The ROI in a horizontal plane was defined as surrounding the inter-radicular area of the maxillary first molar (Figure 3B), and the ROI in a vertical plane was determined at the most occlusal point of the furcation to the apex of the

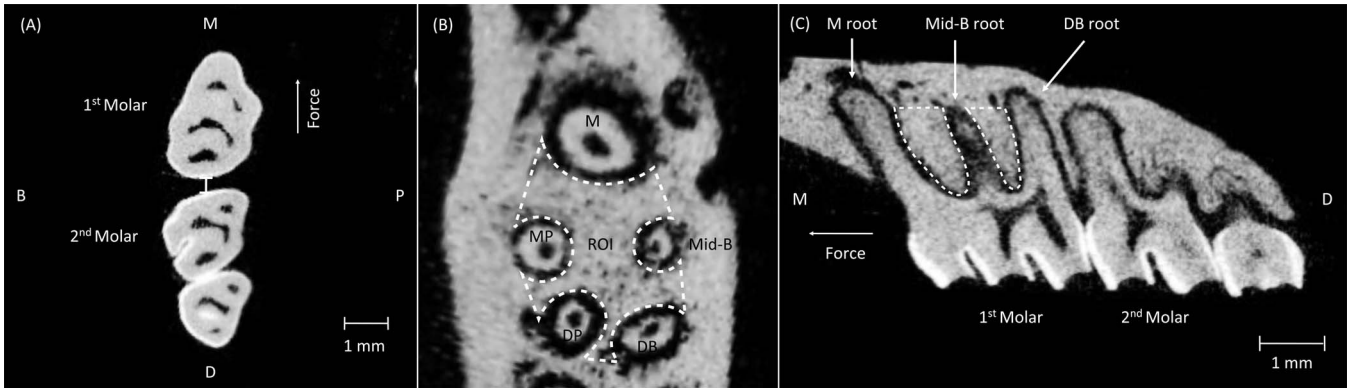


**Figure 3.** Micro-CT radiographs. (A) Tooth movement distance measurement. (B) ROI in the axial view of the inter-radicular bone at the maxillary first molar area used for bone volume measurements. (C) ROI in the sagittal view. DB indicates distobuccal root; DP, distopalatal root; M, mesial root; Mid-B, mid-buccal root; and MP, mesiopalatal root.

shortest root, which was usually the mid-buccal root (Figure 3C).

### Statistical Analysis

All data measurements were repeated twice at a 1-month interval by the same examiner. The intraclass correlation coefficient was used to assess intraobserver reliability. The means and standard deviations of each group were reported, and the data were statistically analyzed using SPSS version 25.0 (IBM Corp, Armonk, NY). The Shapiro-Wilk test revealed that all data had a normal distribution, and one-way analysis of variance was used to evaluate between-group differences at each time point. Statistical significance was set at $P < .05$.

## RESULTS

The intraclass correlation coefficients for tooth movement and BV/TV were 0.989 and 0.941, respectively, which implied excellent reliability.

### Amount and Rate of Tooth Movement

Tooth movement in the OTMI group was significantly less than the OTM group ($P < .02$), and the COTMI group had slightly less tooth movement than the COTM group, with no statistically significant differences (day 7, $P = .157$; day 14, $P = .285$; day 21, $P = .850$) (Figure 4A).

Tooth movement rate in the COTM group dramatically increased to a peak greater than the other groups during the first week of force application. The rate then slightly decreased from the second to the third week. The COTMI group had a slightly lower rate in the first week than the COTM group; however, the rate increased to nearly match the COTM group in the second and third weeks. The rates of tooth movement were not significantly different between the COTM and COTMI groups at any time point (day 7, $P = .157$; day 14, $P = .276$; day 21, $P = .841$). However, the OTM group was significantly lower than the surgery groups by 1.7 to 2 times at the first week. The OTMI group had a twofold lower tooth movement rate than the OTM group and a 3.5 to 4 times lower rate than the surgery groups. The OTMI group had a statistically significantly lower tooth movement rate throughout the experimental period compared with the OTM group ($P < .02$) (Figure 4B).

### Bone Volume Fraction

All experimental groups had a significant decrease in bone volume compared with baseline. The bone volume decreased in the first 7 days and then slightly increased from days 14 to 21. In all periods, the surgery groups had a significant decrease in BV/TV greater than the orthodontic groups ($P < .03$).

BV/TV in the orthodontic groups reduced to 63.9% in the OTM group and 70.0% in the OTMI group on day 7 compared with baseline. After 21 days, bone volume steadily increased and nearly returned to baseline. The OTMI group had a slightly higher bone volume than the OTM group at all time points, but the difference was not statistically significant.

In the surgery groups, the BV/TV decreased to 40.3% in the COTM group in the first week and 43.0% in the COTMI group compared with baseline. Bone volume increased during the next 3 weeks and increased to 61.7% and 63.1% in the COTM and COTMI groups, respectively. The COTMI group had higher bone volumes at all time points than the COTM group; however, the differences were not statistically significant (Figure 4C).

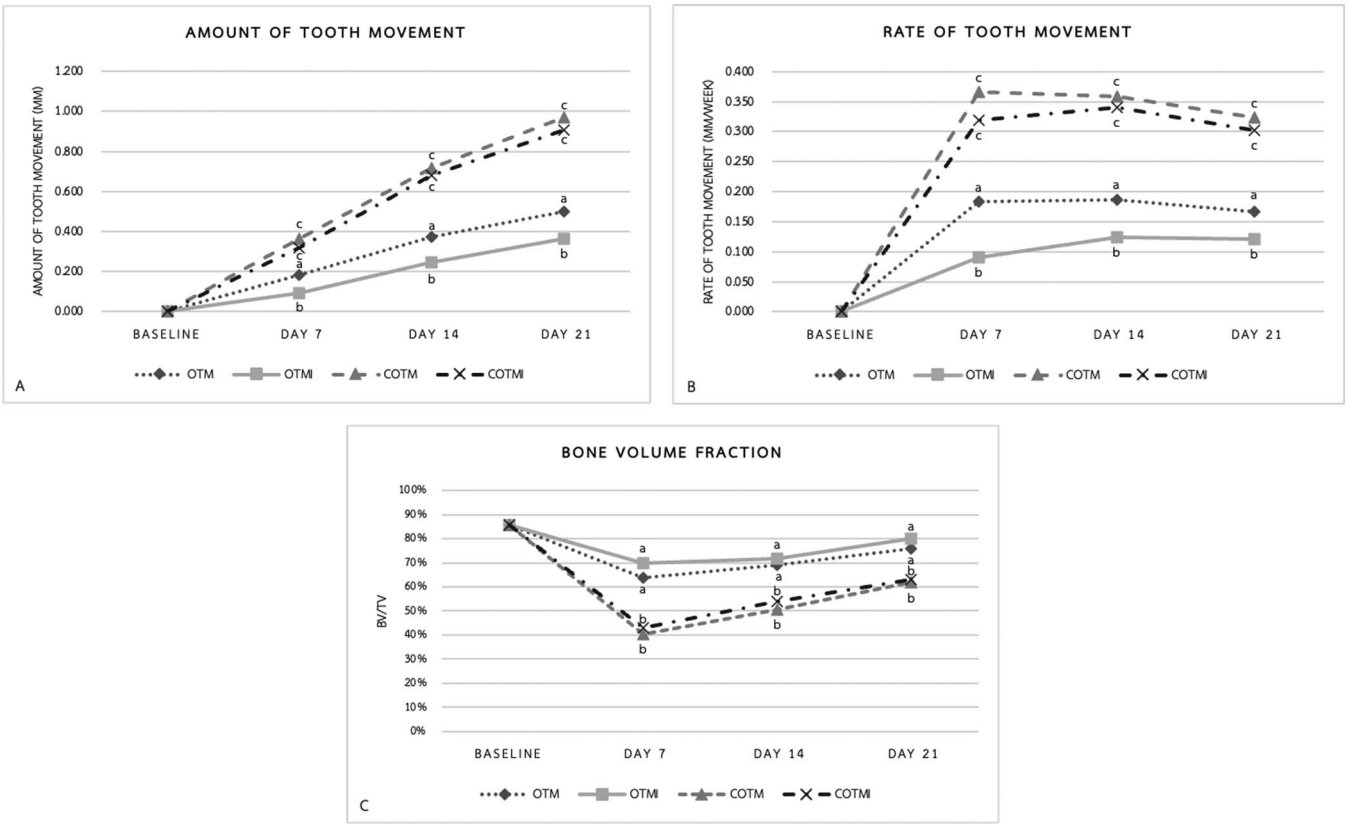


**Figure 4.** Comparison of OTM, COTM, OTMI, and COTMI groups. (A) Tooth movement (mm). (B) Tooth movement rate (mm/wk). (C) Bone volume fraction. Different letters show statistically significant differences between groups ($P < .05$).

## DISCUSSION

Orthodontic treatment can take a long time, and several attempts have been undertaken to speed up the process. However, when the orthodontic force exceeds the biologic tissue capacity threshold, pathologic responses such as ankylosis, root resorption, and hyalinization can occur.[16] As a result, increasing the velocity of alveolar bone turnover should be the basis for "facilitating" faster orthodontic tooth movement without increasing the magnitude of force.[17] According to Al-Naoum et al.,[4] patients had a two to four times faster velocity in space closure after buccal and palatal corticotomy for canine retraction, followed by moderate to severe pain and discomfort while eating during the first 2 days. However, the pain decreased on the third day and continued to diminish until the seventh day. The properties of ibuprofen provided faster onset and longer duration for the reduction of moderate to severe postoperative dental pain as well as a lower percentage of patients who required rescue medication compared with acetaminophen.[18]

The present study investigated the amount and rate of tooth movement and BV/TV in orthodontic and corticotomy-assisted conditions. The results comparing tooth movement between the OTM and OTMI groups revealed that tooth movement in the OTMI group was significantly less than the OTM group throughout the study period. Also, the tooth movement rate in the first week in the OTMI group was twofold lower than in the OTM group but gradually increased in the second and third weeks. These results were consistent with a study by Kehoe et al.,[12] who investigated the effects of ibuprofen on orthodontic tooth movement in guinea pigs. In their study, the distance of incisor tooth separation in the ibuprofen group was 1.3 times lower than the control group on experimental day 11. In addition, the current findings were similar to those of Arias et al.,[14] who examined the effect of ibuprofen on orthodontic tooth movement in Wistar rats. They found that the average tooth movement in the ibuprofen group was considerably lower than the controls on the second day after drug administration. In this study, BV/TV was not statistically significantly different between the OTM and OTMI groups.

Ibuprofen inhibits cyclooxygenase activity, which regulates the synthesis of prostaglandins from arachidonic acid in the cellular plasma membrane.[9] Therefore, the production of prostaglandins, specifically $PGE_2$, is inhibited. $PGE_2$ is related to bone remodeling by acting on osteoblasts, which decreases RANKL,

followed by an increase in osteoprotegerin levels.[3,6,16] Previous histology assay results showed a lower number of osteoblasts and osteoclasts that suppressed osteoclastogenesis in the ibuprofen intake group, which indicated a reduction in bone resorption and a delay in tooth movement.[12,14]

Micro-CT confirmed that the surgery groups had a higher amount and faster rate of tooth movement than the orthodontic groups with lower BV/TV in the surgical groups than the orthodontic groups. These findings were in agreement with a study by Baloul et al.[3] that found the tooth movement rate was highest in the first 7 days after decortication. In addition, maximum BV/TV decreased during the first 7 days before gradually returning to baseline on day 28. Selective alveolar decortication causes significant therapeutically induced osteopenia, which can be explained by two principal effects of cortical bone decortication. The biological response caused local inflammatory mediators to increase, leading to an increase in osteoblast markers, osteoclast regulation, and activity markers as well as an increase in osteoclastogenesis-promoting cytokines.[3] Then, a local reaction of tissues to noxious stimuli by tissue regenerates faster than normal in a regional regeneration and remodeling process, which is a physiological response that leads to reduced bone mineral density followed by a decrease in bone resistance known as transient osteopenia.[19] The current findings revealed a significant reduction in BV/TV after alveolar decortication throughout all periods. This implied that mechanical damage to the cortical bone facilitated bone remodeling, which accelerated the recovery and repair processes.

The COTMI group had less tooth movement and a slower tooth movement rate than the COTM group without statistically significant differences. In the first week, the tooth movement rate in the COTMI group did not reach its maximum point compared with the COTM group, which resulted in slightly less total tooth movement distance. From the second to third weeks of treatment, the tooth movement rate in the COTMI group increased at a similar rate to the COTM group. However, no statistically significant differences in the amount and rate of tooth movement were observed at each time point. The COTMI group had higher BV/TV than the COTM group at each time point but without a statistically significant difference.

Corticotomy decreases bone density by creating transient osteopenia and reduces bone resistance. In addition, the release of cytokines causes an increase in biological markers followed by a higher rate of bone turnover, both of which promote osteoclastogenesis.[3,16] Although ibuprofen reduces inflammation and discomfort in corticotomy, ibuprofen did not significantly affect the osteopenia phenomenon as shown by the BV/TV values in the COTM and COTMI groups. The findings showed that ibuprofen consumption combined with corticotomy had no statistically significant effect on tooth movement acceleration as evidenced by tooth movement distance, tooth movement rate, and BV/TV, which were not different between the COTM and COTMI groups.

Although drug dosage, route of administration, duration, and regulation of drug intake differed in previous studies, the current study used 15 mg/kg of ibuprofen, which is the recommended dosage for NSAID in rodents.[20] However, tooth movement produced by the orthodontic appliance was consistent with earlier findings.

In summary, ibuprofen had an inhibitory effect on tooth movement when orthodontic force was applied, but it had no statistically significant effect on tooth movement or bone structure regulation with corticotomy assistance. However, further histomorphometry and immunohistochemistry studies are required to fully understand how ibuprofen interacts with bone-tissue responses.

## CONCLUSIONS

- Administration of ibuprofen for 7 days significantly decreased the amount and rate of orthodontic tooth movement compared with orthodontic tooth movement alone.
- Alveolar decortication caused a significant increase in the amount and rate of orthodontic tooth movement and a decrease in BV/TV compared with orthodontic tooth movement alone.
- Orthodontic tooth movement between corticotomy-assisted groups with or without ibuprofen intake did not show statistically significant differences in the amount and rate of orthodontic tooth movement or BV/TV after 7 days of ibuprofen administration.

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## REFERENCES

1. Köle H. Surgical operations on the alveolar ridge to correct occlusal abnormalities. *Oral Surg Oral Med Oral Pathol*. 1959;12(5):515–529.
2. Frost HM. The regional acceleratory phenomenon: a review. *Henry Ford Hosp Med J*. 1983;31(1):3–9.
3. Baloul SS, Gerstenfeld LC, Morgan EF, Carvalho RS, Van Dyke TE, Kantarci A. Mechanism of action and morphologic changes in the alveolar bone in response to selective alveolar decortication–facilitated tooth movement. *Am J Orthod Dentofacial Orthop*. 2011;139(4):S83–S101.

4. Al-Naoum F, Hajeer MY, Al-Jundi A. Does alveolar corticotomy accelerate orthodontic tooth movement when retracting upper canines? A split-mouth design randomized controlled trial. *J Oral Maxillofac Surg*. 2014;72(10):1880–1889.
5. Kawabata A. Prostaglandin E2 and pain—an update. *Biol Pharm Bull*. 2011;34(8):1170–1173.
6. Liu XH. Interactive effect of interleukin-6 and prostaglandin E2 on osteoclastogenesis via the OPG/RANKL/RANK system. *Ann N Y Acad Sci*. 2006;1068(1):225–233.
7. Xiaoting L, Yin T, Yangxi C. Interventions for pain during fixed orthodontic appliance therapy: a systematic review. *Angle Orthod*. 2010;80(5):925–932.
8. Phillips WJ, Currier BL. Analgesic pharmacology: II. Specific analgesics. *J Am Acad Orthop Surg*. 2004;12(4):221–233.
9. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol*. 2011;31(5):986–1000.
10. Cheng C, Xie T, Wang J. The efficacy of analgesics in controlling orthodontic pain: a systematic review and meta-analysis. *BMC Oral Health*. 2020;20(1):259.
11. Becker DE, Phero JC. Drug therapy in dental practice: nonopioid and opioid analgesics. *Anesth Prog*. 2005;52(4):140–149.
12. Kehoe MJ, Cohen SM, Zarrinnia K, Cowan A. 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):339–349.
13. Shetty N, Patil AK, Ganeshkar SV, Hegde S. Comparison of the effects of ibuprofen and acetaminophen on PGE2 levels in the GCF during orthodontic tooth movement: a human study. *Prog Orthod*. 2013;14(1):6.
14. Arias OR, Marquez-Orozco MC. Aspirin, acetaminophen, and ibuprofen: their effects on orthodontic tooth movement. *Am J Orthod Dentofacial Orthop*. 2006;130(3):364–370.
15. Kraiwattanapong K, Samruajbenjakun B. Effects of different force magnitudes on corticotomy-assisted orthodontic tooth movement in rats. *Angle Orthod*. 2018;88(5):632–637.
16. Krishnan V, Kuijpers-Jagtman AM, Davidovitch Z. Cellular and molecular biology behind orthodontic tooth movement. In: Krishnan V, Davidovitch Z, eds. *Biological Mechanisms of Tooth Movement*. 2nd ed. Sussex, West UK: Wiley-Blackwell; 2015:30–50.
17. Verna C. The rate and the type of orthodontic tooth movement is influenced by bone turnover in a rat model. *Eur J Orthod*. 2000;22(4):343–352.
18. Olson MsNZ, Otero AM, Marrero I, et al. Onset of analgesia for liquigel ibuprofen 400 mg, acetaminophen 1000 mg, ketoprofen 25 mg, and placebo in the treatment of postoperative dental pain. *J Clin Pharmacol*. 2001;41(11):1238–1247.
19. Sebaoun JD, Kantarci A, Turner JW, Carvalho RS, Van Dyke TE, Ferguson DJ. Modeling of trabecular bone and lamina dura following selective alveolar decortication in rats. *J Periodontol*. 2008;79(9):1679–1688.
20. Flecknell PA. Analgesia and post-operative care. In: Flecknell PA, ed. *Laboratory Animal Anaesthesia*. 4th ed. Waltham, MA: Elsevier; 2016:141–192.