

THE EFFECTS OF COMMONLY USED DRUGS ON ORTHODONTIC TOOTH MOVEMENT : A SYSTEMATIC REVIEW

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ABSTRACT

Objective: The objective of this review of literature is to evaluate the effect of different types of drugs being used in orthodontic. This review will brief out the different views by various authors regarding the group of drug that effect orthodontic tooth movement.

Method: The electronic database of PubMed, Wiley online library, and Science Direct were used. The search strategies are presented in Appendix 1. The period of electronic search was from January 1970 to November 2012. A single author conducted the electronic search independently based on the inclusion criteria.

Results: The search revealed a total of 189 articles and abstracts found through Pub med, Wiley online library and science direct. After reading the title and abstract 75 was excluded from the review of literature. Application of inclusion criteria resulted in 48 articles used for data extraction and subsequent review

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 treatment involving tooth movement.

Keywords: Drugs, Orthodontic tooth movement, Systematic review

INTRODUCTION

Tooth movement is the key principle behind any orthodontic treatment. Orthodontic tooth movement (OTM) is mainly a biological response towards mechanical force. It is induced by the prolonged application of controlled mechanical force on the tooth, which eventually causes remodeling of the tooth socket by creating pressure and tension zones in the alveolar bone and periodontal ligament[1-2]. Strains of periodontal cells, bone-related cells, and extracellular matrix play a key role in orthodontic tooth movement (OTM)[3]. This strain forms changes in gene expression in the cells by interactions between the cells and the extracellular matrix, whereby integrins play an important role[4]. Various cell-signaling pathways are activated, ultimately leading to stimulation of periodontal ligament metabolism, and localized bone resorption and bone deposition[3-5]. These interactions are regulated by local factors such as cytokines (IL-1), and growth factors, as well as by systemic factors such as parathyroid hormone, vitamin D, estrogen, or calcitonin[6-7].

Drugs that alter or interfere with the inflammatory process will therefore have an effect on the tooth movement. Several studies have proposed the effect of short and long term administration of medication on orthodontic tooth movement. Davidovitch et al.[10] and Yamasaki et al.[11] concluded in their study that the rate of orthodontic tooth movement can be altered by administrating certain drugs locally or systemically. The drugs used in orthodontics can be broadly classified into two major groups, promoter drugs and suppressor agents. Promoter drugs are agents that act with the secondary and primary inflammatory mediators and enhance the tooth movement, examples being; Prostaglandin, Leukotrienes, Cytokines, Vitamin D, Osteocalcin, and Corticosteroids. Suppressor agents are drugs which reduces bone resorption examples are; Nonsteroidal anti-inflammatory agents and bisphosphonates.

As a clinician, this information is very important because orthodontic treatment does involve postoperative pain and the form of pain management is very important because not all drugs favours tooth movement. Many patients use over the counter medications for immediate pain relief, which may interfere with the treatment plan. Therefore, practitioners should have a proper knowledge of the drugs being prescribed and the patient should be well informed.

Material and Methods

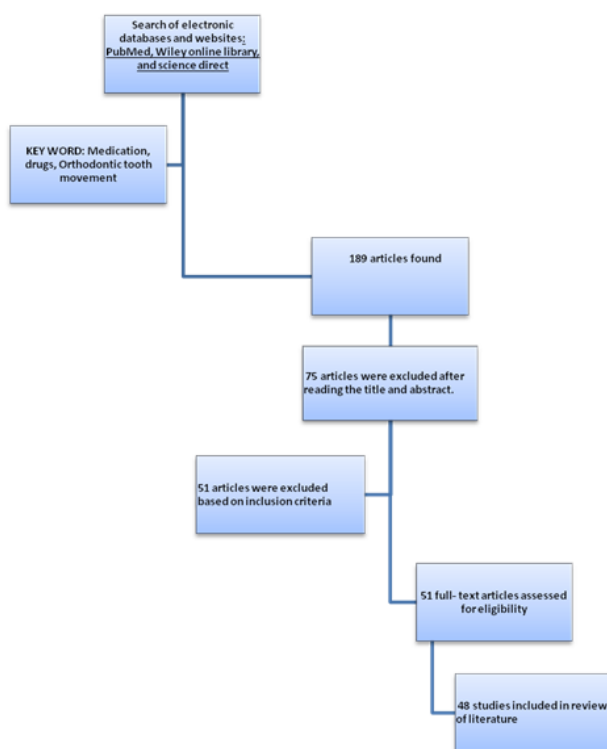
Search Methods:

The electronic database of **PubMed**, **Wiley online library**, and **Science Direct** were used. The search strategies are presented in Table 1. The period of electronic search was from January 1970 to November 2012. A single author conducted the electronic search independently based on the inclusion criteria.

Search inclusion criteria

- Clinical investigation that included at least 1 experimental group and a control.
- Systemic or local administration of well-defined medications or dietary supplements that are supposed to interfere with the physiologic process of bone or that might have side effects related to bone physiology.
- Adequate description of dosages and administration regimens.
- Adequate description of the force magnitude of the study.
- Adequate description of the technique used for measuring the rate of tooth movement.
- Adequate statistical analysis.

Appendix 1



Results

The search revealed a total of 189 articles and abstracts found through Pub med, Wiley online library and science direct. After reading the title and abstract 75 was excluded from the review of literature. Application of inclusion criteria resulted in 48 articles used for data extraction and subsequent review.

Promoter drugs:

Prostaglandins

Prostaglandins (PGE) are a group of chemical messengers belonging to the family of hormones called eicosanoids. It acts by regulating the synthesis of cyclic AMP in many tissues. Cyclic AMP is responsible in controlling the action of various hormones. This allows prostaglandin to affect a wide range of cellular and tissue functions. Prostaglandins are responsible in stimulating contraction of the smooth muscles of the uterus, affects blood flow, sleep cycle and also response to hormones such as adrenaline and glucagon. It also plays a role in elevating body temperature, which leads to inflammation and pain. According to Klein and Raisz[10], Raisz *et al* [11], Dowsett *et al*[12], prostaglandins play an important role in promoting bone resorption. It is believed that, prostaglandins promote resorption by stimulating cells to produce cyclic AMP, which is a very important chemical messenger for bone resorption. In 1973, Goldhaber *et al*[13]. reported that there is an increase in level of prostaglandins in periodontal diseases.

In Orthodontics, Yamasaki and his teams[14] were the first to introduce the use of prostaglandins in controlling the rate of tooth movement. First attempt was in 1982, where the rate of orthodontic

tooth movement and the possible side effects on gingival tissues in monkeys was studied by Yamasaki *et al* [15]. Results have showed that the local administration of PGE1 or PGE2 in the gingiva near the distal area of canines to be retracted, caused double the rate of tooth movement compared to the opposite, control side. Also, no side effects were seen in the gingiva. Studies on humans were conducted in 1984, where Yamasaki *et al*[9] studied the effects of PGE1 administration on orthodontic tooth movement. The author reported that, the rate of tooth movement was doubled compared to control sides. Lee[16] in a later study, compared lidocaine and PGE 1 and reported that PGE 1 was more effective in bone resorption but

it had certain side effects such as local irritation and phlebitis. Investigation in humans by Spielmann T. *et al*[17] in 1989 with a split-mouth design showed significant increases in the rate of palatal premolar movement after multiple local injections of PGE1 at a dosage of 10 g. In India, Bhalajhi and Shetty[18] conducted a study on the effect of exogenous administration of PGE2 in young rabbits. The study concluded that, there was a significant increase in the rate of tooth movement clinically, and microscopically there were increase in the number of osteoclasts and resorption of lacunae. But there was a frequent need of administration of the drug as PGE2 gets metabolised rapidly in the lungs.

Leukotrienes

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[19]. 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*. 1989, leukotrienes causes increase in orthodontic tooth movement, through bone remodeling whereas, leukotriene inhibitors work the other way round[20]. 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.

Vitamin D₃

Vitamin D₃ is an important regulator of calcium homeostasis. 1,25 dihydroxycholecalciferol (1,25[OH]2D3) is the active metabolite of vitamin D₃. Together with parathyroid hormones and calcitonin help in regulating the calcium and phosphate serum levels in the body. It also promotes the calcium and phosphate absorption in the intestine and reabsorption in the kidneys. Recent studies have proven that Vitamin D₃ is very effective in treating osteoporosis and this explains how Vitamin D₃ is considered as an active suppressor drug. It has been proven that it increases the bone mass, thus reduces fractures in osteoporotic patients[21-22]. But some authors consider vitamin D₃ to be a resorption promoting agent because it has stimulatory effects on osteoclasts²³. Collins *et al* in 1988[23], demonstrated that local application of vitamin D₃ improves the rate of tooth movement in rats. This effect was due to the well-balanced bone turnover induced by vitamin D₃. So more studies have to be conducted in determining the exact role of Vitamin D₃ in orthodontic tooth movement.

Corticosteroids

Adrenal cortex is a part of the adrenal gland, which is responsible for production of androgen (sex hormone) and corticoid hormones. According to their biological effects, corticoid can be classified as glucocorticoid (cortisol) and mineralocorticoid (aldosterone)²⁴. Glucocorticoids are prescribed for various inflammatory and autoimmune conditions, including rheumatoid arthritis, dermatitis, allergies, and asthma. They are also used as immunosuppressive medications after organ transplantation. 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[25]. They play a vital role in inhibiting the intestinal calcium absorption, which leads to direct inhibition of osteoblastic function, and increase in bone resorption.

In 2004, Kalia and colleagues[26] evaluated the rate of tooth movement in rats during short and long term corticosteroid therapy. They concluded that bone remodeling seemed to slow down in acute administrations, whereas the rate of tooth movement increased in chronic treatment. This suggests that orthodontic treatment should

be postponed in patient undergoing short term corticosteroids whereas, patient with long term corticosteroid therapy treatment can be continued with minimal adverse effect and more extensive retention may be helpful in retaining these teeth if the dentist decides to proceed with the orthodontic treatment.

Thyroid hormones

Thyroxine and calcitonin are hormones produced by thyroid gland. Thyroxine (T₄) is a prohormone that can be converted to its active form tri-iodothyronine (T₃). This active form of thyroxine is very important in metabolism of cells and plays a vital role in physical development and growth. Administration of thyroxine will lead to increase in bone remodeling, increase in bone resorption activity and reduces bone density[27-29]. Thyroxin produces interleukin 1 (IL-1β), a type of cytokine which involves in bone formation through osteoclastic reaction[30]. Studies on rat have been conducted to determine the relationship between exogenous thyroxine and tooth movement. Results show that there was a significant increase in orthodontic movement compared to the control[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[32-33].

Suppressor Agents:

Estrogens

Estrogen are female sex hormones that present in 3 forms; estradiole, estrone and estriole. Estradiole is the most prominent form. It is produced from menarche to menopause and is important in the regulation of the estrous cycle. The next most important estrogen is estrone, it is produced after menopause when the total amount of estrogens has decreased. The third form estriole is seen mostly during pregnancy. Estrogens do not appear to have any anabolic effects on bone tissue[34] but there are studies indicating that estrogen directly stimulate the bone-forming activity of osteoblasts[35-40]. They act by inhibiting interleukin-1(IL-1), tumour necrosis factor-α (TNF-α), and interleukin 6 (IL-6) which appears to be involved in bone resorption by stimulating osteoclastic activity[41-44]. In 1996, Miyajima and colleagues concluded that female patients have slow alveolar bone turn over due their menopausal status and the duration of estrogen supplements intake[45]. Oral contraceptive pills contains estrogen, when taken by younger woman for a long span, it can influence the rate of tooth movement[45]. Therefore, it is extremely important for the dentist to consider this factor during history taking and treatment planning in females.

Bisphosphonates

Bisphosphonates are synthetic class of pyrophosphate analogues and they are powerful inhibitors of bone resorption. Bisphosphonates are widely used in treating osteoporosis, Paget's disease, bone metastases, and bone pain from some types of cancer[46-48]. They act by inhibiting the osteoclastic activity[49] and decreasing the number of osteoclasts[50]. This leads to inhibition of orthodontic tooth movement and hence delays orthodontic treatment. Few studies have been reported on the effect of bisphosphonates in orthodontic tooth movement. All showed a dose-dependent decrease in the rate of OTM, with either topical or systemic administration of bisphosphonates[51-53]. Topical application of bisphosphonates is also said to be very useful in anchoring and retaining teeth under orthodontic treatment. Long term, use of bisphosphonate are very dangerous. They can cause osteonecrosis, especially in the alveolar bones of maxilla and the mandible[54].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Nonsteroidal Anti-Inflammatory Drugs or generally called as NSAIDs is a very common drug in pain control. They have analgesic, antipyretic, and anti-inflammatory effects, and are prescribed for many conditions, such as rheumatoid arthritis, osteoarthritis, gout, dysmenorrhea, headache, migraine, and postoperative pain, as well

as for the prevention of cardiovascular diseases and colorectal cancer. In cases of pain and headache, NSAIDs are taken incidentally because it is freely available over the counter. Patients should be advised not to take these drugs during orthodontic treatment, without the dentist's knowledge. NSAID acts by inhibiting the production of all prostanoids (thromboxanes, prostacyclins, and prostaglandins) through blocking an enzyme called cyclooxygenase (COX) during transformation of arachidonic acid. Prostanoids play a significant role in bone resorption during orthodontic therapy. NSAIDs can be broadly classified into Salicylates, Arylalkanoic acids, Arylpropionic acids (profens), and Oxicams Coxibs. All NSAIDs have more or less similar effects and mechanisms of action. Several studies were conducted in determining the effect of NSAIDs in orthodontic tooth movement. All the studies revealed that there was some amount of retardation in the rate of orthodontic tooth movement[55-57].

Paracetamol

Paracetamol also known as acetaminophen is an analgesic which is a weak COX-1 and COX-2 inhibitor. The difference between NSAIDs and paracetamol is, NSAIDs acts by blocking COX-1 and COX-2, whereas paracetamol acts on a third isoform, COX-3, which is expressed only in the brain and the spinal cord. As a result, paracetamol has minimal effects on prostaglandin synthesis. Comparative studies have been demonstrated to determine the effectiveness of acetaminophen in controlling pain and discomfort associated with orthodontic treatment. Studies have proven that acetaminophen are effective[58]. In 1997, Roche JJ et al.[59] reported that acetaminophen showed no effect on tooth movement when tested on rats. Generally, studies suggests that paracetamol does not affect orthodontic tooth movement, so it's safe to use as a choice of pain management in orthodontic treatment.

Discussion And Conclusion

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[60], these groups of drug has an effect on OTM. Some of these drugs are promoter drugs where it promotes orthodontic tooth movement, but others have an inhibitory effect.

Eicosanoids such as prostaglandins and leukotrienes are group of drugs, which increases the rate of OTM. They act by stimulating bone resorption. Eicosanoid inhibitors on the other hand acts in preventing OTM. Example of eicosanoid inhibitors are 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[55]. 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 OTM.

Role of vitamin D₃ and Corticosteroids in OTM still remains unclear. Some author have reported that it promotes tooth movement but there are also studies that demonstrate bone formation after application of these drugs. So, it is important to have more clinical trials on determining the exact role of Vitamin D₃ and Corticosteroids in orthodontic tooth movement. Bisphosphonates are drugs which also effect the calcium homeostasis. It is known for its role in inhibiting tooth movement. They are used in cases of prevention of orthodontic relapse but it should be used with great caution because of its severe side effects on long term use.

Hormones also play an important role in tooth movement. Hormones such as thyroxine is known to increase the rate of tooth movement by directly stimulating the action of osteoclast. Calcitonin and estrogen have the opposite effect on tooth movement. It is very important to know if the patient is under any oral contraceptive pills. It contains estrogens, which inhibits tooth movement.

So proper history elucidation is very important in avoiding such complications.

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.

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