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Review article

A Systematic Review on the Effects of various Drugs which hamper or enhance Orthodontic Tooth Movement

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ABSTRACT

The objective of this review of literature is to evaluate the effect of different types of drugs being used in orthodontic treatment which would hamper the orthodontic tooth movement. This review will brief out the different views given by various authors regarding various group of drug that effect orthodontic tooth movement. As more and more chemical analogues are being used in the form of new drugs to avoid resistance, today's clinicians should mandatorily update their knowledge on the clinical efficacy of the new drugs as well as the beneficial and harmful effects on human tissues. The administration of these drugs however play an important role on the orthodontic tooth movement and thus 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 with a detailed medical history.

KEYWORDS: Drugs, Orthodontic tooth movement, Systematic review

INTRODUCTION

The pain during tooth movement caused by orthodontic intervention has always been a matter of concern for the specialist as well as patient [1][2][3]. The usual wire changing appointments scheduled at every four weeks span are associated with the pain by the patients especially during initial wire placement or any appliance placement. Pain during fixed orthodontic treatment increases gradually from the fourth hour to is not aware of the problem; it still exists for the patient after the delivery of the appliance or the change of the archwire [4][5].

The tooth in the alveolar bone is gomphosis type of joint where its root is surrounded by fibrous tissue called periodontal ligament. It's this type of joint that makes the tooth movement possible unlike lower animals where they are ankylosed. The exact mechanism by which the tooth moves has not yet been determined. But as the tooth moves inflammation occurs in periodontal ligament & bone: & inflammation is always associated with the pain which is undesired. It was reported that 95% of orthodontic patients experienced varying degrees of discomfort during treatment[5].

Although the histology of this remodeling process has been studied extensively, the biochemical mediators that initiate or facilitate it are still not fully understood[6]. Inflammation

is 'double edge sword' for our specialty. Inflammation is always associated with mediators like cyclic nucleotides & prostaglandins (PGs) which are suggested to be the mediators of bone resorption & tooth movement. Prostaglandins like PGE1. PGE2, PGI2 (arachidonic metabolites) etc are desired mediators as they accelerate teeth movement by stimulating production of osteoclasts & osteoblasts which carry out tooth movement [7].

On the contrary PGs cause classic sign of inflammation the pain: which is not desired. So in attempt to alleviate the pain, the over the counter painkillers i.e. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are usually prescribed by the doctors.NSAID are usually PG inhibitors by affecting cyclo-oxygenase enzymes. But this decelerates tooth movement by further inhibiting of PGs which is undesired[8].

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is the preferred method to control pain related to fixed orthodontic appliances. However, to date, no standard medication protocol has been developed on this subject. For

the control of orthodontic pain, anti- inflammatory drugs like aspirin & ibuprofen have been evaluated in the literature. In the first studies on analgesics Ngan et al[9]found that the placebo group felt more pain then patients who received aspirin after separator or archwire insertion. Recently, most of the studies in both medical & dental literature on pain control have been reported on preoperative analgesics.

This approach provides blockage of afferent nerve impulses before they reach the central nervous system. As a result, the treatment is preventive, not symptomatic. If NSAIDs are given before the procedure, the body absorbs the NSAIDs before tissue damage occurs with subsequent prostaglandin production. Law et al[10], Bernhardt et al[11]&Polat et al [12] evaluated the efficacy of preoperative analgesic consumption & found that ibuprofen taken one hour before separator placement lowers the pain levels from two hours after bonding until night time.

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.

Pain in orthodontics:

Burstone C. J. [13], in the year 1964 studied pain in orthodontics. Burstone has classified the pain response into three different degrees:

1. First degree pain— produced by heavy pressure placed on the tooth with an instrument. This is usually elicited most easily by applying the force in the same direction as the fixed appliance. The patient is not aware of first degree pain unless the orthodontist manipulates the teeth being actively moved with the appliance.

2 Second degree pain— characterized by pain or discomfort during tooth clenching or heavy "biting." The patient maintains the ability to masticate a normal diet without difficulty.

3. Third degree pain— present when the patient is suffering from spontaneous pain or is unable to masticate food of a normal consistency

Burstone[13] noted both an immediate & a delayed pain response in one study. He speculated that the former was related to the initial compression of periodontal ligament immediately after placement of wire. The latter response which started a few hours later,was labeledhyperalgesia of the periodontal ligament, an increased sensitivity of nerve fibers to noxious stimuli such as prostaglandins, histamines & substance P. Substance P increases the firing rate of neurons that relay nociceptive information.

If the source of pain is the development of ischemic areas, strategies to temporarily relieve pressure & allow blood to flow through compressed areas thereby preventing build up of metabolic products that stimulate pain receptors. In fact if light forces are used the amount of pain experienced by the patients can be decreased by having them engage in repetitive chewing (of sugarless gum.. a plastic wafer placed between the teeth or whatever) during the first 8 hours after the orthodontic appliance is activated.

Many drugs used to control pain have the potential to affect tooth movement because of their effects on the prostaglandins. It has been suggested that acetaminophen should be a better analgesic for orthodontic patients than aspirin, ibuprofen, naproxen & similar prostaglandin inhibitor because it acts centrally rather than as a prostaglandin inhibitor. With moderate dose of these drugs given initially from 3-4 days do not affect initial tooth movement. Chronic use of the prostaglandin inhibitors like in the patients with arthritis can inhibit tooth movement.

Drugs promoting the orthodontic tooth movement:

Prostaglandins

In Orthodontics, Yamasaki[7] and his teams 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 studies by Yamasaki et al [14].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[7] 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.

In india, Bhalajhi and Shetty[15] 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 [16].Leukotrienesalso 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[17] 1989, leukotrienes causes increase in orthodontic tooth movement, through bone remodeling whereas, leukotrine 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.

Vitamin D3

Vitamin D3 is an important regulator of calcium homeostasis. 1,25dihydroxycholecalciferolis the active metabolite of vitamin D3. Together with parathyroid harmones 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[18][19].

But some authors consider vitamin D3 to be a resorption promoting agent because it has stimulatory effects on osteoclasts. Collins et al [20] in 1988, 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 morestudies 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)[21]. 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, 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[22]. They play a vital role in inhibiting the intestinal calcium absorption, which leads to direct inhibition of osteoblastic function, and increase in bone resorption.

Thyroid hormones

Thyroxin 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[23][24][25]. Thyroxin produces interleukin 1 (IL-IB),a type of cytokine which involves in bone formation through osteoclastic reaction[26]. 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 [27].

Drugs hampering the orthodontic tooth movement:

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[28]but there are studies indicating that estrogen directly stimulate the bone-forming activity of osteoblasts[29][30].

They act by inhibiting interleukin-1(IL-1), tumour necrosis factor-a (TNF-a), and interleukin 6 (IL-6} which appears to be involved in bone resorption by stimulating osteoclastic activity[31]. In 1996, Miyajima et al [32] concluded that female patients have slow alveolar bone turn over due their menopausal status and the duration of estrogen supplements intake. Oral contraceptive pills contains estrogen, when taken by younger woman for a long span, it can influence the rate of tooth movement [32]. 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 [33]. They act by inhibiting the osteoclasticactivity [34] and decreasing the number of osteoclasts. 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 [35][36][37]. Topical application of bisphosphonates is also said to be very useful in anchoring and retaining teeth under orthodontic treatment. Long term uses of bisphosphonate are very dangerous. They can cause osteonecrosis, especially in the alveolar bones of maxilla and the mandible[38].

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 prostaglandins through blocking an enzyme called cyclooxygenase (COX) during transformation of arachidonic acid. Prostaglandin plays a significant role in bone resorption during orthodontic therapy. 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 [39][40].

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 acetaminophens are effective [41]. In 1997, Roche JJ et al [42]reported that acetaminophen showed no effect on tooth movement when tested on rats. Generally, studies suggest that paracetamol does not affect orthodontic tooth movement, so it's safe to use as a choice of pain management in orthodontic treatment.

Several other classes of drugs can affect prostaglandinlevels, and therefore could affect the response to orthodontic force. Tricyclic antidepressants (doxepin, amitriptyline, imipramine), antiarrhythmic agents (procaine), antimalarialdrugs (quinine, quinidine, chloroquine), and & methyl xanthine fall into this category. In addition, the anticonvulsant drug phenytoin has been reported to decrease tooth movement in rats, and some tetracyclines (e.g., doxycycline) inhibit osteoclast recruitment, an effect similar to bisphosphonates. It is possible that unusual responses to orthodontic force could be encountered in patients taking any of these medications.

CONCLUSION

In addition to applied force, bone remodeling changes induced by systemic factors such as nutritional factors, metabolic bone disease, age or the use of drugs, play an important role in regulating the rate of tooth movement.Certain pharmacological agents that affect bone tissue metabolism can influence the velocity of tooth movement.Estrogens, androgens, calcitonin, bisphosphonates, vitamin D, fluoride, and salicylates may decrease the velocity of tooth movement.In contradiction, thyroid hormones, corticosteroid, prostaglandins, and leukotrines can enhance orthodontic tooth movement.

The dentist should always discuss the patients current drug therapy in order to accurately evaluate the treatment time and to select the best therapeutic strategy in every individual case.Moreover, studies related to intake of thyroid hormones, bisphosphonates, prostaglandins, and leukotrienes are required in order to have future and beneficial clinical applications of these drugs for orthodontic tooth movement.

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