Medicine®

SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

Escaping the Adverse Impacts of NSAIDs on Tooth Movement During Orthodontics

Current Evidence Based on a Meta-Analysis

Jie Fang, DDS, PhD, Yifei Li, MD, PhD, Keke Zhang, PhD, Zhihe Zhao, DDS, PhD, and Li Mei, DDS, PhD

Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to relieve pain during orthodontic treatments; however, the possible inhibition of orthodontic tooth movement (OTM) by NSAIDs has been debated. The aim of this study was to evaluate the influence of some commonly used NSAIDs on OTM during orthodontic treatments.

A review of the literature identified relevant studies up to August 2014. A meta-analysis was performed following the guidelines of the Cochrane review group and the PRISMA statement. Studies were identified by searching PUBMED, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials, and the WHO Clinical Trials Registry Platform. Meta-analysis was performed in a fixed/random-effect model using Revman 5.1.1.

Five studies, including 128 subjects and 3 main NSAIDs (celecoxib, acetaminophen, and aspirin), were included for quantitative synthesis and analysis. Celecoxib did not inhibit OTM except with middle-term use (2–3 weeks) (95% CI [−6.47 to −0.43], $P = 0.03$). Acetaminophen did not inhibit OTM except with long-term use (>1 month) and low-dose use (~100 mg/kg per day), (95% CI [−2.96 to −0.78], $P = 0.0008$; 95%CI [−2.42, −0.46], $P = 0.004$; respectively). Aspirin was found to inhibit OTM (95%CI [−2.40 to −0.64], $P = 0.0008$).

Our systematic review with meta-analysis suggests that aspirin might inhibit OTM in rat models, whereas the short-term (<1 week) use of celecoxib and acetaminophen for relieving orthodontic pain would not inhibit OTM. Well-designed human research should be completed before a solid conclusion can be reached.

(*Medicine* 95(16):e3256)

Abbreviations: CI = confidence interval, COX = cyclooxygenase, MMP-13 = matrix metalloproteinases 13, NSAIDs = nonsteroidal anti-inflammatory drugs, OTM = orthodontic tooth movement, PGs = prostaglandins.

Editor: Kazuo Hanaoka.
Received: October 15, 2015; revised: March 9, 2016; accepted: March 10, 2016.
From the State Key Laboratory of Oral Diseases (JF, KZ, ZZ, LM), West China Hospital of Stomatology; Department of Pediatric Cardiology (YL), West China Second University Hospital, Sichuan University, Chengdu, China; and Discipline of Orthodontics (LM), Department of Oral Sciences, Faculty of Dentistry, University of Otago, Otago, New Zealand.
Correspondence: Zhihe Zhao, State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, China, (e-mail: zhzhao@scu.edu.cn).
JF and YL contributed to this study equally.
Funding: this study was supported by grants from the National Natural Science Foundation of China (No. 81301476), Doctoral Fund of Ministry of Education of China (20120181120004), and Research Fund of Sichuan University (YJ2012014).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003256

INTRODUCTION

Demand for orthodontic treatment has increased due to its benefits in improving aesthetics, self-esteem, and jaw function. However, during tooth movement, most patients experience intolerable pain, producing a considerable amount of distress in the daily life of patients and difficulties in chewing and biting. Orthodontic pain is considered a major concern for patients, parents, and clinicians. It has been reported that >90% of patients experience pain during orthodontic treatment, discouraging patients from seeking treatment and causing many patients to discontinue treatment.[1–3]

Currently, the primary medication treatments for managing orthodontic pain are nonsteroidal anti-inflammatory drugs (NSAIDs) such as celecoxib, acetaminophen, and aspirin.[4–6] NSAIDs exert pain-relieving effects through the inhibition of cyclooxygenase (COX), which is the essential enzyme in the synthetic pathways of the prostanoids.[7–9] By virtue of their ability to inhibit COX and thus inhibit the release of prostaglandins (PGs), NSAIDs can suppress biochemical inflammatory responses and relieve the pain.

PGs are of great importance for bone remodeling as well.[10,11] It has been reported that PG has the capacity to alter the activity or numbers of osteoclasts or osteoclast-like cells.[12] Moreover, some researchers noted that NSAIDs had some adverse impacts that could inhibit orthodontic tooth movement (OTM) while relieving pain, but this standpoint was still under debate. Many studies have been conducted on this issue in recent years, which suggested that acetaminophen,[4] potassium diclofenac,[10] rofecoxib,[11] celecoxib,[13,14] and indomethacin[12,15] would slow down the velocity of OTM and thus were inappropriate therapies for pain relief during orthodontic treatment. Conversely, some studies showed that acetaminophen,[6,16–18] celecoxib,[4,11,16,19] aspirin[7] had no influence on OTM and could be alternatives as therapeutic pain medications.

At present, only a limited number of human studies have investigated the influence of NSAIDs on OTM.[20,21] Most of them have been underpowered, have lacked a proper control group, and have had quite low evidence levels. As were difficulties in performing such research among clinical patients, an increasing number of rodent studies have investigated the influence of NSAIDs on OTM during the past decade; their use of statistically accurate evaluation systems has consummated these studies, making them acceptable and credible. Therefore, analysis of rodent experiments and pooling of the results would be a better alternative for demonstrating this issue than reviewing the existing human clinical research. Thus, a systematic review with meta-analysis has been carried out to assess the impacts of NSAIDs on OTM in rat models.

MATERIALS AND METHODS

Search Strategy and Data Sources

Systematic strategies were used for searching each database to identify all the studies relevant to this review. The search strategy for Medline was ((((((anti-inflammatory drugs) OR Non-steroidal) OR NSAIDs) OR NSAID[MeSH Terms]) OR Non-steroid)) AND ((((((orthodontics[MeSH Terms]) OR orthodontics) OR tooth movement[MeSH Terms]) OR orthodontic tooth movement) OR malocclusion) OR malocclusion[MeSH Terms]) and was revised appropriately for other databases. The following databases were searched:

1. MEDLINE via PubMed (1970–Aug 2014)
2. Web of Science (1970–Aug 2014)
3. EMBASE (1970–Aug 2014)
4. CENTRAL (The Cochrane Library, Aug 2014)
5. Science Direct (1970–Aug 2014)

The reference lists of all eligible studies were also hand searched for additional studies. Language restriction was used to include only papers published in English. Unpublished literature was searched for on ClinicalTrial.gov, the National Research Register, and the World Health Organization's International Clinical Trial Registry Platform.

Selection Criteria

Types of Studies

Studies evaluated the influence of NSAIDs on OTM during abirritation. Only experimental animal studies were included.

Types of Subjects

Any group of rats undergoing orthodontic tooth movement.

Types of Interventions

1. Systematic administration of NSAIDs versus no NSAIDs/lacebo.
2. Systematic administration of different NSAIDs.
3. Systematic administration of different doses or durations of the same NSAIDs.

Outcome Measures

The OTM outcomes were directly measured using vernier calipers intraorally or indirectly measured from digitized radiographs.

Data Collection and Quality Assessment

Study Selection

The titles and abstracts (when available) of all identified reports were assessed independently by 2 reviewers. For studies appearing to meet the inclusion criteria or for which there were insufficient data in the title and abstract to make a clear decision, the full reports were obtained and assessed to establish whether these studies met the inclusion criteria or not. Disagreements were resolved by discussion and by consulting a third reviewer if needed.

Data Extraction

The following data were recorded for each report:

1. Authors and year of publication.
2. Details of the rats studied, including species, gender, age, and average weights.

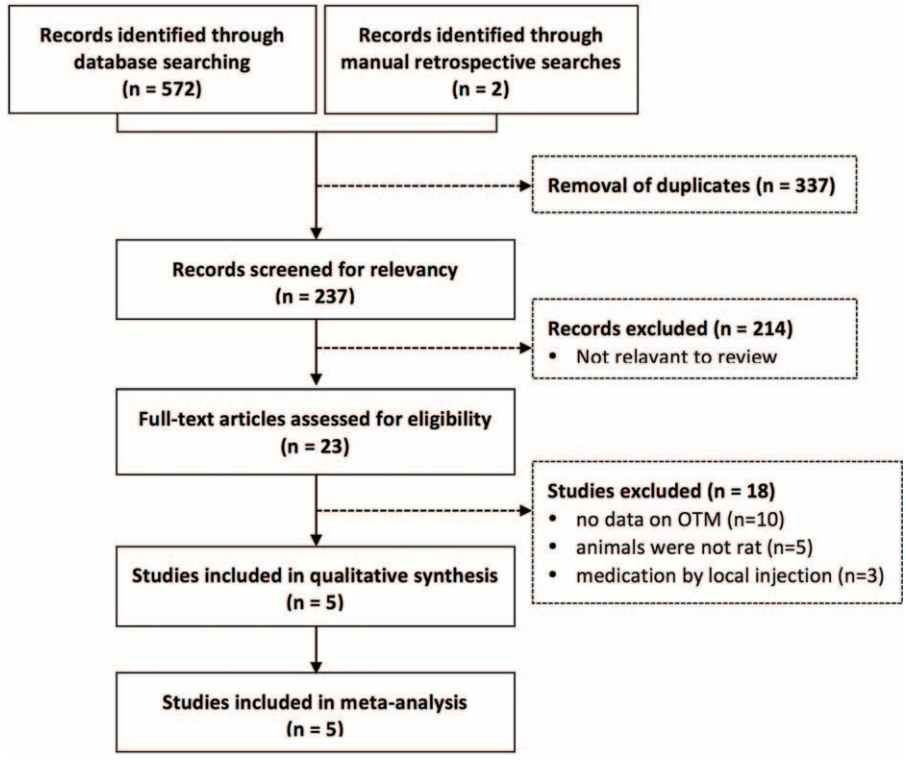

FIGURE 1. Flow diagram of the literature search process.

3. Details of the interventions, including the type of NSAIDs, applications, and orthodontic force magnitude.
4. Details of the outcomes reported, including methods of assessment.

Quality Assessment

Quality assessments were performed on the included trials using the Recommendations for Ensuring Good Scientific Inquiry guidelines.[22]

Statistical Analysis

The heterogeneity of the included studies was assessed using the Cochrane Q test and I^2 statistics. If the research effect size was not heterogeneous ($I^2 < 50\%$), count data were analyzed using a fixed effect model. If the research effect size was heterogeneous ($I^2 \geq 50\%$), the random effect model was used.

The publication bias of included studies was evaluated using Begg's funnel plot in STATA 11.0 (Stata Corporation, College Station, TX). When the funnel plot was symmetric, the data were considered to have no biases of publication. If the funnel plot was asymmetric, bias of publication was considered to exist, and the degree of the asymmetry was measured by Egger's test. $P < 0.05$ was considered to be statistically significant.

All analyses were conducted using Revman (Review Manager) version 5.1.1 software (Cochrane Collaboration, Oxford, England). Combined odds ratios and 95% confidence intervals (95% CI) were recorded. Measurement data were analyzed using the weighted mean difference and 95% CI. Sensitivity analysis was unable to be performed due to the limited number of studies included.

Besides, ethical approval was not necessary as this was a pooled analysis from published articles.

RESULTS

Study Characteristics

A total of 237 records were screened for relevancy after removal of duplicates. Five studies,[4,6,13,14,16] including 128 subjects and 3 main NSAIDs (celecoxib, acetaminophen, and aspirin), were finally included for quantitative synthesis and analysis (Figure 1). The details of the included studies and their quality assessments are presented in Tables 1 and 2, respectively. The methods used to measure OTM in these studies are summarized in Table 3.

Effects of Interventions

Celecoxib Therapy

A total of 58 cases were enrolled for overall comparison, consisting of 29 cases in the celecoxib group and 29 cases in the control group (Figure 2). No significant difference was found between celecoxib and control groups, with a summarized standardized mean difference of −1.39 (95% CI [−3.06 to 0.29], $P = 0.11$). Heterogeneity was found across studies ($P = 0.0004$, $I^2 = 83\%$) and the data were analyzed using the random effect model (Figure 2).

To assess the publication bias of the studies on celecoxib, Begg's funnel plot was constructed and Egger's test was performed. The funnel plot seemed symmetrical, indicating the absence of publication bias (Figure 3); this was quantitatively confirmed by Egger's test ($t = -1.98$, $P = 0.186$).

TABLE 1. Main Characteristics of Included Studies

Author	Year	Interventions	No. of cases	Species	Gender	Age (week)	Average Weight (g)	Appliances	Force Magnitude	Evaluation Indicator	Randomization Method	Blind Method
Hammad	2012	Control; Celecoxib; Acetaminophen	10; 10; 10	NG	Male	12	230–250	Closed coil spring	50 cN	Tooth movement	Yes	YES
Stabile	2009	Control; Celecoxib; Acetaminophen	5; 5; 5	Wistar	Male	NG	400	Open Loop	30 g	Tooth movement	NG	NG
Gonzales	2009	Control; Celecoxib; Acetaminophen; Aspirin	5; 5; 5; 5	Wistar	Male	10	230–250	Closed coil spring	50 g	Tooth movement	Yes	NG
Hauber	2008	Control; Celecoxib	9; 9	Wistar	Male	NG	300–400	Closed coil spring	50 g	Tooth movement	Yes	Yes
Arias	2006	Control; Acetaminophen; Aspirin	9; 9; 9	Wistar	Male	NG	250–300	Open Loop	35 g	Tooth movement	Yes	Yes

NG = not given.

TABLE 2. Main Quality Evaluation of Included Studies

Studies	Sample Size Calculation	Inclusion and Exclusion Criteria	Randomization	Allocation Concealment	Reporting of Data Excluded From Analysis	Blinded Assessment of Outcome	Reporting Potential Conflicts of Interest and Study Funding
Hammad	NG	Basic inclusion criteria and experimental procedure were stated	The allocation was randomized, but provided no randomized methods.	NG	NG	Blinded assessment was performed in data calculated with detail stated.	NG
Stabile	NG	Basic inclusion criteria and experimental procedure were stated	NG	NG	NG	NG	Declared no conflict of interest
Gonzales	NG	Basic inclusion criteria and experimental procedure were stated	The allocation was randomized, but provided no randomized methods.	NG	Some data were excluded with certain reasons.	NG	NG
Hauber	NG	Basic inclusion criteria and experimental procedure were stated	The allocation was randomized, but provided no randomized methods.	NG	NG	NG	NG
Arias	NG	Inclusion criteria and experimental procedure were stated in detail	The allocation was randomized, but provided no randomized methods.	Allocation concealments in operators and observers were stated in detail	NG	NG	NG

NG = not given.
The qualities of all the articles were acceptable.

TABLE 3. Details of Methods on How to Measure Orthodontic Tooth Movements (OTM)

Studies	Methodology of OTM Measurement
Hammad	The magnitude of OTM was determined by measuring the relative separation between the first and second maxillary molar using vernier calipers with sharpened tips inserted into occlusal pits. The distance between the mesial occlusal pits on the first and second molars was measured intraorally before appliance insertion and immediately after sacrifice. Measurements were performed by the same operator and were repeated 5 times for each rat.
Stabile	The photographies (Sony DSC S-90, 4 mega pixels, ''fine'' image quality) and radiographies (Kodak E-speedy x-ray film; Dabi Atlante's intraoral x-ray machine70 kVp, 8 mA; 0.3 s of exposition) of maxillas were digitalized and analyzed by the Image J program (Wayne Rasband, National Institutes of Health, USA). They measured the distance between the incisors and the distance between the 2 palatine bones, respectively. A periodontal probe was used for calibration.
Gonzales	Tooth movement was measured on digitized lateral cephalometric radiographs. The amount of tooth movement was determined by the change in the distance between the most posterior point of the posterior border of the maxillary first molar crown and the most anterior point of the anterior border of the maxillary second molar crown.
Hauber	The distance between the mesial surface of the first and the distal surface of the third molar was measured bilaterally with an electronic caliper for high accuracy (Digimatic-Mitutoyo, Telford, UK) under a dental operating microscope (DF Vasconcellos SA, Sao Paulo, P, Brazil) at 16× magnification. Tooth movement was estimated by subtracting the mean of the repeated measured values from the untreated and treated sides.
Arias	Before the appliances were placed, it was determined that there was no measurable space between the maxillary incisors. Measurements of incisor separation were recorded at the same time in the morning, by using a caliper accurate to 0.01 mm. Measurements were made by 2 observers who were blinded to treatment allocation; they recorded the average from 3 assays.

The reliability of each methodology was acceptable.

Subgroup Analysis According to Medication Duration

The short-term group referred to medication duration <1 week. Only 1 study was included, consisting of 5 cases in the celecoxib group and 5 cases in the control group. No significant difference was found between the 2 groups, with a standardized mean difference of 0.00 (95% CI [−1.24 to 1.24], $P = 1.00$) (Figure 2).

The middle-term group referred to medication duration of 2 to 3 weeks. Two studies were included, consisting of 14 cases in the celecoxib group and 14 cases in the control group. OTM was found to be significantly inhibited in the celecoxib group, with a summarized standardized mean difference of −3.45 (95% CI [−6.47 to −0.43], $P = 0.03$). Heterogeneity was detected ($P = 0.08$, $I^2 = 68\%$) (Figure 2).

The long-term group referred to medication duration was >1 month. One study was enrolled, consisting of 10 cases in the celecoxib group and 10 cases in the control group. No significant difference was found between the 2 groups, with a standardized mean difference of 0.07 (95% CI [−0.81 to 0.94], $P = 0.88$) (Figure 2).

Subgroup Analysis According to Medication Dosage

The high-dose group referred to medication dosage of ∼100 mg/kg per day. One study was enrolled, consisting of 5 cases in the celecoxib group and 5 cases in the control group. No significant difference was found between the 2 groups, with a standardized mean difference of 0.00 (95% CI [−1.24 to 1.24], $P = 1.00$) (Figure 4).

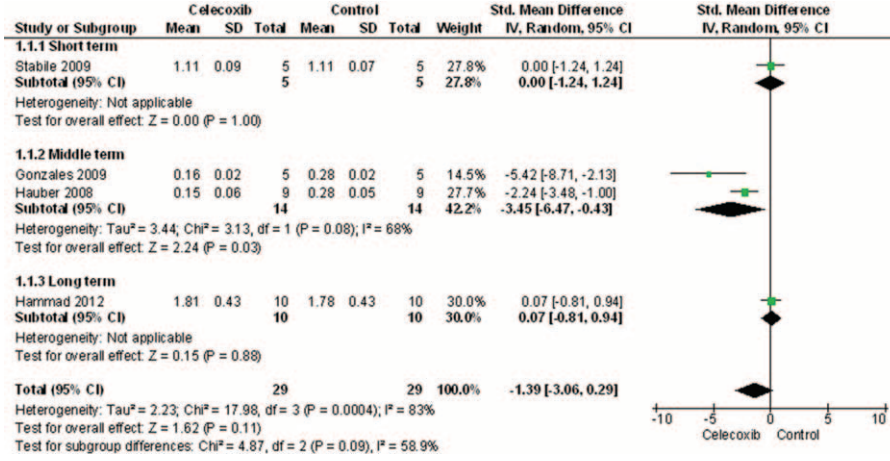

FIGURE 2. The influence of celecoxib versus control on orthodontic tooth movement, according to medication duration.

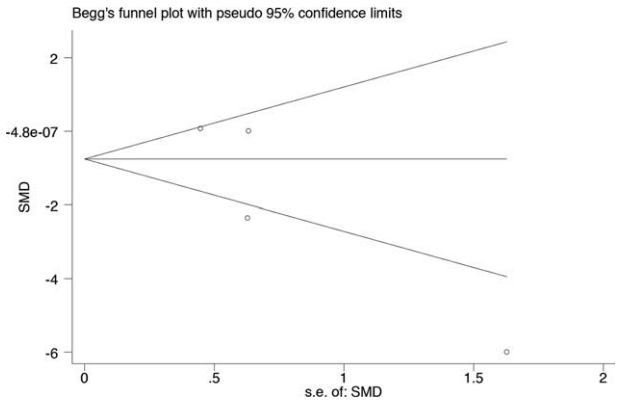

FIGURE 3. Begg's funnel plot assessing publication bias of the studies on celecoxib.

The low-dose group referred to medication dosage of ~15 mg/kg per day. Three studies were enrolled, consisting of 24 cases in the celecoxib group and 24 cases in the control group. No significant difference was found between the 2 groups, with a summarized standardized mean difference of −2.08 (95% CI [−4.52 to 0.35], $P = 0.09$). Heterogeneity was detected ($P = 0.0003$, $I^2 = 83\%$) (Figure 4).

Acetaminophen Therapy

A total of 76 cases were enrolled for overall comparison, consisting of 38 cases in the acetaminophen group and 38 cases in the control group. No significant difference was found between the 2 groups, with a summarized standardized mean difference of −0.43 (95% CI [−1.34 to 0.49], $P = 0.36$). Heterogeneity was found across studies ($P = 0.009$, $I^2 = 70\%$), and data were analyzed by the random effect model (Figure 5).

To assess the publication bias of studies on acetaminophen, Begg's funnel plot was constructed and Egger's test was performed. The funnel plot seemed symmetrical, indicating the absence of publication bias (Figure 6). Egger's test provided quantitative evidence for the lack of publication bias ($t = 0.34$, $P = 0.754$).

Subgroup Analysis According to Medication Duration

The short-term group referred to medication duration of <1 week. Two studies were included, consisting of 14 cases in the acetaminophen group and 14 cases in the control group. No significant difference was found, with a summarized standardized mean difference of 0.52 (95% CI [−0.61 to 1.64], $P = 0.37$). No heterogeneity was detected ($P = 0.17$, $I^2 = 46\%$) (Figure 5).

The middle-term group referred to medication duration of 2 to 3 weeks. Two studies were included, consisting of 14 cases in the acetaminophen group and 14 cases in the control group. No significant difference was found between the 2 groups, with a summarized standardized mean difference of −0.62 (95% CI [−1.39 to 0.15], $P = 0.11$). No heterogeneity was detected ($P = 0.67$, $I^2 = 0\%$) (Figure 5).

The long-term group referred to medication duration of >1 month. One study was enrolled, consisting of 10 cases in the acetaminophen group and 10 cases in the control group. OTM was found to be significantly inhibited in the acetaminophen group, with a standardized mean difference of −1.87 (95% CI [−2.96 to −0.78], $P = 0.0008$) (Figure 5).

Subgroup Analysis According to Medication Dosage

The high-dose group referred to medication dosage of ~400 mg/kg per day. Two studies were enrolled, consisting of 14 cases in the acetaminophen group and 14 cases in the control group. No significant difference was found, with a summarized standardized mean difference of 0.28 (95% CI [−1.42 to 1.97], $P = 0.75$). Heterogeneity was detected ($P = 0.05$, $I^2 = 75\%$) (Figure 7).

The low-dose group referred to medication dosage of ~100 mg/kg per day. Two studies were enrolled, consisting of 15 cases in the acetaminophen group and 15 cases in the control group. OTM was found to be significantly inhibited in the acetaminophen group, with a summarized standardized mean difference of −1.44 (95% CI [−2.42 to −0.46], $P = 0.004$). No heterogeneity was detected ($P = 0.25$, $I^2 = 25\%$) (Figure 7).

Aspirin Therapy

A total of 28 cases were enrolled for overall comparison, consisting of 14 cases in the aspirin group and 14 cases in the

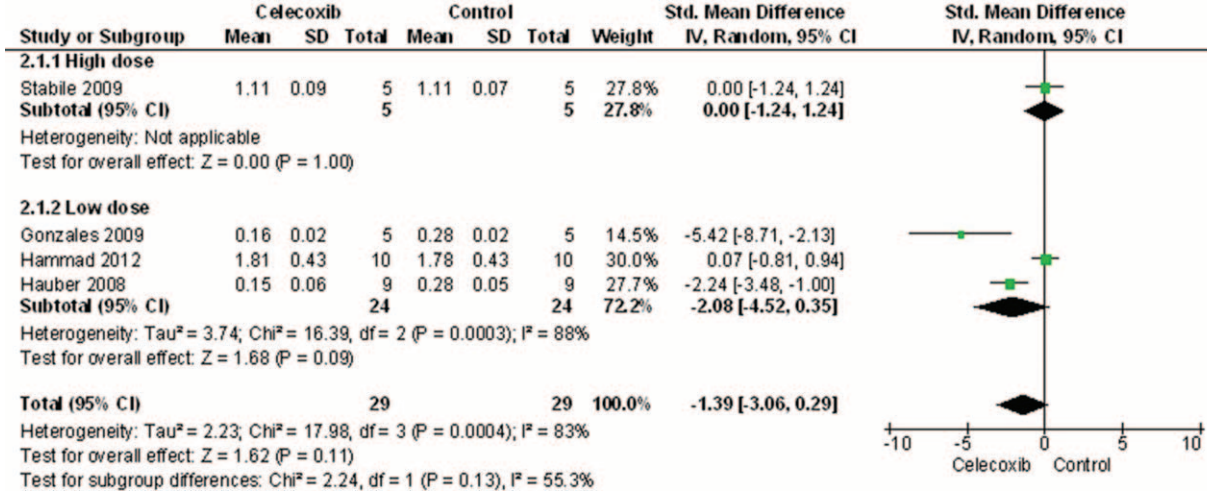

FIGURE 4. The influence of celecoxib versus control on orthodontic tooth movement, according to medication dosage.

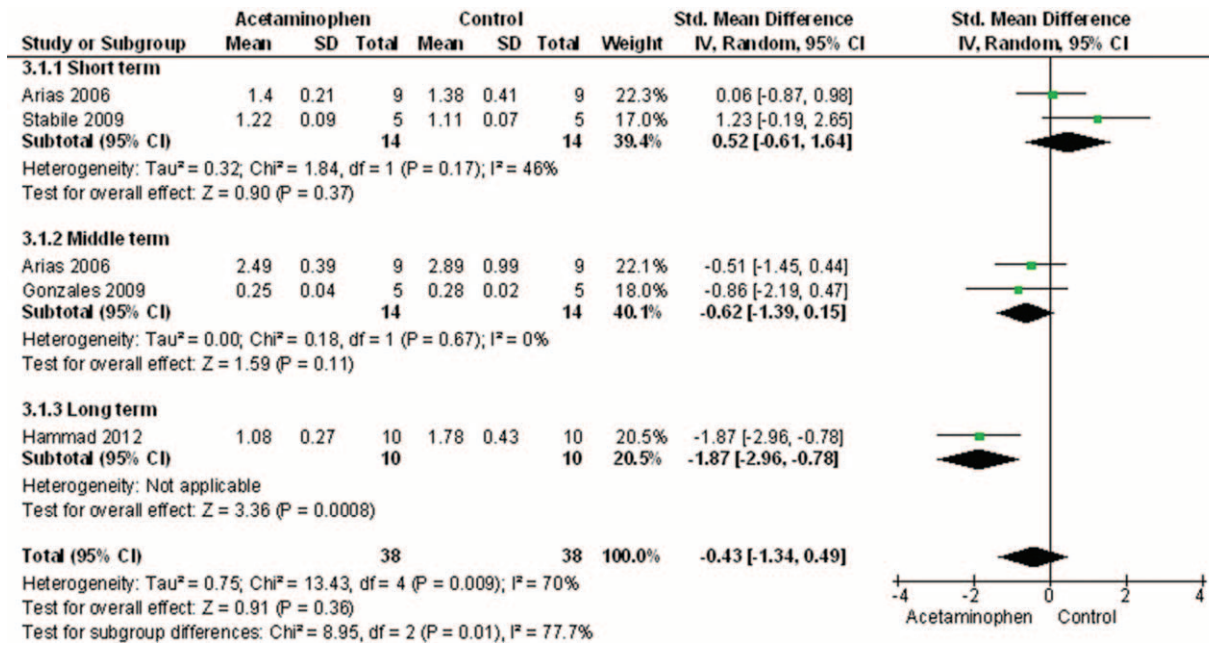

FIGURE 5. The influence of acetaminophen versus control on orthodontic tooth movement, according to medication duration.

control group. The medication dosage was ~250 mg/kg per day and the medicine duration was around 2 weeks. OTM was found to be significantly inhibited in the aspirin group, with a summarized standardized mean difference of −1.52 (95% CI [−2.40 to −0.64], $P = 0.0008$). No heterogeneity was detected ($P = 0.67$, $I^2 = 0\%$) (Figure 8).

DISCUSSION

Although NSAIDs are the most commonly recommended analgesic for pain relief during orthodontic treatment, controversy over whether they will reduce OTM still exists. Therefore, we performed a systematic literature review and meta-analysis based on experimental data of OTM after pharmaceutical interventions. Unfortunately, there are only a few human clinical trials.[20,21,23] As a result, this review focused on well-controlled animal studies. To the best of our knowledge, this is the first meta-analysis ever conducted evaluating the impacts of NSAIDs during orthodontic tooth movement, in an area of investigation lacking randomized controlled trials and large sample size cohort studies. Consequently, the level of the evidence of this study is elevated and thus leads to some evidence-based progress in this medical field.

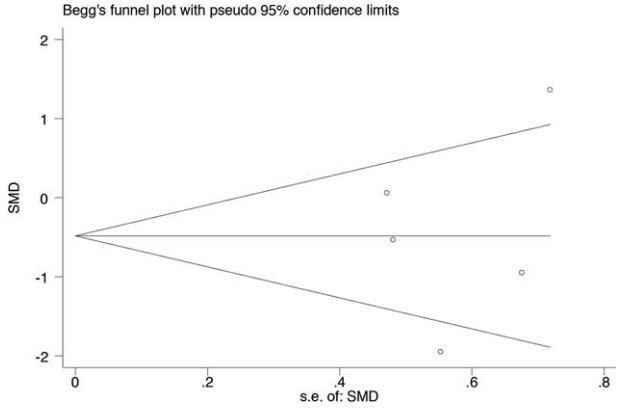

FIGURE 6. Begg's funnel plot assessing publication bias of the studies on acetaminophen.

Of 5 included articles, 4 studies focused on celecoxib, 5 focused on acetaminophen, and 2 focused on aspirin, including 128 total rats. All of the included studies were well randomized and controlled. Wistar rats were used in 4 articles, but the species of rats is unfortunately not given in 1 article. Among the studies, only male rats were included, taking into account the interference of estrogen on tooth movement.[24,25] Two articles applied force between the upper incisors, and 3 articles distributed the force between the maxillary first molars and incisors. The force magnitude was at 30 to 50 g level, which was appropriate for rats according to previous studies.[6,14,26–28] Given all these considerations, the quality of all the articles was acceptable.

To compare overall pharmaceutical interventions, it is suggested that celecoxib and acetaminophen have no effects on OTM and that aspirin may slow OTM. The differences may result from the varying mechanisms and chemical structures of different classes of NSAIDs. Prostaglandins (PGs) are generated by the oxygenation of AA by PGHS, of which there are 2 major isoforms—the constitutive PGHS-1 and the (generally) inducible PGHS-2. These enzymes are also commonly referred to as cyclooxygenase (COX) 1 and 2. Within the canine cerebral cortex, COX-3 was found as an enzyme that is the product of an alternatively spliced translation of COX-1 gene expression. However, the name COX-3 is controversial because it is a product of alternative splicing of COX-1 and not a genetically distinct entity.[13,20,29–33] Aspirin is regarded as a potent irreversible inhibitor of both COX-1 and COX-2, also known as nonselective COX inhibition, whereas celecoxib is a highly specific COX-2 inhibitor.[4,13,34,35] Acetaminophen differs from

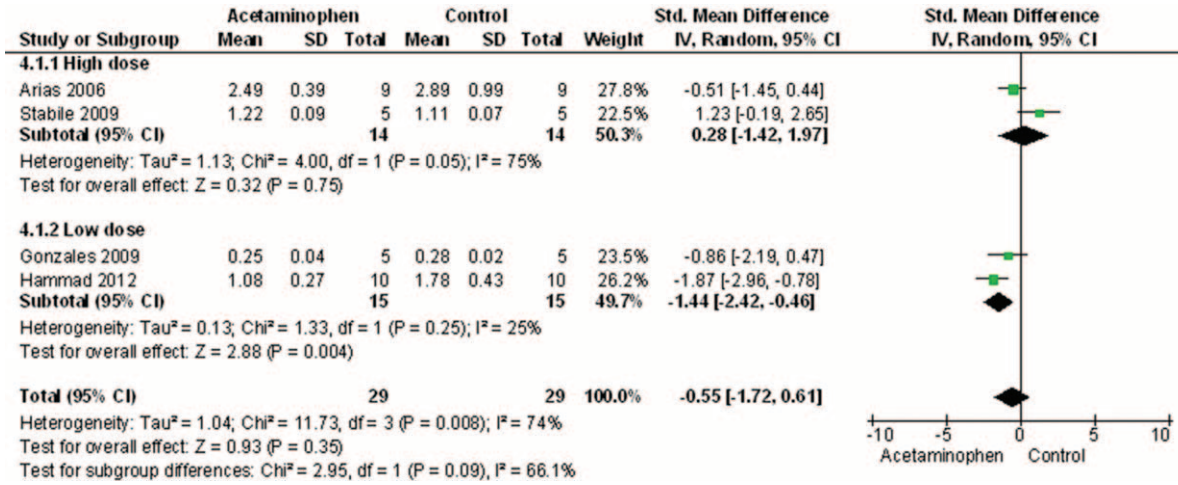

FIGURE 7. The influence of acetaminophen versus control on orthodontic tooth movement, according to medication dosage.

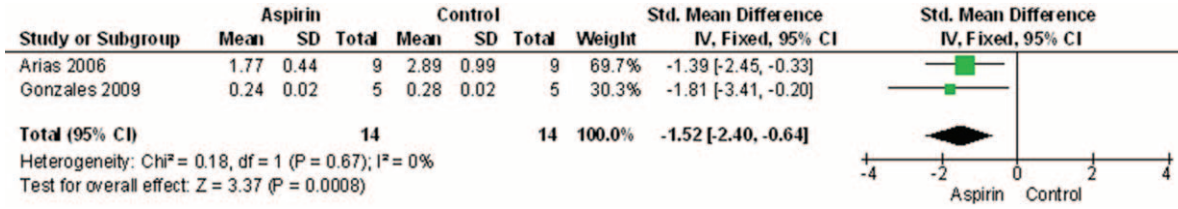

FIGURE 8. The influence of aspirin versus control on orthodontic tooth movement.

the majority of NSAIDs in its lack of significant anti-inflammatory activity, and its mechanism is still unclear despite being used clinically for more than a century. One of the more recent proposals put forward an explanation of the unusual effects of acetaminophen as being due to inhibition of COX-3, but further analysis is needed. It was hypothesized that COX inhibitors with differences in COX selectivity and mechanisms could affect OTM in different manners.[4]

The inhibition of celecoxib on OTM was found in only the middle-term (2–3 weeks) group and had no relevance with the medication dosage. This inhibition may occur because the decrease of active osteoclasts, which slows down OTM, has been found in only the middle-term group.[4,14,19] Additionally, 2 to 3 weeks of repeated injections and force applications may also arouse the stress response in rats, stimulating the generation of endogenous glucocorticoids and thereby inhibiting bone turnover.[14,36]

The inhibition of acetaminophen on OTM was found in both the long-term (>1 month) group and the low-dose (~100 mg/kg per day) group. The pharmacological mechanism of this inhibition is unclear. Some studies have found a decreased expression of matrix metalloproteinases 13 (MMP-13) and a decreased number of osteoclasts after the long-term use of acetaminophen, and these may slow OTM in rats.[4,6]

Considering that orthodontic pain usually occurs for a short term, from a few hours after the application of orthodontic forces up to approximately a week, we recommend celecoxib and acetaminophen as the analgesics for pain relief during orthodontic treatments. In addition, the possible side effects of medication, patient's history of drugs, and hypersensitivity should also be taken into consideration in clinical practice.

CONCLUSION

Our systematic review with meta-analysis suggests that aspirin might inhibit OTM in rat models and that the short-term (<1 week) use of celecoxib and acetaminophen for relieving orthodontic pain might not inhibit OTM. These results should be interpreted in light of the known limitations of animal study design and methodological quality. Well-designed human studies are needed before a conclusion can be made.

REFERENCES

1. Yozgatian JH, Zeredo JL, Hotokezaka H, et al. Emotional stress- and pain-related behaviors evoked by experimental tooth movement. *Angle Orthod.* 2008;78:487–494.
2. Krishnan V. Orthodontic pain: from causes to management—a review. *Eur J Orthod.* 2007;29:170–179.
3. Xiaoting L, Yin T, Yangxi C. Interventions for pain during fixed orthodontic appliance therapy: a systematic review. *Angle Orthod.* 2010;80:925–932.
4. Hammad SM, El-Hawary YM, El-Hawary AK. The use of different analgesics in orthodontic tooth movements. *Angle Orthod.* 2012;82:820–826.
5. Karthi M, Anbuslevan GJ, Senthilkumar KP, et al. NSAIDs in orthodontic tooth movement. *J Pharm Bioallied Sci.* 2012;4(Suppl 2):S304–306.
6. Arias OR, Marquez-Orozco MC. Aspirin, acetaminophen, and ibuprofen: their effects on orthodontic tooth movement. *Am J Orthod Dentofacial Orthop.* 2006;130:364–370.
7. Wong A, Reynolds EC, West VC. The effect of acetylsalicylic acid on orthodontic tooth movement in the guinea pig. *Am J Orthod Dentofacial Orthop.* 1992;102:360–365.

8. Laudanno OM, Cesolari JA, Esnarriaga J, et al. Gastrointestinal damage induced by celecoxib and rofecoxib in rats. *Dig Dis Sci.* 2001;46:779–784.
9. Seibert K, Zhang Y, Leahy K, et al. Pharmacological and biochemical demonstration of the role of cyclooxygenase 2 in inflammation and pain. *Proc Natl Acad Sci U S A.* 1994;91: 12013–12017.
10. Knop LA, Shintcovsk RL, Retamoso LB, et al. Non-steroidal and steroidal anti-inflammatory use in the context of orthodontic movement. *Eur J Orthod.* 2012;34:531–535.
11. de Carlos F, Cobo J, Perillan C, et al. Orthodontic tooth movement after different coxib therapies. *Eur J Orthod.* 2007;29:596–599.
12. Yamasaki K, Miura F, Suda T. Prostaglandin as a mediator of bone resorption induced by experimental tooth movement in rats. *J Dent Res.* 1980;59:1635–1642.
13. Gonzales C, Hotokezaka H, Matsuo K, et al. Effects of steroidal and nonsteroidal drugs on tooth movement and root resorption in the rat molar. *Angle Orthod.* 2009;79:715–726.
14. Hauber Gameiro G, Nouer DF, Pereira Neto JS, et al. Effects of short- and long-term celecoxib on orthodontic tooth movement. *Angle Orthod.* 2008;78:860–865.
15. Giunta D, Keller J, Nielsen FF, et al. Influence of indomethacin on bone turnover related to orthodontic tooth movement in miniature pigs. *Am J Orthod Dentofacial Orthop.* 1995;108:361–366.
16. Stabile AC, Stuani MB, Leite-Panissi CR, et al. Effects of short-term acetaminophen and celecoxib treatment on orthodontic tooth movement and neuronal activation in rat. *Brain Res Bull.* 2009;79:396–401.
17. Roche JJ, Cisneros GJ, Acs G. The effect of acetaminophen on tooth movement in rabbits. *Angle Orthod.* 1997;67:231–236.
18. Kehoe 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;66:339–349.
19. Carvalho-Filho EP, Stabile AC, Ervolino E, et al. Celecoxib treatment does not alter recruitment and activation of osteoclasts in the initial phase of experimental tooth movement. *Eur J Histochem.* 2012;56:e43.
20. Yamasaki K, Shibata Y, Imai S, et al. Clinical application of prostaglandin E1 (PGE1) upon orthodontic tooth movement. *Am J Orthod.* 1984;85:508–518.
21. Sari E, Olmez H, Gurton AU. Comparison of some effects of acetylsalicylic acid and rofecoxib during orthodontic tooth movement. *Am J Orthod Dentofacial Orthop.* 2004;125:310–315.
22. Fisher M, Feuerstein G, Howells DW, et al. Update of the stroke therapy academic industry roundtable preclinical recommendations. *Stroke.* 2009;40:2244–2250.
23. Bartzela T, Turp JC, Motschall E, et al. Medication effects on the rate of orthodontic tooth movement: a systematic literature review. *Am J Orthod Dentofacial Orthop.* 2009;135:16–26.
24. Yamashiro T, Takano-Yamamoto T. Influences of ovariectomy on experimental tooth movement in the rat. *J Dent Res.* 2001;80: 1858–1861.
25. Carlsten H. Immune responses and bone loss: the estrogen connection. *Immunol Rev.* 2005;208:194–206.
26. King GJ, Keeling SD, McCoy EA, et al. Measuring dental drift and orthodontic tooth movement in response to various initial forces in adult rats. *Am J Orthod Dentofacial Orthop.* 1991;99:456–465.
27. Bridges T, King G, Mohammed A. The effect of age on tooth movement and mineral density in the alveolar tissues of the rat. *Am J Orthod Dentofacial Orthop.* 1988;93:245–250.
28. Rody WJ Jr, King GJ, Gu G. Osteoclast recruitment to sites of compression in orthodontic tooth movement. *Am J Orthod Dentofacial Orthop.* 2001;120:477–489.
29. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. *Clin Pharmacol Ther.* 2006;79:9–19.
30. Davies NM, Good RL, Roupe KA, et al. Cyclooxygenase-3: axiom, dogma, anomaly, enigma or splice error?–Not as easy as 1, 2, 3. *J Pharm Pharm Sci.* 2004;7:217–226.
31. Snipes JA, Kis B, Shelness GS, et al. Cloning and characterization of cyclooxygenase-1b (putative cyclooxygenase-3) in rat. *J Pharmacol Exp Ther.* 2005;313:668–676.
32. Gameiro GH, Pereira-Neto JS, Magnani MB, et al. The influence of drugs and systemic factors on orthodontic tooth movement. *J Clin Orthod.* 2007;41:73–78quiz 71.
33. Yamasaki K, Shibata Y, Fukuhara T. The effect of prostaglandins on experimental tooth movement in monkeys (Macaca fuscata). *J Dent Res.* 1982;61:1444–1446.
34. Thompson JS, Palmieri GM, Eliel LP, et al. The effect of porcine calcitonin on osteoporosis induced by adrenal cortical steroids. *J Bone Joint Surg Am.* 1972;54:1490–1500.
35. Ashcraft MB, Southard KA, Tolley EA. The effect of corticosteroid-induced osteoporosis on orthodontic tooth movement. *Am J Orthod Dentofacial Orthop.* 1992;102:310–319.
36. Kalia S, Melsen B, Verna C. Tissue reaction to orthodontic tooth movement in acute and chronic corticosteroid treatment. *Orthod Craniofac Res.* 2004;7:26–34.