

# Effects of COXIB in Orthodontic Tooth Movement - A Literature Review

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## ABSTRACT

Pain measurements help to determine the severity, type and duration of pain and are used to make an accurate diagnosis and evaluate the effectiveness of treatment. Pain relief can be achieved pharmacologically or non pharmacologically. Pharmacologically, NSAIDs are the drugs of choice. They act by inhibition of enzyme cyclooxygenase which mediates the transformation of prostaglandins from arachidonic acid in the cellular plasma membrane. PGs such as PGE and PGE2 are important mediators of bone resorption. COX-1 is considered important in tissue homeostasis. COX-2 is transcriptionally induced by cytokines and is important in the development of inflammation. Non pharmacological methods include application of low level laser therapy to periodontal tissues, Transcutaneous Electrical Nerve Stimulation and vibratory stimulation of periodontal ligament. All these methods are only partially successful in achieving pain relief. However, the use of NSAIDs is the preferred method for pain control related to fixed orthodontic appliances.

Orthodontic tooth movement is mainly a biological response to a mechanical force. Tooth movement is induced by prolonged application of controlled mechanical forces which creates pressure and tension zones in the periodontal ligament and alveolar bone causing remodeling of tooth sockets. When a tooth is moved by application of orthodontic force, there is bone resorption on the pressure side and new bone formation on the tension side. Orthodontists often prescribe NSAIDs to manage pain from force application. However NSAIDs block prostaglandin synthesis and results in slower tooth movement. NSAIDs also have gastrointestinal side effects. The review describes the effect of NSAID, on orthodontic tooth movement.

**Keywords:** NSAIDs, orthodontic tooth movement, Prostaglandins, COX inhibitors, Pain.

## INTRODUCTION

Pain is an unpleasant experience often caused by intense or damaging stimuli. Pain measurements help to determine the severity, type and duration of pain and are used to make an accurate diagnosis, determine a treatment plan and evaluate the effectiveness of treatment. [1] The 3d's principle- diagnosis, dental treatment, drugs-should be used to manage pain. [2] Pain management drugs include

non-narcotic analgesics (example- NSAIDS, paracetamol, etc) or opioids (narcotics). NSAIDS provides excellent pain relief due to their anti inflammatory, analgesic action. The most common NSAIDS are aspirin and ibuprofen. Paracetamol gives very effective analgesic, but has little anti inflammatory action. Opioids are powerful analgesic but have significant side effects and therefore they should be reserved for severe pain only. The regularly used opioid agent is

codeine, usually in combination with paracetamol. NSAIDS is a class of analgesic medication that reduces pain, fever and inflammation. NSAIDS such as ibuprofen and naproxen are often a effective treatment option.

NSAIDS are cleared from the blood by the kidney: thus precautions should be taken to avoid kidney damage and disease when NSAIDS are taken over an extended period.

**Methods to control pain in orthodontics:**

**Pharmacological:**

The most common group of medications used in orthodontics for Pain relief consists of NSAIDS. [3,4] These drugs function by inhibition of enzyme cyclo-oxygenase (CO-X) which modulates the transformation of prostaglandins(PGs) from arachidonic acid in the cellular plasma membrane PGS such as PGE1 and PGE2 are important mediators of bone resorption. [5]

Two isoforms of mammalian COX have been described: the constitutive COX-1 and the inducible COX-2. COX1 is considered important in tissue hemostasis. COX-2 is transcriptionally induced by cytokines and is important in the development of inflammation [6-9] Non selective COX inhibitors like aspirin, Acetaminophen, indomethacin and naproxen provide effective pain relief for inflammations.

**Non-pharmacological:**

The methods which are used for controlling pain during the orthodontic

treatment range from anesthetics, analgesics. The application of low level laser therapy to the periodontal tissues, [10] Transcutaneous Electrical Nerve Stimulation (TENS) and vibratory stimulation of the periodontal ligament. [11-13] All these methods have been partially successful in achieving pain relief. However, the use of NSAIDS is the preferred method of pain control which is related to fixed orthodontic appliances.

**Classification: [14]**

**I. Analgesics and anti-inflammatory**

**A. Non selective COX inhibitors (traditional NSAIDS)**

1. Salicylates: Aspirin
2. Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3. Fenamate: Mepheneamic acid
4. Enolic acid derivatives: Pyroxicam, Tenoxicam
5. Acetic acid derivatives: Ketorolac, Indomethacin, Nabumetone
6. Pyrazolone derivatives: Phenyl butazone, Oxyphenbutazone.

**B. Preferential COX-2 inhibitors:**

Nimesulide, Diclofenac, Aceclofenac, Naloxecam, Etodolac.

**C. Selective COX-2 inhibitors:**

Celecoxib, Etoricoxib, Parecoxib.

**II. Analgesics but poorly anti-inflammatory:**

1. Para aminophenol derivatives: Paracetamol (Acetaminophen)
2. Pyrazolone derivatives: Metamizol (dipyzone), Propiphenazone
3. Benzoxazocine derivative: Nefopam.

**Groups and subgroups of NASIDs: [15]**

GROUP	SUB GROUP	BRAND NAMES
Salicylate	Aspirin Diflunisal	Aspirin, Acetol, acetophen, over 100 more Dolobid.
Arylalkanoic acid	Diclofenac Indomethacin	Voltaren, Voltarol, Diclon, Dicloflex, Difen, Difene, Cataflam, Pennsaid, Rhumalgan, Abitron Indocid, Indochron.
Arylalkanoic acids (profens)	Ibuprofen Flurbiprofen Naproxen Pyroxicam Meloxicam	Nurofen, Advil, Brufen, Dorival, Panafen, Ibumatin, Ibumprom ANSAID Aleve, Anaprox, Naprogesic, Naprosyn, Naprelon. Feldene Movalis, Melox, Recoxamobic.
Coxib	Celecoxibs Rofecoxibs Valdecoxib	Celebrex, celebra Vioxx, ceoxx, ceoxxx Bextra

**Features of Non selective COX inhibitor & selective COX 2 inhibitor:**

Action	COX-1/COX-2 Inhibitor	COX-2 Inhibitor
Analgesic	+	+
Antipyretic	+	+
Anti inflammatory	+	+
Anti platelet aggregatory	+	-
Gastric mucosal damage	+	-
Renal salt/water retention	+	+
Delay/prolongation of labour	+	+
Ductus arteriosus closure	+	?
Aspirin sensitive asthma precipitation	+	-

**NON-STEROIDAL ANTI-INFLAMMATORY DRUGS**

**Aspirin:**

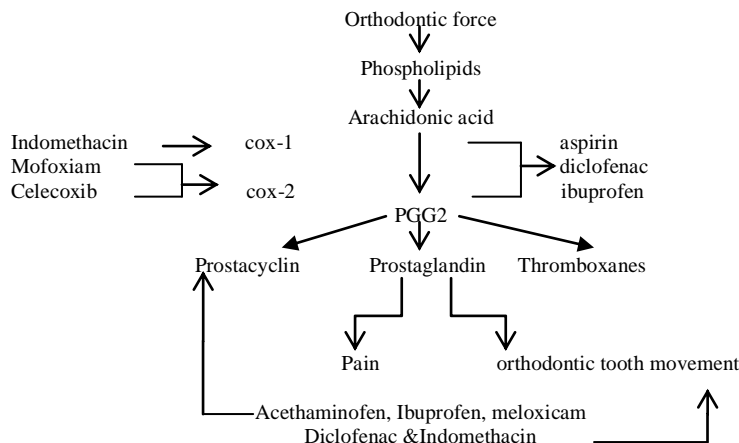
Aspirin modifies enzyme cox-1&cox-2, irreversibly inhibiting their activity. Aspirin is rapidly deacetylated in the gutwall, liver, plasma, and other tissues and releases salicylic acid which is its major circulating and active form. Aspirin significantly reduced the numbers of resorption lacunae and osteoclasts in the pressure areas of orthodontic tooth movement.

**Paracetamol:**

It is a part of a class of drugs known as ‘aniline analgesics. [16] Since it is inactive as an anti-inflammatory agent in peripheral tissues, it does not have any adverse effect on PG biosynthesis and subsequent bone resorption associated with orthodontic tooth movement.

Acetaminophen raises the threshold to painful stimuli thus exerting an analgesic effect against pain due to a variety of etiologies. Roche JJ et al 1997 reported that

**Mechanism of action: [23-27]**



acetaminophen showed no effect on tooth movement when tested on rabbits. [17]

**Acetic acid derivatives (Diclofenac):**

Kehoe et al found that ibuprofen significantly inhibits the production of prostaglandin E in the periodontal ligament and therefore decreases the rate of tooth movement. [18]

Bartzela et al also in their systematic literature review reported that after ibuprofen administration of 30mg/kg twice a day in rats, the rate of orthodontic tooth movement decreases significantly. [19]

**Nimesulide:**

It is a weak inhibitor of prostaglandin synthesis and is cyclo oxygenase-2 selective.

A histological study on guinea pigs revealed that nimesulide decrease the rate of bone resorption and appearance of osteoclasts and therefore, reduced the amount of tooth movement. [20]

**Celecoxib:**

It is highly effective cyclooxygenase enzyme-2 inhibitors. In relation to its effects during orthodontic treatment, it was found to have no effect on rate of tooth movement. [21]

**Indomethacin:**

This is a highly potent inhibitor of prostaglandin synthesis and suppresses neutrophil motility. When administered to mongrel cats as shown by chumbley the rate of tooth movement was found to be decreased. [22]

Prostaglandin (PGs) is typical inflammatory and pain mediators which result from the degradation of arachidonic acid. Their synthesis is mediated by two different cox isoenzymes. The constitutive cox-1 does not exhibit a dynamic regulation, while the cox-2 expression is subjected to regulation by several environmental conditions cox-1 is implicated in general homeostasis and it is found in most of the organs and the tissues (it is a constitutive isoenzyme). [28]

In contrast, cox-2 is not detected in the tissue and it only appears in response to certain stimuli (inducible iso enzyme).

Based on the hypothesis that a selective cox-2 inhibition would induce the desired anti-inflammatory effects without undesirable side effects (particularly at the gastric level). Which are associated with the cox-1 inhibition drugs known as “coxibs” or selective cox-2 inhibitors have been developed.

Coxibs shows anti inflammatory properties thus preserving the cox-1 pathway and therefore allowing the natural production of some PGs which are important because of their GI protective roles. [29]

#### **Pharmacokinetics:**

Most NSAID drugs are weak acids with a pKa of 3-5. They are absorbed well from the stomach and intestinal mucosa. They are highly protein bound in plasma (typically >95%), usually to albumin, so that their volume of distribution typically approximates to plasma volume.

Most of the NSAIDs are metabolized in the liver by oxidation and conjugation to inactive metabolites that typically are excreted in the urine, though some drugs are partially excreted in bile. Metabolism may be incorrect in certain diseases and accumulation may occur even with normal dose level.

Ibuprofen and diclofenac have short plasma  $t_{1/2}$  of 2-3 hrs. Some NSAIDs (typically oxicams) have very long plasma  $t_{1/2}$  of 20-60 hrs.

#### **Adverse effect of NSAIDs:**

#### **Gastrointestinal:**

Nausea, anorexia, gastric irritation, erosions peptic ulcerations, gastric bleeding/perforation esophagitis.

#### **Renal:**

Na<sup>+</sup> and H<sub>2</sub>O retention, chronic renal failure, nephropathy, papillary necrosis.

#### **Cardio Vascular System:**

Rise in blood pressure, risk of myocardial infection (especially with cox-2 inhibitor)

#### **Hepatic:**

Raised transamines, hepatic failure.

#### **Central Nervous System:**

Headache, mental confusion, vertigo, behavioural disturbances, seizure precipitation.

#### **Haematological:**

Bleeding, thrombocytopenia, hemolytic anemia, agranulocytosis.

#### **Others:**

Asthma exacerbation, rhinitis, nasal polyposis, skin rashes, pruritis, angioedema, platelet dysfunction.

#### **Adverse drug reactions:**

#### **Gastro Intestinal effects:**

GI complications are well recognized risks of NSAIDs as a class and vary by the respective NSAID used as well as by dose (i.e., higher doses: more GI risk). [30-33] Aspirin increases bleeding risk, even at low cardioprotective doses (e.g: 75-300 mg) [34,35]

Investigators found that rates of GI events were significantly ( $p < 0.05$ ) in the acetaminophen group taking concurrent therapy plus corticosteroids compared with those taking either ibuprofen or aspirin with concurrent therapy plus corticosteroids. [36]

In comparisons of GI AEs among NSAID users, results from several meta analysis. Further support a lower risk of GI AEs with ibuprofen compared with other NSAIDs. [34,35,37,38]

#### **Cardio Vascular Risks:**

All non aspirin NSAIDs may be associated with a potential increase in CV thrombotic risk. [39] Labelling for OTC NSAIDs currently states, the risk of heart attack or stroke may increase if you use

more than directed or for longer than directed. [40,41]

A majority of the data on CV risk among NSAID users is from epidemiological studies of prescription NSAIDs. COX-2 inhibitors were developed as prescription NSAIDs with lower GI risks, but some have been posited to have increased CV risks. [42,43]

#### **Renal toxicity:**

All NSAIDs can alter renal function by inhibiting COX-1 (which regulates renal hemodynamics and glomerular filtration) and/or COX-2 (which mediates salt and water excretion) expressed in the kidneys. [44]

Further more, individuals experiencing renal stress (e.g., dehydration) from exercise in hot environments may be at a small increased risk for acute renal failure with ibuprofen. [45]

Randomized control trials (RCTs) have found no increased risk for renal failure in children taking ibuprofen for fever. Despite evidence from large clinical trials case studies reported that renal failure in children taking OTC ibuprofen; dehydration may have been a contributing factor. [46,47]

#### **Drug interaction:**

##### 1) Anti-hypertensives:

Hypertension and chronic pain can be frequent comorbidities in the elderly and these with chronic disease; therefore concomitant use of NSAIDs and anti-hypertensives is common. [48] Some trials found increased risk of DDIs when prescription strength NSAIDs and anti-hypertensives were co-administered over a period of multiple weeks. [48,49] Efficacy of medications that act on renal prostaglandin or modify their effects may be reduced resulting in increased blood pressure with NSAID co-administration. [50] Other trials found no significant effect on BP when OTC doses of Ibuprofen or Naproxen or prescription dose ibuprofen. [51-53]

##### 2) Renin – angiotensin – aldosterone system inhibitors :

Aldosterone antagonist (e.g.: spironolactone) are associated with an

increased risk of GI bleeding and possibly impaired healing of gastric or duodenal erosions. [54]

Thus, risk of GI bleeding in patients taking these agents may be further increased when NSAIDs are used concomitantly. [55]

##### 3) Diuretics:

Topical diclofenac had no effect on furosemide pharmacokinetics or pharmacodynamics and oral diclofenac compared with furosemide alone decreased urine output, but neither formulation was associated with alterations in BP. [56]

#### **Aspirin:**

Co administration of aspirin and most NSAIDs other than diclofenac and ketorolac can lead to pharmacodynamics DDIs resulting from competition for access to the acetylation site of platelet expressed COX-1. [57-59]

The NSAID driven effect on aspirin is of particular concern in individuals at high cardiovascular risk who take low dose aspirin daily to reduce the risk of a thrombotic event. [57,58]

Case reports in which ibuprofen may have precipitated on asthma exacerbation in adults and children with aspirin sensitive asthma. [60-63]

#### **Warfarin:**

Even with short term use, acetaminophen given concurrently with anticoagulants may increase international normalized ratio (INR) implying an increase in bleeding risk and necessitating close INR monitoring and possible warfarin dosage adjustments. [64-67]

#### **Anti-depressants /mood stabilizers:**

Anti-depressants are psychiatric medications used to alleviate mood and anxiety disorders some may be associated with an increased risk for bleeding, which may be additively enhanced by co-administration of NSAIDs.

#### **Selective serotonin re uptake inhibitors and tricyclic anti-depressants:**

SSRIs increase bleeding risk of inhibiting platelet adhesion and function. [68-70] Co administration of NSAIDs in patients



taking SSRIS can substantially increase the risk of bleeding. [71,72]

**NSAID’s in orthodontic tooth movement:**

Orthodontic treatment mainly involves tooth movement. Orthodontic tooth movement is mainly a biological response towards mechanical force the movement is induced by prolonged application of controlled mechanical forces which create pressure and tension zones in the periodontal ligament and alveolar bone causing remodelling of tooth sockets orthodontists often prescribes drugs to manage pain from force application to biological tissues. NSAIDs are the drugs usually prescribed. NSAIDs block prostaglandin synthesis and result in slower tooth movement. [73]

When force is applied on a tooth to bring about orthodontic treatment, it results

in formation of areas of pressure and tension around the tooth. Pressure areas are formed in the direction of the tooth movement while tension areas form in the opposite direction. When a tooth is moved due to orthodontic force there is bone resorption on the pressure side and new bone formation on the side of tension.

Whenever extreme forces are applied to tooth, it results in crushing or total compression of the periodontal ligament.

Whenever mild forces are applied to teeth it results in 1) changes on tension side (on application of force periodontal ligament on the tension side gets stretched) 2)changes on pressure side (frontal resorption). PDL in the direction of tooth movement gets compressed to almost one third of its original thickness.

NSAID	Effects on Bone metabolism	Effects on tooth movement
Aspirin	Reduced bone resorption	Reduced tooth movement
Diclofenac	Reduced bone resorption	Reduced tooth movement
Indomethacin	Reduced bone resorption	Reduced tooth movement
Ibuprofen	Reduced bone resorption	Reduced tooth movement
Flurbiprofen	Reduced bone resorption	Reduced tooth movement
Naproxen	Reduced bone resorption	Reduced tooth movement
Celecoxib	No effect on bone resorption	No influence on tooth movement
Acetaminophen	No effect on bone resorption	No influence on tooth movement

**DISCUSSION**

It is well documented that tooth movement can be enhanced by Topical injection of prostaglandins. [74-78]

Furthermore, previous animal and clinical studies have suggested that NSAIDs can have adverse effects on orthodontic treatment. [75,79-82] Effects of NSAIDs on the molecular Mechanism meditating tooth movement. During, the initial phases of tooth movement under the pressure of sustained orthodontic forces, PDC components, including collagenous fibers and vessels are over compressed. [83-85] Vascular compression and blood flow alteration during tooth movement are thought to play key roles in initiating the cascade of events leading to periodontal remodeling decrease of blood flow in the pressure side versus vascular proliferation

and increase of blood supply in the tension side.

In order to supply adequate blood flow for remodeling periodontal structures; PDL vessels need to be constantly degraded and reconstructed throughout tooth movement. [84-86]

Recently reported that, prostaglandins exert an anti-inflammatory effect through activating the poroxisom proliferator activated receptor. [87,88] The use of anti – inflammatory drugs by our patients may thus influence orthodontic tooth movement by altering biochemical pathways that mediate extra cellular matrix remodeling.

The most important inhibitors are the NSAIDs which have both analgesic and anti inflammatory effects. Although they all show a similar action, their effects on the rate of OTM were all performed over

relatively short experiment periods. The effects found in these studies, might underestimate the effects of prolonged administration e.g.: in rheumatoid arthritis patients.

A case report of a post menopausal orthodontic patient suggested that the estrogens used to treat osteoporosis might have delayed OTM. It might have inhibited alveolar bone loss in the chronic, stable phase of this patient's periodontitis.

## CONCLUSION

NSAIDs and their influence on the duration of orthodontic treatment. The Ibuprofen administered one hour before separator placement and 3 and 7 hours after placement, reduced post separator placement pain compared with placebo. The analgesic effects diminished by day 2, resulting in peak pain levels and decreased chewing efficiency at this time. Certain drug combinations might be necessary to relieve pain. Drugs play a crucial role on the rate of tooth movement and information on their consumption is essential to adequately discuss treatment planning with patients. Bisphosphonates use is associated with longer treatment times among extraction patients, increased odds of poor root parallelism. Bisphosphonates play an important role in treating osteoporosis. They act by decreasing the resorption of bone.

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