

Review Article**Influence of drugs on orthodontic tooth movement**

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Orthodontics is a specialty, using biomechanical principles of physiological mechanisms that can correct dental malposition and malformations of the jaws to restore a functional and aesthetic dentition. Orthodontic treatments are limited to dental displacements, using either fixed or removable systems. Only the alveolar bone needs to be remodeled. Dentofacial orthopedics treatments also include the control and modification of jaw positions and facial growth by controlling the growth sites in the maxilla and mandible [1, 2]. When a force is applied to the crown of a tooth, it is transmitted through the root of the tooth to the periodontal ligament and alveolar bone. According to the direction of the force, there will be areas of pressure and areas of tension on these supporting structures [1]. For the tooth to move, there must be resorption of alveolar bone in response to this stress, and if the tooth is to remain firmly attached there must also be deposition of bone to maintain the integrity of the attachment mechanism. In effect, the socket of the tooth must move, concomitant with movement of the tooth through the alveolar bone. Although the general nature of the cellular reactions to force on the teeth, which result in bone resorption and deposition, are not in dispute, the intermediary causes of these reactions have been the subject of more recent investigation. The classical theory of tooth movement suggests that the cellular reactions are simply the result of differential pressure induced in the periodontal ligament, and that the response to force is confined to the cellular elements of the ligament and the endosteal marrow spaces [1, 2, 3].

This concept has been challenged by several investigators; Baumrind has suggested that the ligament should be considered as a continuous hydrostatic system, in which differential pressures cannot exist. If this is so, the pressure-tension concept of the classical theory must be questioned [4, 5, and 6]. It has also been shown that bone which is deformed by stress becomes electrically charged, concave surfaces taking a negative polarity and

convex surfaces a positive polarity [6, 7, 8, 9, 10, 11]. Justus and Luft have put forward a mechanochemical hypothesis for the remodeling of bone under stress. Their experiments have suggested that altered physical stress in the bone changes the solubility of the hydroxyapatite crystals, which in turn induces the osteoblastic and osteoclastic activity which results in bone remodeling [12, 13]. The forces used in successful orthodontic treatment have usually been determined empirically, and no doubt sometimes cause pressures greater than capillary blood pressure [1,2,3,4,5,6] In considering these forces it is necessary to review the different types of tooth movement which are commonly required. Table.1 Several different types of tooth movement occur during orthodontic treatment. Because of the nature of the attachment of the teeth to the alveolar bone all these movements are likely to be complex, but they can be considered in simplified form as follows;

- Tipping movements.
- Rotational movements.
- Bodily movements.
- Torque movements.
- Vertical movements

Force and Center of resistance

Intuitively, the point of force application also has an influence on the quality of the tooth movement. There is only one point on a tooth through which a force can be applied that will move the tooth in the direction of the force without tipping or rotating it. This point is the center of resistance and force acting through it will cause pure translation of the tooth [1, 2, 5].

Forces and Moment

When a force is applied at any point other than through the center of resistance, in addition to moving the center of resistance in the direction of the force, a moment is created. A moment is defined as a tendency to rotate and may refer to rotation, tipping, or torque in orthodontic terminology. If a distal force is applied buccal to the center of resistance, the center of resistance of the tooth will move distally and the tooth will rotate mesiobuccally [1].

Effect of individual drugs on the orthodontic tooth movement can be summarized as:**Analgesics**

Analgesic is a drug that selectively relieves pain by acting on the CNS or peripheral pain mechanisms, without significantly altering consciousness. NSAIDs are a relatively weak inhibitor of PG synthesis [3, 5]. The whole process is controlled by inhibition of COX activity, leading to altered vascular and extravascular matrix remodeling, causing a reduction in the pace of the tooth movement [5, 6, 7]. A recent study reported that nabumetone, a drug 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 [1,5].

Acetaminophen

Paracetamol (acetaminophen) was first identified in the late nineteenth century and it was available in the UK on prescription in 1956, and over-the-counter in 1963. Since then, it has become one of the most popular antipyretic and analgesic drugs worldwide, and it is often also used in combination with other drugs. The lack of a significant anti-inflammatory activity of paracetamol implies a mode of action which is distinct from that of the non-steroidal anti-inflammatory drugs. Yet, the Cochrane Systematic Review, 2004 concluded that paracetamol was effective against the postoperative pain in adults [1 5]. Acetaminophen (paracetamol) is effective for controlling pain and discomfort associated with orthodontic treatment [5].

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 [22]. 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 [23,24,25,26].

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 [4,5,6].

Fluorides

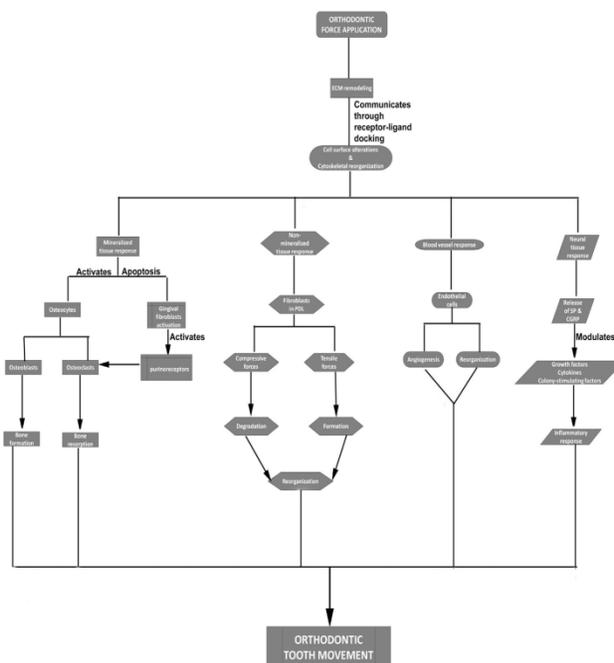
Fluoride is one of the trace elements having an effect on tissue metabolism. Fluoride increases bone mass and mineral density, and because of these skeletal actions, it has been used in the treatment of metabolic bone disease, osteoporosis. Even a very active caries treatment with sodium fluoride during 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 [27].

Corticosteroids

These drugs are used as anti inflammatory and immunosuppressive agent in treatment of a wide range of chronic medical conditions. A low dose(1mg/kg body weight)decreases orthodontic tooth movement by suppressing osteoclastic activity. At high dose(15mg/kg body weight)it increases osteoclastic activity thus produces more rapid orthodontic tooth movement and subsequent relapse [28]. The main effect of corticosteroid on bone tissue is direct inhibition of osteoblastic function and thus the decrease of total bone formation.[28] Decrease in bone formation is due to elevated parathyroid hormone levels caused by inhibition of intestinal calcium absorption which are induced by corticosteroids. Corticosteroids increase the rate of tooth movement, and since new bone formation can be difficult in treated patient, they decrease the stability of tooth movement and stability of orthodontic treatment in general [28,29,30]. When they are used for longer periods of time, the main side effect is osteoporosis. It has been demonstrated in animals 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 no indication of bone formation. A more extensive retention may be required [29,30]. Corticosteroids acts by preventing the formation of prostaglandins by influencing the arachidonic acid pathway. An endogenous protein, lipocortin formed by steroids acts by blocking the activity of phospholipase A₂, thus

inhibits the release of arachidonic acid which in return influences the synthesis of prostaglandin, leukotrienes or thromboxanes. Corticosteroids also act by reducing the release of lymphokines, serotonin and bradykinin at the injured site [18]. They play a vital role in inhibiting the intestinal calcium absorption, which leads to direct inhibition of osteoblastic function, and increase in bone resorption [28,29,30].

Fig 1: Orthodontic tooth movement



Thyroid hormones

Thyroid hormones are recommended for the treatment of hypothyroidism and used after thyroidectomy in substitutive therapy. Thyroxin administration lead to increased bone remodeling, increased bone resorptive activity, and reduced bone density. Effects on bone tissue may be related to the augmentation of interleukin-1 (IL-1B) production that thyroid hormones induce at low concentrations, cytokine stimulate osteoclast formation and osteoclastic bone resorption. The speed of orthodontic tooth movement increased in patients undergoing such medication. Low-dosage and short-term thyroxin administrations are reported to lower the frequency of “force induced” root resorption. Decrease in resorption may be correlated to a change in bone remodeling process and a reinforcement of the protection of the cementum and dentin to “force induced” osteoclastic resorption [31]. Calcitonin has the opposite effects. It is a peptide hormone secreted

by the thyroid, which decreases the intestinal calcium and renal calcium reabsorption. In bones, calcitonin inactivates osteoclasts and hence inhibits bone resorption. It also stimulates the bone forming activity of osteoblasts.[5,7,31].

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Sex hormones

Sex hormones play a role of bone metabolism. Estrogen has a direct effect on bone. It preserves calcium in bone by suppressing the activation frequency of bone remodeling. The remodeling activation will increase when menopause starts and the result is rapid bone loss leading to symptomatic osteoporosis. Estrogen directly stimulates the bone-forming activity of osteoblasts, so it is reasonable to expect a slower rate of orthodontic tooth movement [32]. Androgens also inhibit bone resorption and modulate the growth of the muscular system. Thus, the excessive use of these drugs by athletes, in an attempt to achieve better athletic scores, may affect the duration and results of the orthodontic treatment [32,33].

Parathyroid hormone

The function of parathyroid is to maintain a normal level of diffuse calcium and phosphorus in the blood plasma and to keep constant the ratio of these minerals to each other. The act as a check on the thyroid gland parathyroids are important organs in ca metabolism and play a leading role in calcification of teeth. However, once the teeth are formed, there is no evidence found of calcium withdrawal from teeth due to parathyroid disturbances. The parathyroids are important in regulating blood ca level, but have little or no direct effect on growth or tooth eruption.[5,7]. 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 legend), 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 [33]. Parathyroid hormone affects both bone resorption and formation process. If PTH appears around bone cells, the effect of bone will be resorption. By contrast, low level of PTH results in bone formation. When the calcium level in blood decreases, PTH will stimulate osteoclastic activity to increase calcium and phosphate absorption in the gut, and decrease calcium excretion and tubular phosphate reabsorption in the kidney. This plays a role as regulator of calcium homeostasis by PTH.[33,34]

Anti Convulsants

Valporic acid has a potential to induce gingival bleeding even with minor trauma making orthodontic maneuvers difficult. Phenytoin induces gingival hyperplasia due overgrowth of gingival collagen fibers, which involves the interdental papilla, making application of orthodontic mechanics difficult and difficulty in maintaining oral hygiene. Gabapentin produce xerostomia, making oral hygiene maintenance difficult during orthodontic treatment. In these cases, clinician should be aware of possible difficulties during Treatment period, and discuss it with the patients and or parents and educate them so that adequate measures to maintain oral hygiene are followed [35].

Alcohol

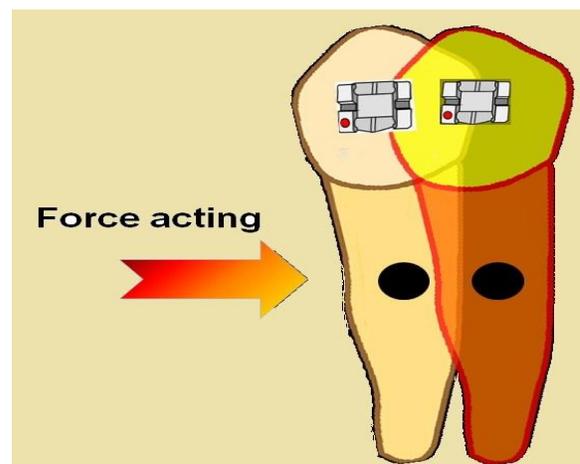
Chronic ingestion of large amounts on daily basis may have devastating effects on a number of tissue systems, including skeletal system. Alcoholism may lead to severe complications, such as liver cirrhosis, neuropathies, osteoporosis, and spontaneous bone fractures. Circulating ethanol inhibits the hydroxylation of vitamin D3 in liver, thus impending calcium homeostasis. In such cases the synthesis of PTH is increased, tipping the balance of cellular function towards the enhanced resorption of mineralized tissues, including root resorption in order to maintain normal levels of calcium in blood. It was found that chronic alcoholics receiving orthodontic treatment are high risk of developing severe root resorption during course of orthodontic treatment [36].

Prostaglandins and analogs

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 µg) 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 remodeling 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 [37].

Fig: 2 Center of resistance, shown throughout as a solid black dot. A force acting through the center of resistance results in pure translation of the tooth



INSULIN

Insulin is a polypeptide hormone secreted by the beta cells of the Langerhans islets of the pancreas. A normal non-obese man secretes approximately 50U/day, with a basal plasma insulin concentration of 10-50 microns/ml. Its main function is to maintain the blood glucose level. Insulin deficiency produces a clinical state called diabetes mellitus, while its excess leads to hypoglycemia. Diabetes mellitus is diagnosed in 3-4% of the population treated in our day-to-day orthodontic practice. The orthodontic practitioner should have a basic knowledge and understanding of this disease and of its impact on the oral cavity, as well as of its consequences upon the dental treatment [38] Informed on the oral complications induced by diabetes mellitus, the dental practitioner should consider them when treating a DM patient; the key to any orthodontic treatment is a good medical control.

Anaesthetic Gels

Anaesthetic gels are safer alternatives to analgesics in reducing the pain which results from orthodontic procedures. Keim et al in their study, stated that they may be of use when orthodontic procedures are performed, such as band placement and cementation, arch wire ligation, and band/bracket removal. The advantage of this system is its delivery method, which simply introduces the gel into the gingival crevice and makes it entirely painless [39].

Cytokines

Cytokines are small proteins that are identified as mediators of bone resorption. One cytokine, Interferon (IFN)- γ , acts as a bone resorption inhibitor that is opposite to other cytokines. Leukotrienes are a type of eicosanoid which is a product of arachidonic acid conversion and are the only eicosanoids that are formed independently from cyclooxygenase (COX). They are produced when arachidonic acid is metabolised by lipoxygenase enzymes[15,16,17]. Leukotrienes also play an important role in Inflammation, allergies, and diseases such as asthma. These conditions can be cured by using leukotriene inhibitors which block leukotriene receptors hence counteracts their effects. Examples of medication are montelukast and zafirlukast. According to Mohammed AH et al leukotrienes causes increase in orthodontic tooth movement, through bone remodeling whereas, leukotriene inhibitors work the other way round. Therefore, the use of leukotriene inhibitors can delay orthodontic treatment, leukotrienes can be used in future clinical applications that could result in increasing tooth movement.[21]

Cyclosporine

It increases gingival hyperplasia. In most patients the greatest changes in the gingival occurs in first six months of cyclosporine therapy. Severe gingival hyperplasia, make 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 user of cemented bands. Removable appliances in these cases are not recommended, due to improper fit [5,7].

Anti Histamines

Histamine (H(1)) receptor antagonists are widely used drugs for treatment of allergic conditions. Although

histamine was shown drugs may have varying effects on orthodontic tooth movement.[38]

Relaxin

Relaxin has been known for decades 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. It has also been shown to have effects on a multitude of other physiological processes, including the regulation of vasotonus, plasma osmolality, angiogenesis, collagen turnover, and renal function.[43]. Relaxin's influences on soft tissue remodeling and on several mediators that stimulate osteoclast formation have attracted attention from orthodontics researchers.[43,44].

Table: . Tooth movements

| Type of Movement | | |
|---|----------------------|-------------------------|
| X translation (Expansion/Constriction) | (-) is lingual | (+) is buccal |
| X rotation (Tipping) | | |
| Upper & Lower right quadrants | (-) is distal | (+) is mesial |
| Upper & Lower left quadrants | (-) is mesial | (+) is distal |
| Y translation (Mesialization/Distalization) | | |
| Upper left & Lower right quadrants | (-) is distal | (+) is mesial |
| Upper right & Lower left quadrants | (-) is mesial | (+) is distal |
| Y rotation (Torquing) | (-) is lingual crown | (+) is buccal crown |
| Z translation (Intrusion/Extrusion) | (-) is intrusion | (+) is extrusion |
| Z rotation (Pure Rotation) | (-) is clockwise | (+) is counterclockwise |

EP4 agonist

Bone anabolic responses to external loading are induced by stimulation of prostaglandin receptor EP4.

Discussion

This systematic review of literature summarizes the effects of medications, such as anti-inflammatory and anti-asthmatic, anti-arthritis, analgesics, corticosteroids, estrogens and other hormones, and calcium regulators in orthodontic tooth movement. As described by Krishnan V and Davidovitch Z, these groups of drug have an effect on OTM. Some of these drugs are promoter drugs where it promotes orthodontic tooth movement, but others have an inhibitory effect [40,41]. Orthodontic tooth movement is accompanied by bone remodeling (alveolar bone turnover). The remodeling of bone is a cycle that starts with activation followed by resorption, reversal and formation phases. The activation period is about 10 days. There are cells recruitment, differentiation, proliferation and migration in this period followed by resorption. The resorption period takes 21 days that

occurs by osteoclast activity [40]. The next stage is reversal stage when inactive osteoblasts become activated and begin to form bone. Bone formation is determined by rate and duration of osteoblast activity. The new bone formation is completed over a period of 6 months with mineralization. The remodeling cycle from activation through to the start of the formation phase requires about 4 months in humans. The amount of bone remodeling is related to the amount of tooth movement at that site [41,42]. During orthodontic tooth movement, bone remodeling process is related to the expression of mediators. Acute inflammatory response is presented in the early phase of orthodontic tooth movement. Inflammatory mediators may stimulate the biological processes that associated with alveolar bone resorption and deposition. Furthermore, orthodontic forces can induce the bone remodeling process by the local mediators, such as prostaglandins, cytokines and growth factors that play an important role in bone remodeling. PGE2 has been involved in bone remodeling and especially recognized as a potent stimulator of bone resorption [37]. There are several studies showing the usage of pharmacologic agents to induce bone resorption and deposition for control of tooth movement. For example, the study of Yamasaki shows the usage of local injection of prostaglandin to stimulate tooth movement. Other pharmacologic agents such as calcitonin, and 1,25(OH)2D3 can also induce tooth movement. The daily injection of osteocalcin into the palatal subperiosteum in rat showed it can stimulate tooth movement significantly in the early period but not significantly after day 5th. One injection of 1,25(OH)2D3 per 7 days into the PDL of cats increased tooth movement 60% as well as in the human that received PGE1 submucosal injection. Although the pharmacologic agents can induce the tooth movement in both human and animal study but they have side effects during the injection procedure such as local pain and discomfort, so these techniques are not practical to use for the patient [5]. They act by stimulating bone resorption. Eicosanoid inhibitors on the other hand acts in preventing OTM. Example of eicosanoid inhibitors is NSAIDs where it inhibits the synthesis of prostanoids which is an important mediator of bone resorption. So, it is important that the patient does not take NSAIDs such as aspirin or other related compounds for long periods of time during orthodontic treatment [31]. The alternative that can be suggested to patients is paracetamols. Paracetamol also known as acetaminophen is a type of analgesic, which does not have any deleterious effect on orthodontic tooth movement. Orthodontists should be aware of the

patients who under short- and long- term therapy with COX-2 inhibitors because these drugs can decrease the rate of orthodontic tooth movement. Acetaminophen acts at the central nervous system and does not stimulate PGs synthesis, so it does not interfere with the orthodontic tooth movement. The numbers of osteoclasts in the pressure areas are not decreased, and the bone regeneration does not change by acetaminophen. So, it is a drug of choice that orthodontists should recommend to their patients for relieving the discomfort during orthodontic treatment [5,7,19, 20,37].

Conclusion

As more and more chemical analogues are being used in the form of new drugs to avoid resistance, today's clinicians should mandatorily update his knowledge on the clinical efficacy of the new drugs as well as the beneficial and harmful effects on human tissues . It is always advisable for a dentist to confirm with the family physician or the concerned physician for fitness of the patients who undergo orthodontics involving tooth movement. Orthodontists should assume that many patients are taking prescription or over-the counter medications regularly. The orthodontist must identify these patients by carefully questioning them about their medication history and their consumption of food supplements and it should consider a part of every orthodontic diagnosis.

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