Escaping the Adverse Impacts of NSAIDs on Tooth Movement During Orthodontics

Current Evidence Based on a Meta-Analysis

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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 [0.64, 0.90], P = 0.0008; respectively). Aspirin was found to inhibit OTM (95% CI [2.42, 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.

IMPACTS OF NSAIDS ON OTM

NSAIDs exert pain-relieving effects through the inhibition of cyclooxygenase (COX), which is the essential enzyme in the synthetic pathways of the prostanoids.2–9 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,7 potassium diclofenac,16 rofecoxib,17 celecoxib,13,14 and indomethacin12,13 would slow down the velocity of OTM and thus were inappropriate therapies for pain relief during orthodontic treatment. Conversely, some studies showed that acetaminophen,5,16,18 celecoxib,3,11,16,19 aspirin1 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 ClinicalTrials.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/ placebo.
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 I² statistics. If the research effect size was not heterogeneous (I² < 50%), count data were analyzed using a fixed effect model. If the research effect size was heterogeneous (I² ≥ 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,3,6,13,14,16 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, I² = 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).
| 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 | | 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.
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 >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).

### 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 photographs (Sony DSC S-90, 4 mega pixels, “fine” image quality) and radiographies (Kodak E-speedy x-ray film; Dabi Atlante’s intraoral x-ray machine 70 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.

FIGURE 2. The influence of celecoxib versus control on orthodontic tooth movement, according to medication duration.
The low-dose group referred to medication dosage of $\sim 15$ 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 $\sim 400$ 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 $\sim 100$ 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
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, I² = 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.

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...
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.

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