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Review Article

Analgesics and Orthodontic Tooth Movement

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Abstract

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 to manage pain from force application. However, analgesics block prostaglandin synthesis by inhibiting cyclooxygenase enzymes (COX)and results in slower tooth movement. Analgesics also have gastrointestinal side effects. The review describes the effect of analgesics, on orthodontic tooth movement.

Keywords: Analgesics; Orthodontic Tooth Movement; Prostaglandins; COX Inhibitors; Pain

Introduction

Orthodontics, the first specialty of dentistry, has evolved and progressed from its inception to the present time, and the credits for this evolution belong to pioneers, who aimed at improving their clinical capabilities [1]. The evolution of clinical orthodontics is rooted in strong foundations, based on scientific studies and mechanical principles [1]. However, as the specialty began prospering, interest in its association with biological facts began to decline. For a while, orthodontics was taught predominantly as a mechanical endeavor. It can be taught in a short course lasting a few days, usually without any associated clinical exposure [2]. However, recent advancements in medicine have provided orthodontic researchers with investigative tools that enable them to pave new roads toward the target of personalized orthodontics, adapted to the biological profile and needs of each individual patient [1,2].

Orthodontic tooth movement (OTM) is facilitated by remodeling of the dental and paradental tissues which, when exposed to varying degrees of magnitude, frequency, and duration of mechanical loading, express extensive physical and chemical changes that differ from the processes of physiological dental drift, or tooth eruption. In OTM, a tooth moves as a result of mechanical forces derived from external devices, while forces leading to mesial migration of teeth are derived from the individual's own musculature, and tooth eruption results from complex interactions between dental and paradental cells [3]. The common denominator of all these phenomena is the generation of mechanical forces, either physiologically or therapeutically. OTM resembles tooth eruption because both processes depend on remodeling of the periodontal ligament (PDL) and the alveolar bone, but the two processes present different models of bone remodeling [3,4].

OTM is the result of a biological response to interference in the physiological equilibrium of the dentofacial complex by an externally applied force. The biological foundation of force-induced tooth movement, along with some concepts related to it, has been

extensively investigated since the onset of the twentieth century [1,5]. From the classic reports by Sandstedt in 1904 , the race was set for exploring the biological foundations of OTM, using histology, radiology, and clinical observations as the main investigative tools. A list of the then prevailing hypotheses aimed at explaining the biological reasons for OTM is presented below.

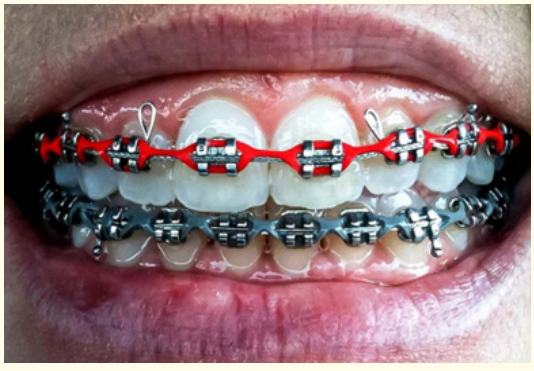

Figure 1: Orthodontic Treatment.

The old pressure hypothesis of Schwalbe–Flourens, which postulated that pressure moves teeth, preceded the concept that alveolar bone resorption takes place on one side of the dental root, while deposition occurs on the opposite side, until the pressure is eliminated. Hecht (1900), Sandstedt (1904), Pfaff (1906), and Angle (1907) supported this hypothesis (Oppenheim, 1911) [1,6,7].

Based on his vast clinical experience, Kingsley (1881) stated that slow OTM is associated with favorable tissue-remodeling changes (resorption and deposition of alveolar bone), while quick movements displace the entire bony lamellae along with the teeth, while retaining their functional and structural integrity. He attributed these features to the elasticity, compressibility, and flexibility of bone tissue. This report is one of the first written explanations for the biological basis of OTM, although it is not frequently cited [1,2,7,8].

OTM causes inflammatory reactions in the periodontium and dental pulp, which will stimulate release of various biochemical mediators. The perception of orthodontic pain is the result of a hyperalgesic response elicited by these mediators. Periodontal pain is caused by a process involving the development of pressure, ischemia, inflammation, and edema. Burstone identified both immediate and delayed pain responses, which begin a few hours after the application of an orthodontic force and last for approximately 5 days . Krukemeyer., *et al.* concluded from a survey conducted on 118 patients that 58.5% indicated that they experienced pain for a few days after their appointment, out of which only 26.5% of the patients used pain medication immediately following and 1 day after the last appointment [1,5-12].

Painful sensations result, in part, from the stretching and distortion of tissues by the mechanical loads, as well as from interac-

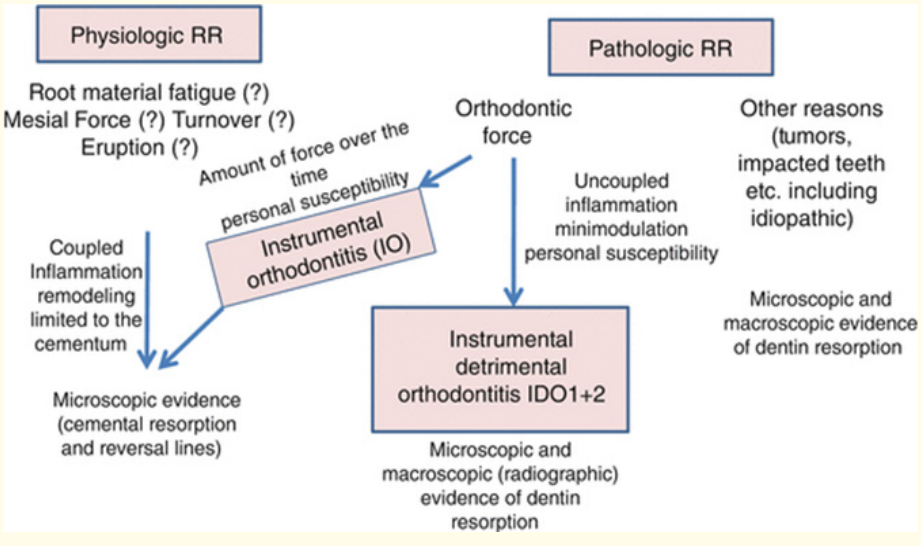

Figure 2: The Inflammation Behind Tooth Movement and Orthodontic Root Resorption.

tions of multiple inflammatory mediators with local pain receptors . According to a review by Krishnan, the perception of orthodontic pain is due to the changes in blood flow caused by the appliances, correlated with the release and presence of various substances, such as SP, histamine, enkephalin, dopamine, serotonin, glycine, glutamate, gammaaminobutyric acid, PGs, leukotrienes, and cytokines [13,14].

It is imperative that pain control be considered an important aspect of orthodontic mechanotherapy, and that the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) remains the preferred method for pain control during orthodontic treatment. NSAIDs have been used for the relief of orthodontic pain for decades [13]. It has been well documented that the synthesis of prostaglandin is mediated by COX enzymes and NSAIDs inhibit the activity of COX enzymes. Therefore, NSAIDs could relieve orthodontic pain by inhibiting the release of prostaglandin [15]. The major concern regarding NSAIDs is the interference with the inflammatory process associated with tooth movement. NSAIDs intake may induce a decrease in levels of prostaglandin, and as a result may inhibit osteoclasts and reduce the rate of tooth movement [12]. Therefore, their effects on the rate of tooth movement need to be validated in future studies [13].

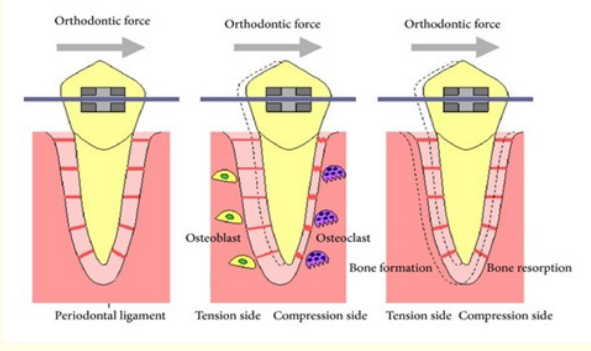

Figure 3: Schematic diagram of tooth movement. Applying orthodontic force to the tooth causes compression of the periodontal ligament.

During orthodontic treatment, forces are applied to teeth and consequently the teeth are being displaced in a manner determined by the line of action of the force applied. As the shortest distance between two points is a straight line, this could according to Burstone be formulated in orthodontic terms as: for a well-defined tooth movement, there is only one correct line of action of the force. This force, however, can be generated by many different appliances. Already the description of the change in tooth position can pose a problem. When a tooth is being translated, all parts of the tooth have the same amount of movement in the same direction, and when submitted to a couple, all parts are rotated around the centre of resistance (CR), the position of which may be in different localizations in different planes of space . Apart from the situations where a tooth is purely translated or rotated, all other displacements are combinations of translations and rotations. These movements are expressed by the distance between the CR and the CRot (centre of rotation). When analysing tooth movement, Viecilli calculated the localization of the CR in various teeth in three-dimensions (3D) mostly focusing on the tooth morphology only mentioning the influence of the surrounding periodontium [15,16]. Indeed, when localizing the CR in the three planes of space in addition to the morphology of the various teeth, tooth position and quality and level of the surrounding bone play a decisive role [16].

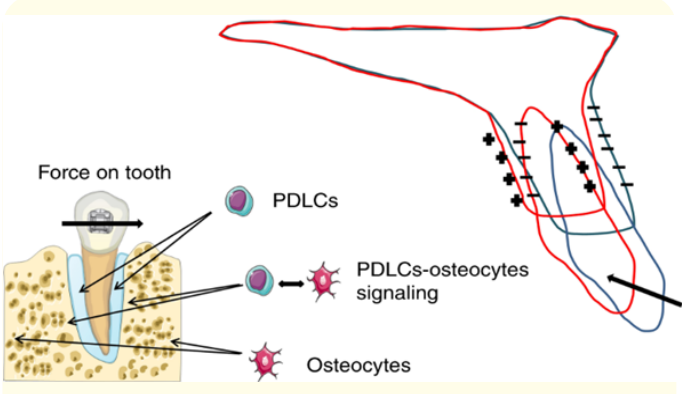

Figure 4: Biomechanical and biological responses of periodontium in orthodontic tooth movement.

The line of action of an orthodontic force with respect to the CR is controlling the displacement of the tooth and thereby the load transfer from tooth to the periodontium. The perpendicular distance from the CR to the line-of-action of the applied force can be expressed as the moment-to-force ratio (M/F) of a force applied at the bracket. In relation to an incisor with the longitudinal axis vertical, a M/F of respectively 0, –5, –10 and –12 mm at the bracket is associated with an M/F of 10, 5, 0 and –2 mm at the CR, consequently resulting in an uncontrolled tipping, a controlled tipping, a pure translation, and a root movement, respectively [13]. These theories are based on four assumptions, which since the introduction of the rationale of segmented arch have received little attention [14].

- The force added to a tooth is via the periodontal ligament (PDL) transferred to the alveolar wall, the area of which is assumed to be mirroring the root surface [15].
- The PDL behaves linearly and generates equal (yet oppositely directed) reaction forces to both the tension and compression side of the alveolus [15,16].
- The root is uniformly supported on all sides by alveolar bone, and therefore the CR is located on the central axis of the root [15,17].
- The magnitude of the external force has no influence on the load transfer, as it appears both above and below the division line of the M/F, and is thus cancelled out and of no further consequence.[16,18,19]

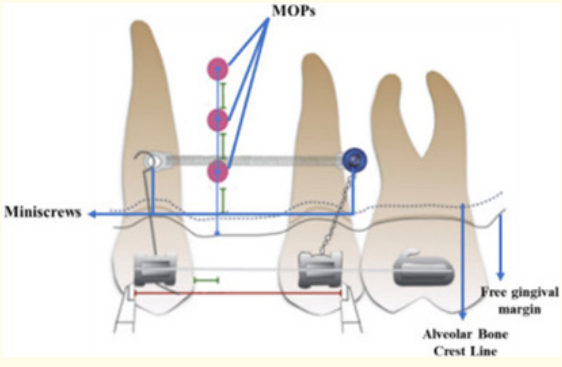

Figure 5: Effective techniques and emerging alternatives in orthodontic tooth movement.

According to WHO (1966), drug is any substance or product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. During orthodontic treatment, drugs are prescribed to manage pain from force application to biological tissues, manage temporomandibular joint (TMJ) problems and tackle some infection throughout the course of treatment. Apart from these drugs, patients who consume vitamins, minerals, hormonal supplements, and other compounds for the prevention or treatment of various diseases can also be found in every orthodontic practice [21]. Some of these drugs may have profound effects on the short- and long-term outcomes of orthodontic practice. Hence, it is necessary to review the mechanism of action and effects of commonly used drugs on tissue remodeling and orthodontic tooth movement [13-21].

The objective of this review is to outline the mechanisms of action and effects of some commonly used analgesics drugs on tissue remodeling and orthodontic tooth movement.

Analgesics

Analgesic is a drug that selectively relieves pain by acting on the CNS or peripheral pain mechanisms, without significantly altering consciousness. Nonsteroidal anti-inflammatory drugs (NSAIDs) do not affect the tenderness induced by direct application of PGs, but block the pain-sensitizing mechanism induced by bradykinins, tumor necrosis factors (TNFs), interleukins (ILs), etc. The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG mediated sensitization of nerve endings. NSAIDs are a relatively weak inhibitor of PG synthesis and anti-inflammatory action may be exerted by reduced generation of superoxide by neutrophils, and TNF release, free radical scavenging, and inhibition of metalloprotease activity in cartilage.

	Effects on Bone Metabolism	Effects on Tooth Movement
Non-Steroidal Anti-Inflammatory Drugs		
Aspirin	↓ bone resorption	↓ tooth movement
Diclofenac	↓ bone resorption	↓ tooth movement
Ibuprofen	↓ bone resorption	↓ tooth movement
Indometacin	↓ bone resorption	↓ tooth movement
Celecoxib	↓ bone resorption (in vitro)	no influence
Corticosteroids	↑ bone resorption (chronic use)	↑ tooth movement
Bisphosphonates	↓ bone resorption	↓ tooth movement
Acetaminophen	unproven	no influence

Figure 6: Effects of drugs on induced tooth movement.

Most commonly used medications in orthodontics are for control of pain following mechanical force application to tooth. Inhibition of the inflammatory reaction produced by PGs slows the tooth movement. Recent research demonstrated the molecular mechanisms behind the inhibition of tooth movement by NSAIDs. The levels of matrix metalloproteinases (MMP9 and MMP2) were found to be increased, along with elevated collagenase activity, followed by a reduction in procollagen synthesis which is essential for bone and periodontal remodeling. The whole process is controlled by inhibition of cyclooxygenase (COX) activity, leading to altered vascular and extravascular matrix remodeling, causing a reduction in the pace of the tooth movement [12,22].

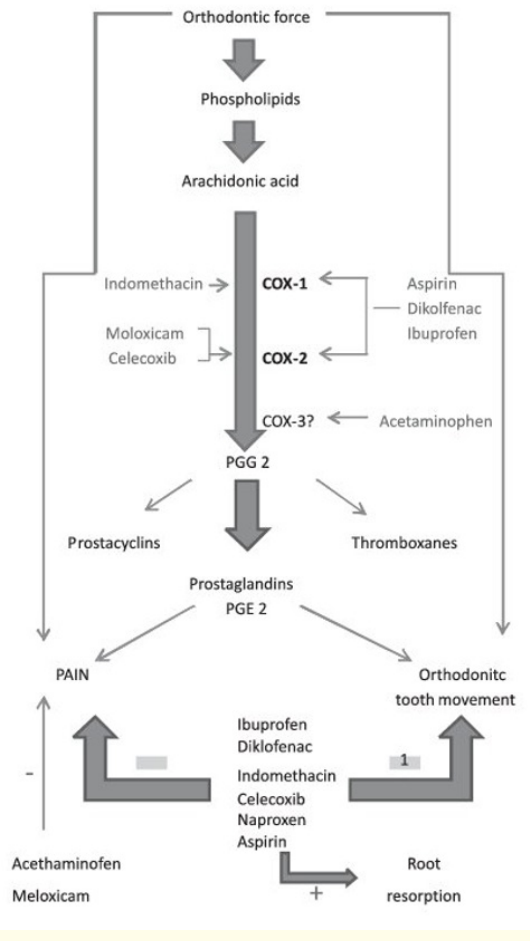

Figure 7: Mechanism of analgesic effect of NSAIDs in tooth movement.

Kyrkanides ., *et al.* investigated the effect of indomethacin on orthodontic tooth movement. Their results indicated loss of prostaglandin mediated cellular effects subsequent to cyclooxygenase inhibition by this drug [22].

Chan ., *et al.* reported that new COX-2 specific inhibitors decreased serious gastrointestinal perforations, obstructions and bleeding when compared with conventional NSAID [23].

De Carlos ., *et al.* studied orthodontic tooth movement that resulted from the effect of rofecoxib (COX-2 inhibitor) and compared with diclofenac (a traditional NSAID). The results showed both rofecoxib and diclofenac can inhibit COX-2 action that means that the orthodontic tooth movement was inhibited by these drugs [24].

Chumbley and Tuncay recommended that orthodontic patient should avoid to using aspirin and other nonsteroidal anti-inflammatory analgesics to relieve pain because these drugs can prolong orthodontic treatment time [12,25].

Gameiro ., *et al.* reported the short- and long-term effects of celecoxib (COX-2 inhibitor) on orthodontic tooth movement in rats. The short-term treatment was simulated the preoperative administration of analgesics to decrease postoperative pain whereas the long-term effect treatment was simulated the situation that patients receive celecoxib in treatment of chronic. [disease all time of tooth movement. The results showed that tooth movement was inhibited by celecoxib action in both situations. Moreover, they stated that celecoxib not only affected COX-2 level but also affected IL-1 and IL-6 that had the result of bone resorption and tooth movement [26].

Mohammed ., *et al.* foundthat orthodontic tooth movement is inhibited by indomethacin in rats. Furthermore, Arias's study showed the effect of aspirin and ibuprofen on orthodontic tooth movement in the rats. Fewer osteoclasts were observed in the pressure side of the teeth because these drugs inhibited the production of PGs. Because the bone resorption was reduced, the teeth moved less than average [27].

Sari ., *et al.* suggested that the one drug, rofecoxib, can be used to relieve pain or patient discomfort during orthodontic treatment

because the inhibitory effect on PGs synthesis with rofecoxib was less than the inhibition effect of aspirin during the first 24 hours [28].

Wong., *et al*. stated that aspirin does not change the orthodontic tooth movement in guinea pigs. However, they found that the dose of the analgesic used was lower than the dose that can reduce the secretion of PGs because the metabolic rate of these animals is faster than humans. For this reason, they require higher doses than the does to produce the same orthodontic effect in humans [29].

Williams etal studied the effect of ibuprofen on alveolar bone in dogs. Their result showed that ibuprofen can inhibit alveolar bone loss when the dogs were treated with 4 mg/kg of ibuprofen daily for 13 months [30].

Kehoe., *et al.* confirmed that ibuprofen inhibits PGE2 synthesis in the PDL of guinea pig significantly by decreasing the degree and rate of orthodontic tooth movement [31].

Salicylates

Aspirin is the prototype of NSAIDs and is unique among non-selective anti-inflammatory drugs because it irreversibly acetylates cyclooxygenase-1 in the platelet, the major reason for its cardioprotectant use [12,31,32]. Several of the selective cyclooxygenase-2 inhibitors have been removed from the worldwide marketplace because of increased cardiovascular risk and additional scrutiny in this area is underway by regulatory agencies for all non-steroidal anti-inflammatory drugs [12,33]. Some interactions involving non-steroidal anti-inflammatory drugs with lithium, anticoagulants, and oral hypoglycemics have already been discussed in earlier sections of this paper. The following sections will focus on adverse interactions involving non-steroidal anti-inflammatory drugs with other groups of drugs [12,34,35].

Mechanism of Action: Salicylates generally act by virtue of their content of salicylic acid. Aspirin covalently modifies COX-1 and COX-2, irreversibly inhibiting COX activity. This is an important distinction from all the NSAIDs because the duration of aspirin's effects is related to the turnover rate of COXs in different target tissues [12,32]. The duration of effect of non-aspirin NSAIDs, which inhibit the active sites of the COX enzymes competitively, relates to the time course of drug disposition. The importance of enzyme turnover in recovery from aspirin action is most notable in platelets, which, being enucleate, have a markedly limited capacity for protein synthesis [33].

Acetylsalicylic acid administration in a dosage of 65 mg/kg/day in guinea pigs did not result in a reduction in the rate of lateral incisor movement by mild forces of 8 cN [12,36]. On the other hand, the rate of lateral incisor movement in rats, evoked by a force of 35 cN, signifi cantly decreased after application of acetylsalicylic acid at a dosage of 100 mg/kg twice a day [12]. However, acetylsalicylic acid administrated at a dose of 60 or 300 mg/kg/day via drinking water did not affect mesial orthodontic tooth movement induced by a force of 50 cN over a period of 14 days [12,36]. In contrast to this study, molar mesialization was signifi cantly reduced in rats after local injections of 17.5–35 mg/kg/day of Cu salicylate and forces application of 50 or 100 cN for 28 days [35]. The differences in outcome may be related to differences in study design [37,38].

Arylalkanoic acids

Aryl alkanoic acids provide one of the most fascinating class of compounds recognized for various pharmacological activities like antimicrobial anticonvulsant, antipyretic, analgesic, anti-inflammatory activity, used extensively in the treatment of rheumatic fever, arthritis (rheumatic, osteo and jaundice arthritis), myocardial infarctions (disease associated with platelet aggregability, e.g., coronary artery disease and post operative deep vein thrombosis), angiotensin-II receptor antagonist and management of primary dysmenorrhea. Nalidixic acid is well known for its antibacterial activity against chronic urinary tract infections [12,33].

Administration of a single dose of indomethacin (4 mg/kg) in rats resulted in a significant short-lasting inhibitory effect on the mesial movement of molars induced by a force of 40 cN [34]. Other authors employed forces of 60 cN and 50 or 100 cN, respectively, while indomethacin was administered at a dosage of 2.5–5 mg/kg/day [34].

A significant reduction in the rate of molar movement was found during the whole experimental period of 14 and 28 days, respectively, regardless of the force level. The effect of indomethacin on OTM has also been studied in cats and miniature pigs. In cats, the third premolars were moved mesially by a force of 250 cN [33,34]. Using the same application regime for indomethacin as in the pre-

viously mentioned study, significant reduction in the rate of OTM was found [22,29]. In miniature pigs, the incisors were separated by a force of 100 cN. Initially, a dosage of 20 mg/kg/day of indomethacin was given, but this had to be changed during the experimental period to 10 mg/kg/day due to peptic ulcer problems [33,40]. Although no direct tooth movement was measured, the reduced bone turnover strongly suggested a decrease in OTM rate [33].

The effect of diclofenac was studied in a rat model in which mesial tipping of first molars was induced by forces of 50 or 100 cN. Injections of diclofenac (10 mg/ kg at day 1 and day 3) abolished OTM completely [27]. These results point in the same direction as a more recent study in rats on the effect of diclofenac. A force of 30 cN was applied on the first molar for 3, 7, or 14 days. Diclofenac was given in a daily dose of 5 mg/kg/day, and after 3 and 7 days, this leads to fewer blood vessels, Howship lacunae, and osteoclast-like cells, suggesting less OTM during the initial phase of treatment [33,34,41].

Ketorolac is an analgesic that is used for the short-term relief of moderate to severe pain and should not be used for longer than 5 days and for mild pain or for pain from chronic (long-term) conditions. The only study in which the effect of ketorolac on OTM is studied is in rats, in which a dosage of 3 mg/kg/day was administered by gastric gavage for 2 months. This leads to a decrease in mesial OTM after the application of a force of 50 cN [38]. However, the experimental period is far longer than the prescribed maximal period this drug should be taken, and therefore its clinical relevance is questionable [34].

Arylpropionic acids

Arylpropionic acid derivatives are a large and important family of non-steroidal anti-inflammatory drugs (NSAIDs)2-5 . NSAIDs are often used to treat various arthritis and musculoskeletal disorders6-9 . The biological response of NSAIDs is the result of inhibition of prostaglandin biosynthesis (PG), where cyclooxygenase enzyme (COX) plays a key role in prostaglandin biosynthesis derived from arachidonic acid10-14. In the early 1990s, COX was found to have two forms, namely the COX-1 component, which provides gastrointestinal cytoprotection(GI) and renal blood flow and the other inducible COX-2, which mediates inflammation [33,34].

One of the NSAIDs viz. Ibuprofen, a chemical called propionic acid 2- (4-isobutylphenyl), is a popular pain relief. This is known for its use in the relief of arthritis pain. Long-term use of NSAIDs leads results in gastrointestinal ulceration, bleeding and nephrotoxicity, the gastrointestinal damage is generally associated with two factors which include local irritation by carboxylic acid moiety, which is common in most NSAIDs (topical effect) and decreased the production of tissue prostaglandin (PGs), which minimizes the physiological role of cytoprotective prostaglandins in maintaining GI health and homeostasis [34,40].

Administration of ibuprofen at an unknown dose for 5 days resulted in a significant reduction of tipping molar movement induced in rats by a mesial force of 50 cN over a period of 21 days [33,34,41]. Also, studies in which rat incisors were moved laterally by a force of 25 or 35 cN point in the same direction. After ibuprofen administration at a dose of 30 mg/kg twice a day, the rate of OTM decreased significantly [11,34]. On the other hand, no inhibitory effect could be found at a low dose (10 mg/ kg/day) of ibuprofen on the mesial movement of rabbit first molars when a force of 100 cN was applied [8,9].

These clinical studies provide an indirect evaluation of the effect of ibuprofen on the OTM.

Recent clinical studies that have been performed on the effects of ibuprofen on PGE2 release in the gingival crevicular fluid (GCF), as an indirect indication for their effect on OTM, showed conflicting results. The first evaluated the effect of ibuprofen (400 mg/day for 2 days) during canine distalization with a force of 150 cN. This led to a significant decrease in PGE2 release compared to the control group [34]. In the other study, the participants had taken 400 mg ibuprofen, 1 h before and 6 h after bonding, and GCF samples were taken prior to bonding, after bonding, and 1, 3, and 7 days thereafter. Neither time-related differences nor placebo group differences in PGE2 release was observed [33,34].

OTM is a multifactorial process over a long period of time, and the effect of long-term use of ibuprofen therefore may differ. In patients with chronic illnesses like juvenile rheumatoid arthritis, osteoarthritis, or gout, where long-term analgesic consumption is needed, the inhibiting effects on OTM may become more evident [34,42].

Oxicams

Oxicams are a class of nonsteroidal anti-inflammatory drugs (NSAIDs) structurally related to the enolic acid class of 4-hydroxy-1,2-benzothiazine carboxamides. They are used clinically to treat both acute and chronic inflammation by inhibiting the activity of the two cyclooxygenase (COX) isoforms, COX-1 and COX-2. Oxicams are structurally distinct from all other NSAIDs, exhibiting a novel binding pose in the COX active site. The 4-hydroxyl group on the thiazine ring partners with Ser-530 via hydrogen bonding while two coordinated water molecules mediate a polar interaction

between the oxicam and COX. [33]The rotation of Leu-531 in the complex opens a new pocket, which is not used for binding other NSAIDs to the enzyme. This structure provides the basis for understanding documented structure-activity relationships within the oxicam class. In addition, from the oxicam template, a series of potent microsomal prostaglandin E synthase-1 (mPGES-1) inhibitors represents a new direction for drug development [34].

The effect of meloxicam on OTM was studied in rats in which a force of 50 cN was used to move the maxillary left molar to the mesial for 2 weeks. The animals received a high (67 mg/kg/day)- or low (13 mg/kg/day)-dose meloxicam via their drinking water. No effect on OTM was found over the experimental period [33,36,42].

A clinical study also has been performed on the effects of oxicams. In a randomized clinical trial (RCT), bilateral canine retraction was performed over a period of 3 months with monthly reactivation. Tenoxicam (20 mg/day) was given for 3 days around each (re)activation, and the patients had access to additional paracetamol (4 times 750 mg/day). This medication had no effect on OTM [12,33,44,45].

Coxibs

Pain is a major symptom in many dental procedures. Studies show consistently that pain, including dental pain, is not effectively treated; management of pain is a critical and challenging component in dentistry. Improvement and efficacy on the treatment depends on knowing which treatments are the most effective. Knowing how well an analgesic works and its associated adverse effects is fundamental to clinical decision. Therefore, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed analgesic agents in surgical outpatients. Major limitations of NSAIDs are their gastrointestinal (GI) adverse events (perforation, ulceration, and bleeding), impairment of hemostatic function, renal failure (with long-term therapy) and bronchospsm . A new class of NSAIDs, COX2 selective inhibitors (Coxibs), have been developed with the aim of reducing the GI adverse events of traditional NSAIDs while maintaining their effective anti-inflammatory and analgesic properties [12,33,34].

The effect of local injections of rofecoxib (1 mg/kg at day 1 and day 3) was studied in a rat model in which mesial movement of the fi rst molar was induced by forces of 50 or 100 cN [27,34]. It appeared that no OTM occurred when 50 cN were applied, but 100 cN did induce OTM. It was however signifi cantly less than in the controls without medication [27]. In a subsequent study, the same group compared the effects of injections of rofecoxib (0.5 mg/kg), celecoxib (8 mg/kg), or parecoxib (25 mg/kg) on days 0, 3, and 5 after placement of the appliance. OTM was determined after 10 days of treatment. In the rofecoxib-treated animals, no OTM at all was occurred, while OTM in the celecoxib and parecoxib treatment was comparable to the controls [27,33,34].

In a comparable rat study, in which a longer experimental period was used (14 days), a significant reduction in OTM was found after celecoxib administration [40]. In contrast to these studies, no interference with OTM was found after administration of 50 mg/kg celecoxib by oral gavage, prior to placement of an orthodontic appliance exerting a force of 50 cN. The experimental period was restricted to 48 h of active OTM [12,33].

A dose-dependent effect of celecoxib in OTM was found in a rat study where doses of 16 mg/kg/day or 3.2 mg/kg/day were administered through the drinking water for 14 days. Only the high dose inhibited OTM [34,36]. These results are in contrast to a more recent rat study in which celecoxib injections at a low dose (0.3 mg/day) were given every 3 days for a period of 18 days. This resulted in a significant decrease in OTM [12,34]. However, another recent study, in which daily injections of 10 mg/kg celecoxib was administered in rats for a period of 2 months, could not establish an effect on OTM [34,38].

Paracetamol

During the year 2004, and through the Spanish National Health Care System (Sistema Nacional de Salud, SNS), nonsteroidal anti-inflammatory drugs (NSAIDs) and other antipyretic analgesics (paracetamol) were prescribed for a total of 330.33 million euros – representing 3.34% of the total drug prescriptions made through the SNS. Ibuprofen was the NSAID generating the greatest expenditure, with a total of 16.7 million containers, representing approximately 100.3 million euros. In other words, ibuprofen accounted for a little over 30% of the total NSAID prescription costs. The most extensively prescribed analgesic was paracetamol, with 30.8 million containers, representing a total cost of 86.7 million euros. Paracetamol moreover was the most widely SNS-prescribed

drug substance during 2004, followed by omeprazole, with approximately 24.5 million containers, and ibuprofen in third place [12,33,34].

The prescription of drugs by dentists and stomatologists through the SNS in the Valencian Community represented 0.079% of the global prescriptions and 0.0417% of the total cost. Analgesics and anti-inflammatory drugs for the same period and for the same health care professional sector represented approximately 20,000 prescriptions (20,302), of which 60.88% corresponded to ibuprofen, 14.5% to pyrazolones (metamizole), and 10% to paracetamol. Oxicams (5%) and acetic acid derivatives (5%) practically accounted for the total of prescriptions in this therapeutic group. A significant observation is the fact that only three drugs (ibuprofen, paracetamol and metamizole) accounted for 85% of global analgesics-antiinflammatory drug prescription by dental professionals [34,46].

The NSAIDs constitute a heterogeneous group of drugs with analgesic, antipyretic and antiinflammatory properties that rank intermediately between corticoids with antiinflammatory properties on one hand, and major analgesics – opioids on the other [18,33].

The effect of paracetamol on OTM in rabbits has been studied during administration of a dosage of 500 mg/kg/day. No effect on the rate of mesial molar movement was found when using a force of 100 cN [34]. Likewise, a dosage of 200 mg/ kg/day for 2 or 10 days in rats did not influence the rate of lateral displacement of the incisors by applying a force 35 cN [12,46]. Comparable results were found in a rat study where molars were moved to the mesial by a force of 50 cN, and paracetamol was applied via drinking water at a dose of 20 or 100 mg/kg/day for 2 weeks [36]. However, a recent study showed a significant decrease of OTM in rats where a mesial force of 50 cN was applied for 2 months, and paracetamol was administered by gastric gavage at a dose of 150 mg/kg/day throughout the experimental period [38,46]. Paracetamol did not affect the rate of OTM with the given dosages, during the 2-week observational period. For this reason, it is suggested that it should be the analgesic of choice for managing pain associated with orthodontic therapy. However, long-term application might result in a decrease in OTM [12,47].

Opioids

There is little role for opioids in dentistry given that there are established superior analgesics. Identifying and addressing the cause of pain by active dental treatment is the best pain management – analgesia plays an adjunctive role only [12].

In a survey, 16–27% of dentists preferred prescribing an opioid or paracetamol over a non-steroidal anti-inflammatory drug (NSAID) as first choice for dental pain.”” ‘ The most commonly prescribed opioids in dentistry are codeine 30 mg (with paracetamol 500 mg), oxycodone and tramadol. Paracetamol combined with codeine accounts for around 96% of these prescriptions. This is of concern since in 2016 codeine products (both over-the-counter and prescription) were the most commonly misused pharmaceutical products, followed by oxycodone and tramadol [33,34].

Opioids are effective for the treatment of acute and chronic-related pain, i.e., with degenerative conditions such as rheumatoid arthritis, or even during labor and cardiac infraction. They work by binding to opioid receptors, which are found principally in the central and peripheral nervous system and the gastrointestinal tract. Only very few studies have been performed on the effects of opioids on OTM. The opioids tested were only morphine (INN) and tramadol (marketed as Ultram and Tramal and as generics). However, tramadol is under strict control in some countries. In one rat study, it is reported that daily morphine injections at a dose of 5 mg/kg/day over 14 days reduced the rate of OTM induced by a force of 60 cN [5,48]. In another study from the same group, daily tramadol injections at a dose of 20 mg/kg/day during 14 days had no effect [8]. These results are supported by a rat study in which again a force of 60 cN was used to move rat molars to the mesial for 14 days. Administration of tramadol at 10 mg/kg/day had no significant effect on OTM, while after administration of increasing doses up to 60 mg/kg/day, OTM almost completely came to a s tandstill [4,49].

Discussion

The orthodontic tooth movement is characterized by a multiple biological process involving sequential reactions of the periodontal tissue in response to biomechanical forces. Two regions can be observed in the periodontal ligament, the traction zone and the compression zone. New bone is deposited in the alveolar wall on the traction side when light or heavy mechanical forces are applied. On the compression side, under light force, the alveolar bone is directly resorbed by osteoclasts located in Howship’s lacunae [12,34,50].

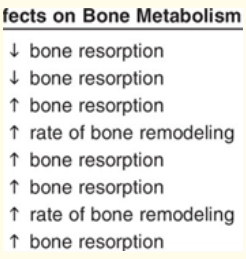

Figure 8: The influence of drugs and systemic factors on orthodontic tooth movement.

Several theories about orthodontic tooth movement have been proposed, and all of them present the bone resorption as one of the biological effects. In the first half of the twentieth century there was already concern about the action mechanism and the events triggered by the applied force on the dental crown. The pressure-tension theory was based on the vitality of the periodontal ligament, i.e., the stimulation applied to the ligament did not involve or require stimulation coming from other structures such as the alveolar bone, for instance. The collagen fibers and the vascular system were essential for the development of this phenomenon [51,52].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common medications taken worldwide for the treatment of pain, inflammation, and fever [3]. NSAIDs act by inhibiting the prostaglandin (PG) synthase enzymes, colloquially known as cyclooxygenases. The inhibition of cyclooxygenase-2 (COX-2) is thought to mediate, in large part, the antipyretic, analgesic, and anti-inflammatory actions of NSAIDs, while the simultaneous inhibition of cyclooxygenase-1 (COX-1) largely but not exclusively accounts for unwanted adverse effects in the GI tract [53].

Orthodontic treatment is based on the biologic principle that prolonged pressure on teeth results in remodeling of periodontal structures, allowing for tooth movement. Periodontal remodeling is a complex process regulated in part by prostaglandins and adversely affected by the use of nonsteroidal anti-inflammatory drugs. Cyclooxygenase inhibition resulted in exacerbation of IL 1β–mediated collagenase B (MMP-9) production and activity, as well as attenuation of type IV pro-collagen synthesis levels by endothelial cells *in vitro* [54]. Two isoforms of mammalian cyclooxygenase(COX) have been described: the constitutive COX-1 and the inducible COX-2. Of these, COX-1 is considered important in tissue homeostasis. However, COX-2 is transcriptionally induced by cytokines (TNFαandIL-1) and appears to be important in the development of inflammation. Prostaglandin production during the inflammatory process depends on the enzymatic degradation of arachidonic acid through the constitutive isoform of COX-1 and the inducible isoform of COX-2 pathways. COX-1 produces prostaglandins that protect the gastrointestinal mucosa [33,55]. The selective inhibition of COX-2 produces anti-inflammatory effects, causing less injury to the gastrointestinal mucosa than the nonselective NSAIDs. Consequently, the use of selective COX-2 inhibitors is increasing, replacing conventional NSAIDs, especially for chronic inflammatory conditions. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been developed that target these cyclooxygenases [34,52-55].

The use of over-the-counter nonsteroidal anti-inflammatory drugs during tooth movement may result in aberrant remodeling of periodontal vasculature and other structures, ultimately affecting orthodontic treatment efficacy. The use of analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the release of prostaglandin (PGs) and stop inflammation are effective in the treatment of pain related to orthodontic treatment. Nevertheless, the extended use of NSAIDs is inappropriate for orthodontic discomfort, because, as research and clinical experience suggests, their use could slow down tooth movement. [3] NSAIDs are a chemically heterogeneous group of compounds, which nevertheless share certain therapeutic actions and adverse effects. The class includes derivatives of salicylic acid (e.g., aspirin, diflusinal), propionic acid (e.g., naproxen, ibuprofen, flurbiprofen, ketoprofen), acetic acid (e.g., indomethacin, etodolac, diclofenac, ketorolac), enolic acid (e.g., piroxicam, phenylbutazone), fenamic acid (e.g., mefenamic acid, meclofenamic acid), alkanones(nabumetone), and diaryl heterocyclic compounds [12,33,34].

Most NSAIDs are rapidly absorbed following oral ingestion, and peak plasma concentrations usually are reached within 2-3 hours. All COX-2–selective NSAIDs are well absorbed. The poor aqueous solubility of most NSAIDs often is reflected by a less than proportional increase in area under the curve (AUC) of plasma concentration–time curves, due to incomplete dissolution, when the dose is increased. Food intake may delay absorption and sometimes decreases systemic availability (i.e., fenoprofen, sulindac). Antacids, commonly prescribed to patients on NSAID therapy, variably delay, but rarely reduce, absorption [56,57].

This review of literature summarizes the effects of medications, such as anti-inflammatory and analgesics in orthodontic tooth movement. Considering the increasing number of drugs available in the market, orthodontists have to constantly update their knowledge about drugs esp. NSAIDS and their influence on the duration of orthodontic treatment. The use of self-ligating brackets should be emphasized allowing use of less forces due to reduced friction [12]. The expected duration of treatment should be prolonged and orthodontic forces be reduced or used at intervals .As orthodontists are routinely using NSAIDs during treatment they must also have understanding of fundamentals of drug therapy. Since NSAIDs effectively reduce the pain caused by orthodontic treatment, they also affect the tooth movement by reducing the inflammatory or bone resorption process. Acetaminophen (paracetamol) has been suggested as a safe and effective analgesic of choice for relieving discomfort associated with orthodontic pain [33]. Thus it becomes imperative for the clinician to update his/her knowledge on the clinical efficacy of the new drugs as well as their beneficial and harmful effects on human tissues. Orthodontist should be aware of the patient's medical history and also converse with patient about the dosage and potential adverse effects. Also it is advisable for the clinician to confirm with the family physician for fitness of the patients undergoing corrective orthodontics [12,33,34].

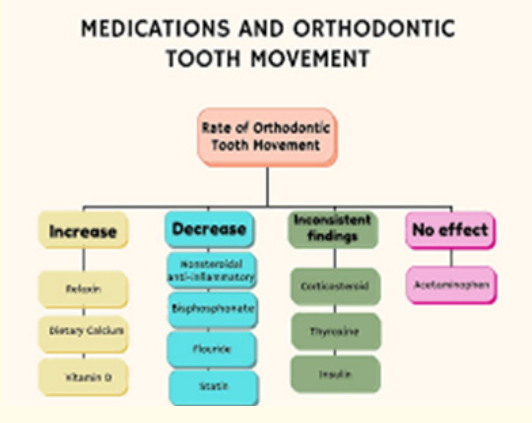

Figure 9: Summary of the effect of the included medications on the tooth movement.

The recent increase in the use of both prescribed and non-prescribed medications across various age groups highlighted the need for more rigorously designed experimental and, where feasible, clinical trials on how these substances affect orthodontic tooth movement. Standardizing research methodologies is essential, along with carefully addressing potential bias risks. Furthermore, it is important to carefully choose study parameters such as duration, dosage, and method of administration, as well as the details of the biomechanical systems used, to closely replicate clinical conditions in humans. However, the challenge of ethical concerns regarding the implementation of a drug on humans without sufficient animal trials must be acknowledged.

Conclusion

Orthodontist should aware of patient medical history and also converse with patient about the dosage, potential adverse effects. The NSAIDs effectively reduce the pain and discomfort caused by orthodontic tooth movement but they also affect the tooth movement by inhibiting or reducing the inflammatory or bone resorption process. Acetaminophen has been suggested as safe and effective the analgesic of choice for relieving the discomfort associated with orthodontic pain. Ibuprofen is also effective in reducing preoperative as well as postoperative orthodontic pain. Thus today's clinicians should mandatorily update the knowledge on the clinical efficacy of the new drugs as well as the beneficial and harmful effects on human tissues.

Consent

It is not applicable.

Ethical Approval

It is not applicable.

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