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Drugs and Orthodontics: A Review

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Abstract

Orthodontic pain, the most cited negative effect arising from orthodontic force application, is a major concern for patients, parents and clinicians. Orthodontic tooth movement is basically a biological response toward a mechanical force. Certain mechanical, chemical, and cellular events take place within these tissues, which allow for structural alterations and contribute to the movement of that tooth. Molecules present in drugs and nutrients consumed regularly by patients can reach the mechanically stressed paradental tissues through the circulation and interact with local target cells. The combined effect of mechanical forces and one or more of these agents may be inhibitory, additive, or synergistic. Current orthodontic research aims to develop methods of increasing the tissue concentration of molecules promoting tooth movement, while simultaneously decreasing the concentration of unwanted elements which can produce harmful side effects. This review attempts to organize the existing published literature regarding pain, which appears as part of orthodontic mechanotherapy and to address questions that might arise in a clinical setting from the viewpoint of clinicians and patients/parents. It also provides an overview of current management strategies employed for alleviating orthodontic pain.

Keyorwds: acetaminophen, NSAIDs, pain, prostaglandins, hormones, immunomodulatory drugs, immunosuppressant drugs.

Introduction

Pain is a subjective response, which shows large individual variations. It is dependent upon factors such as age, gender, individual pain threshold, the magnitude of the force applied, present emotional state and stress, cultural differences, and previous pain experiences.[1,2] Pain, which includes sensations evoked by, and reactions to, noxious stimuli, is a complex experience and often accompanies orthodontic appointments. This, among the most cited negative effects of orthodontic treatment, is of

major concern to patients as well as clinicians and is evident in recent publications.[3]

Orthodontic tooth movement is based on the biologic principle that prolonged pressure on the teeth results in remodelling of periodontal structures including the alveolar bone and periodontal ligament. The early phase of orthodontic tooth movement involves acute inflammatory response characterized by periodontal vasodilatation. There is inflammatory response surrounding the tissues where osteoblastic and osteoclastic activities are carried out. Cyclic adenosine monophosphate (cAMP), calcium, collagenase, and prostaglandins (PGs) play in mediating tooth movement in response to orthodontic force. Depending on the alterations in the periodontium, pain and discomfort are the common experiences among orthodontic patients. Reported pain and discomfort is generally the highest during the first 24 h after the application of an orthodontic force. The periodicity of these complaints peaks at 24 h, but decreases to baseline levels by 7 days.[4–6]

The most common group of medications used in orthodontics for pain relief consists of nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs function by inhibition of enzyme cyclooxygenase (COX), 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.[7-9]

Pain and Orthodontics

It is reported that orthodontic procedures will reduce the proprioceptive and discriminating abilities of the patients for up to 4 days, which result in lowering of the pain threshold and disruption of normal mechanisms associated with proprioception input from nerve endings in the periodontal ligament. At the same time, there will be pressure, ischaemia, inflammation, and oedema in the PDL space. Burstone (1962) reported an immediate and delayed painful response after orthodontic force application. He attributed the initial response to compression and the delayed response to hyperalgesia of the PDL. This hyperalgesia has been related to prostaglandins (PGEs), which make the PDL sensitive to released algogens such as histamine, bradykinin, PGEs, serotonin, and substance P. It is clear that all orthodontic procedures will create tension and compression zones in the PDL space resulting in a painful experience for the patients.[1,10–12]

Mechanism of Orthodontic Pain

There is no doubt that the perception of orthodontic pain is part of an inflammatory reaction causing changes in blood flow following orthodontic force application. This is known to result in the release of various chemical mediators eliciting a hyperalgaesic response. Recent research has started revealing the molecular basis of orthodontic pain with demonstration of the presence as well as elevation in levels of various neuropeptides released. Orthodontic tooth movement is known to cause inflammatory reactions in the periodontium and dental pulp, which will stimulate release of various biochemical mediators causing the sensation of pain. The perception of orthodontic pain is due to changes in blood fl ow caused by the appliances and has been correlated with the release and presence of various substances, such as substance P, histamine, enkephalin, dopamine, serotonin, glycine, glutamate gamma-amino butyric acid, PGEs, leukotriens, and cytokines. The literature regarding the increase in the levels of these mediators, which elicit hyperalgaesia response following force application, is replete in orthodontics.[13–16]

Evaluation of Pain

There is a well defined classification system for orthodontic pain proposed by Burstone (1962). It appears

to be valid even now and to have stood the test of time. In order to study or evaluate pain, patient interview/questionnaire and ratings with VAS, McGill pain questionnaire (MPQ), Verbal Rating Scales (VRS) and algometers can be effectively used.

Classification of pain

Burstone (1962) classified a painful response to orthodontic mechanics in two ways: one depends on the relationship of force application with pain and the other according to the time of onset. According to that author, the degree of pain perceived in response to the amount of force application can be divided into three:

1. First degree: the patient is not aware of pain unless the orthodontist manipulates the teeth to be moved by the appliance, e.g. using instruments such as a band pusher or force gauge.
2. Second degree: pain or discomfort caused during clenching or heavy biting — usually occurs within the first week of appliance placement. The patient will be able to masticate a normal diet with this type of pain.
3. Third degree: if this type of pain appears, the patient might be unable to masticate food of normal consistency.

Based on time of onset, Burstone (1962) further classified pain as follows:

1. Immediate: which is associated with sudden placement of heavy forces on the tooth, e.g. hard figure of eight tie between the central incisors to close a midline diastema.
2. Delayed: produced by variety of force values from light to heavy and representing hyperalgaesia of the periodontal membrane. This type of pain response decreases with time i.e. the pain reaction might start as third degree but become second or a first degree with the passage of time.

Drugs Affecting 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. It is necessary to review the mechanism of action and effects of commonly used drugs on tissue remodelling 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, tumour necrosis factors (TNFs), interleukins (ILs), etc. The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG medicated 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.

Effect of NSAIDs on 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 remodelling. The whole process is controlled by inhibition of cyclooxygenase (COX) activity, leading to altered

vascular and extravascular matrix remodelling, causing a reduction in the pace of the tooth movement.

Aspirin

Acetylsalicylic acid and the related compounds, and their action result from inhibition of COX activity, which converts unsaturated fatty acids in the cell membrane to PGs. Clinical experience shows that orthodontic tooth movement is very slow in patients undergoing long-term acetylsalicylic therapy. Salicylate therapy decreases bone resorption by inhibition of PGs' synthesis and may effect differentiation of osteoclasts from their precursors. Therefore, it is recommended that patients undergoing orthodontic treatment should not be advised to take aspirin and related compounds for longer period during orthodontic treatment.

COX-2 inhibitors

An interesting recent development is seen in prescriptions of a specific *COX-2 inhibitor*, a drug with no effect on PGE2 synthesis. The drug selectively blocks the *COX-2 enzyme* and impedes the production of PGs that cause pain and swelling. Because it selectively blocks *COX-2 enzyme* and not *COX-1 enzyme*, it was suggested that the drug can be safely employed during orthodontic mechanotherapy, without causing negative effects on tooth movement. This drug is no more prescribed due to risk of cardiovascular events. A recent study reported that *nabumetone*, belonging to NSAID group, reduces the amount of root resorption along with control of pain from intrusive orthodontic forces, without affecting the pace of tooth movement.[17]

Acetaminophen (Paracetamol)

It is a weak COX-1 and COX-2 inhibitor that also reduces urinary prostaglandin levels after systemic administration and has shown no effect on orthodontic tooth movement in guinea pigs and rabbits. Comparative studies and clinical experience have shown that *acetaminophen* is effective for controlling pain and discomfort associated with the orthodontic treatment.

Other NSAIDs

Yamasaki et al. administered indomethacin to rats and inserted a piece of elastic between their molar teeth. The appearance of osteoclasts in the interradicular septum of bone of the first molar was found to be inhibited by the indomethacin. They also found *imidazole*, which is a specific inhibitor of *thromboxane A2* synthesis but does not stop the synthesis of other prostaglandins, to have a similar effect. Sandy and Harris found that flurbiprofen inhibited the appearance of osteoclasts, but had no significant effect on tooth movement in rabbits. However, they also found that *AA861*, a leukotriene inhibitor that causes an increase in the production of PGE2, inhibited tooth movement.[18–20]

Vitamin D

Vitamin D and its active metabolite, *1,25,2(OH)D3*, together with *parathyroid hormone (PTH)* and *calcitonin*, regulate the amount of calcium and phosphorus levels. Vitamin D receptors have been demonstrated not only in osteoblasts but also in osteoclast precursors and in active osteoclasts. In 1988, Collins and Sinclair demonstrated that intraligamentary injections of vitamin D metabolite, *1,25-dihydroxy cholecalciferol*, caused increase in the number of osteoclasts and amount of tooth movement during canine retraction with light forces. In 2004, Kale and colleagues observed that local applications of vitamins enhanced the rate of tooth movement in rats due to the well balanced bone turnover induced by vitamin D.[21,22]

Stimulatory action of vitamin D on osteoblasts can help stabilize orthodontic tooth movement. In 1976, Bran and colleagues reported that rats treated with vitamin D showed increased bone formation on the pressure side of

the periodontal ligament after application of orthodontic forces. In 2004, Kawakami observed an increase in the mineral appositional rate on alveolar bone after orthodontic force application; they suggested that local application of vitamin D could intensify the re-establishment of supporting alveolar bone, after orthodontic treatment.

Fluorides

Fluoride is one of the trace elements having an effect on tissue metabolism. Fluoride increases bone mass and mineral density, and because of these skeletal actions, it has been used in the treatment of metabolic bone disease, osteoporosis. Even a very active caries treatment with *sodium fluoride* during orthodontic treatment may delay orthodontic tooth movement and increase the time of orthodontic treatment. *Sodium fluoride* has been shown to inhibit the osteoclastic activity and reduce the number of active osteoclasts.[23]

Bisphosphonates

Bisphosphonates (BPNs) have strong chemical affinity to the solid-phase surface of calcium phosphate; this causes inhibition of hydroxyapatite aggregation, dissolution, and crystal formation. *Bisphosphonates* cause a rise in intracellular calcium levels in osteoclastic-like cell line, reduction of osteoclastic activity, prevention of osteoclastic development from hematopoietic precursors, and production of an osteoclast inhibitory factor. Studies have shown that BPNs can inhibit orthodontic tooth movement and delay the orthodontic treatment. Topical application of BPNs could be helpful in anchoring and retaining teeth under orthodontic treatment.

Hormones

Estrogens

Estrogen is considered to be the most important hormone affecting the bone metabolism in women. It inhibits the production of various cytokines which are involved in bone resorption by stimulating osteoclast formation and osteoclast bone resorption. It also inhibits osteoblasts' responsiveness to PTH. Estrogens do not have any anabolic effects on bone tissue; they directly stimulate the bone forming activity of osteoblasts. Studies have shown that estrogens decrease the velocity of tooth movement. Oral contraceptives, taken for long periods of time, can influence the rate of tooth movement. Androgens also inhibit bone resorption, modulate the growth of the muscular system, and may affect the length and results of the orthodontic treatment.[24]

Thyroid hormones

Thyroid hormones are recommended for the treatment of hypothyroidism and used after thyroidectomy in substitutive therapy. *Thyroxin* administration lead to increased bone remodelling, increased bone resorptive activity and reduced bone density. Effects on bone tissue may be related to the augmentation of interleukin-1 (IL-1B) production induced by thyroid hormones at low concentrations, cytokine stimulated osteoclast formation and osteoclastic bone resorption. The thyroid hormone increases the speed of orthodontic tooth movement in patients undergoing such medication. Low dosage and short-term thyroxine administration are reported to lower the frequency of "force-induced" root resorption. Decrease in resorption may be correlated to a change in bone remodelling process and a reinforcement of the protection of the cementum and dentin to "force-induced" osteoclastic resorption.[25]

Relaxin

Relaxin has been known as a pregnancy hormone. It is released just before child birth to loosen the pubic symphysis, so that the relaxed suture will allow widening of the birth canal for parturition. In 2005, Liu and colleagues showed that the administration of relaxin might accelerate the early stages of orthodontic tooth movements

in rats. Stewart and colleagues used gingival injections of Relaxin to relieve rotational memory in the connective tissues of maxillary lateral incisors that had been orthodontically rotated. In 2000, Nicozis and colleagues suggested that Relaxin might be used as an adjuvant to orthodontic therapy, during or after tooth movement, for promotion of stability, for rapid remodelling of gingival tissue during extraction space closure, for orthopaedic expansion in non – growing patients, by reducing the tension of the stretched soft tissue envelope, particularly the expanded palatal mucosa, after orthognathic surgery.[26]

Calcitonin

Calcitonin inhibits bone resorption by direct action on osteoclasts, decreasing their ruffled surface which forms contact with resorptive pit. It also stimulates the activity of osteoblasts. Because of its physiological role, it is considered to inhibit the tooth movement; consequently, delay in orthodontic treatment can be expected.

Parathyroid hormone

PTH affects osteoblasts' cellular metabolic activity, gene transcriptional activity, and multiple protease secretion. Its effects on osteoclasts occur through the production of RANK-L Receptor activator of nuclear factor kappa –B ligand), a protein playing a crucial role in osteoclasts' formation and activity. In 1970s, animal studies demonstrated that PTH could induce an increase in bone turnover that would accelerate orthodontic tooth movement. More recently, an increased rate of tooth movements has been observed in rats treated with PTH, whether administered systemically or locally. These results indicate that orthodontists should take note of patients being treated with PTH, as for example, in cases of severe osteoporosis. [27]

Corticosteroids

Evidence indicates that the main effect of corticosteroid on bone tissue is direct inhibition of osteoblastic function and thus decreases total bone formation. Decrease in bone formation is due to elevated PTH levels caused by inhibition of intestinal calcium absorption which is induced by corticosteroids. Corticosteroids increase the rate of tooth movement, and since new bone formation can be difficult in a treated patient, they decrease the stability of tooth movement and stability of orthodontic treatment in general.[28]

When they are used for longer periods of time, the main side effect is osteoporosis. It has been demonstrated in animal models with this type of osteoporosis that the rate of active tooth movement is greater, but tooth movement is less stable since little bone is present and there is no indication of bone formation. A more extensive retention may be required.

Prostaglandins

Experiments have shown that PGs may be mediators of mechanical stress during orthodontic tooth movement. They stimulate bone resorption, root resorption, decrease collagen synthesis, and increase cAMP. They stimulate bone resorption by increasing the number of osteoclasts and activating already existing osteoclasts. A lower concentration of *PGE2 (0.1 mg)* appears to be effective in enhancing tooth movement. Higher concentration leads to root resorption. Systemic administration is reported to have better effect than local administration. Researchers have injected PGs locally at the site of orthodontic tooth movement to enhance the bone remodelling process and the pace of tooth movement. The main side effect associated with local injection of PGs is hyperalgesia due to the release of noxious agents.

Interleukin antagonists

IL antagonists inhibit IL-1, produced by monocytes, macrophages, and some specialized cells, which are important for the inflammatory response, and IL-6 and COX-2. These drugs influence the inflammatory response

following force application, reducing the pace of tooth movement and bone remodelling.

TNF-a antagonists

TNF-a antagonists block TNF-a in inflammatory cytokinins released by activated monocytes, macrophages, and T-lymphocytes, which are essential for inflammatory responses following force application.

Echistatin and RGD peptides

Another approach made recently is local injection of integrin inhibitors like *echistatin and RGD (Arginine–Glycine–Aspartic acid)* peptides on rats to prevent tooth movement, thereby enhancing anchorage. Recent research has demonstrated decrease in root resorption following orthodontic force application after administration of *Echistatin*.[28,29]

Immunomodulatory drugs

Most of these drugs used for treatment of Rheumatoid arthritis includes immunomodulatory agents like *Leflunomide, TNFantagonists (Etanercept), interleukin antagonists (Anakinra)*. Immunomodulatory drugs modulate nuclear factor kappa – Beta , tyrosine kinases in signaling pathway, IL – 6, MMPs and PGE2, all of which are essential for the bone remodelling process.[30]

Immunosuppressant drugs

Patients with chronic renal failure or kidney transplants and on immunosuppressant drugs can encounter some difficulty during orthodontic treatment. Drug consumed for prevention of graft rejection *(cyclosporine A)* produce severe gingival hyperplasia, making orthodontic treatment and maintenance of oral hygiene difficult. Treatment should be started or resumed after surgical removal of excessive gingival tissues once there is good oral hygiene. Whenever possible, fixed appliances should be kept to a minimum period with brackets and avoiding the use of cemented bands. Removable appliances in these cases are not recommended due to improper fit.

Anticancer drugs

These are used for the treatment of childhood cancers. There is every chance of observing disturbances in dental as well as general body growth and development due to the adverse effects of the chemotherapeutic agents. It is clearly stated that patients who had been on chemotherapy with *busulfan/cyclophosphamide* belong to the risk group for orthodontic treatment These drugs are known to produce damage to precursor cells involved in bone remodelling process, thereby complicating tooth movement.[30]

Anticonvulsants

Phenytoin

It induces gingival hyperplasia due to overgrowth of gingival collagen fibers, which involve the interdental papilla, making application of orthodontic mechanics and maintaining oral hygiene difficult. If used during pregnancy, it can produce fetal hydantoin syndrome characterized by hypoplastic phalanges, cleft palate, hare lip, and microcephaly. Valproic acid has a potential to induce gingival bleeding even with minor trauma, making orthodontic maneuvers difficult. Gabapentin produces xerostomia, making oral hygiene maintenance difficult during orthodontic treatment.

Alcohol abuse

Alcohol crosses the placental barrier and can stunt fetal growth or weight, create distinctive facial stigmata, damage neurons and brain structures, which can result in psychological or behavioral problems, and cause other physical damage (Fetal Alcohol Syndrome or FAS). The three FAS facial features are a smooth philtrum, thin vermilion, and small palpebral fissures. Chronic ingestion of large amounts on a daily basis may have devastating effects on a number of tissue systems, including skeletal system. Circulating ethanol inhibits the hydroxylation of vitamin D3 in liver, thus impending calcium homeostasis.

In such cases, the synthesis of PTH is increased, tipping the balance of cellular function toward the enhanced resorption of mineralized tissues, including root resorption, in order to maintain normal levels of calcium in blood. Davidovitch et al. have found that chronic alcoholics receiving orthodontic treatment are at high risk of developing severe root resorption during the course of orthodontic treatment.[30]

Conclusion

As reported by Keim (2004) , ‘ pain management and even more important, pain prevention are given short shrift in many orthodontic training programs ’ .Orthodontists have long observed that teeth move at different rates and individuals differ in their response to treatment. Some of the differences are caused by change in bone remodelling induced by drugs and systemic factors. All the drugs reviewed have therapeutic effects as well as side effects that influence the cells targeted by orthodontic forces. The value of a thorough medical history is increasingly significant as young and old alike are exposed to a greater range of therapeutic agents. Therefore, it is imperative that the orthodontists need to pay attention to drug consumption and history of each and every patient, before and during the course of orthodontic treatment, so that the best treatment strategy (including force control and appointment intervals) can be selected for each case. Acetaminophen and celecoxib are the NSAIDs of choice for relief of orthodontic pain without affecting the rate of orthodontic tooth movement.

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