Republic of Iraq
Ministry of Higher Education and Scientific Research
University of Baghdad
College of Dentistry

Medications to accelerate or retard orthodontic tooth movement

A Project Submitted to the College of Dentistry, University of Baghdad, Department of Orthodontics in Partial Fulfillment for the Bachelor of Dental Surgery

By

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May, 2023

Certification of the Supervisor

I certify that this project entitled " **Medication to accelerate or retard orthodontic tooth movement**" was prepared by the fifth-year student **Rand Ihsan Elwan** under my supervision at the College of Dentistry/University of Baghdad in partial fulfilment of the graduation requirements for the Bachelor Degree in Dentistry.

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Date

Dedication

This review is dedicated to my supporting family and friends. I would not have been able to complete dental school without them.

Acknowledgement

This review was not possible without the support and guidance of my wonderful supervisor**.**

Table of Contents

List of Figures

List of Tables

List of Abbreviations

Abbreviation	Meaning
ATP	adenosine tri-phosphate
BMP	bone morphogenic protein
CNS	central nervous system
cAMP	cyclic Adenonise monophosphate
COX	cyclo-oxygenase
FAS	fetal alcoholic syndrome
HGF	hepatocyte growth factor
IL-6	interleukin 6
LIPUS	low-intensity pulse utlrasound
LLLT	low-level laser therapy
MOPs	Micro-Osteoperforations
NSAIDs	non-steroidal anti-inflammatory drugs
OTM	orthodontic tooth movement
PTH	Parathyroid hormone
PDL	periodontal ligament
PAOO	periodontally-accelerated osteogenic orthodontic
PG	prostaglandin
PGE2	prostaglandin E2
RANK	receptor activator of nuclear factor kappa
RANKL	receptor activator of nuclear factor kappa ligand
RAP	Regional Acceleratory Phenomenon
Runx2	runt-related trasnscription factor
TNF	Tumor necrosis factor

Introduction

Orthodontics has been developing greatly in achieving the desired results both clinically and technically. This is especially so by using new technologies, like stimulation software that can assist in treatment planning and translational products. In addition, continuous modification of wires and brackets as a result of the biomechanical efficiencies in orthodontics has greatly improved. However, these biomechanical systems may have reached their limit and there is a need to develop new methods to accelerate teeth movement. Today, it is still very challenging to reduce the duration of orthodontic treatments. It is one of the common deterrents that faces orthodontist and causes irritation among adults plus increasing risks of caries, gingival recession, and root resorption. A number of attempts have been made to create different approaches both preclinically and clinically in order to achieve quicker results, but still there are a lot of uncertainties and unanswered questions towards most of these techniques. Most attempts can broadly be categorized into biological, physical, biomechanical, and surgical approaches. Before going into details of these attempts, we need to understand the basics of orthodontic tooth movements and the factors that initiate inhibition and delayed tooth movement. Orthodontic tooth movement occurs in the presence of a mechanical stimuli sequenced by remodeling of the alveolar bone and periodontal ligament (PDL). Bone remodeling is a process of both bone resorption on the pressure site and bone formation on the tension site. **(Davidovitch, 1991)**

Orthodontic tooth movement can be controlled by the size of the applied force and the biological responses from the PDL. The force applied on the teeth will cause changes in the microenvironment around the PDL due to alterations of blood flow, leading to the secretion of different inflammatory mediators such as cytokines, growth factors, neurotransmitters, colony-stimulating factors, and

arachidonic acid metabolites. As a result of these secretions, remodeling of the bone occurs. **(Davidovitch et al, 1988)**

Orthodontic tooth movement consists of three phases: (1) initial phase, (2) lag phase, and (3) post-lag phase. The initial phase consists of an immediate and rapid movement and occurs within 24 to 48 hours after the initial application of force to the tooth. The rate of movement is largely attributed to the displacement of the tooth in the PDL space, causing its compression and undermining bone resorption on the j pressure side. Bone resorption occurs through osteoclastic activity by creating bone lacunae that will later be filled in by osteoblast cells. The lag phase lasts 20 to 30 days and displays relatively little to no tooth movement. This phase is marked by PDL hyalinization in the region of compression where the blood supply is cut off. No subsequent tooth movement occurs until the cells complete the removal of all of the necrotic tissues. Once the PDL regenerates tooth movement continues. The post-lag phase follows the lag phase, during which the rate of movement increases. **(Fisher et al, 2010)**

Aims of the Project

To review and highlight the contribution of medications in the acceleration or retardation of orthodontic tooth movement.

By critically analyzing the available literature, the review aims to provide a comprehensive overview of the current state of knowledge regarding certain medications use in orthodontics, and to identify potential areas for future research and development.

Chapter One: Review of Literature

Chapter One: Review of Literature

Acceleration of the orthodontic tooth movement

Various Methods to accelerate tooth movements:

1. Surgical methods
2. Non-surgical methods
3. Medication

1.1 Surgical methods

1.1.1. **Corticomy**:

The procedure of corticotomy is to cut the bone surrounding teeth via flap elevation. It can increase bone remodeling and creates transitory state of osteopenia that reduces bone density, which causes less resistance to tooth movement. It can be used in En masse retraction, canine retraction, decrowding, molar uprighting, correction of a scissor bite, and rapid maxillary expansion (Figure 1.1). **(Lee, 2018)**

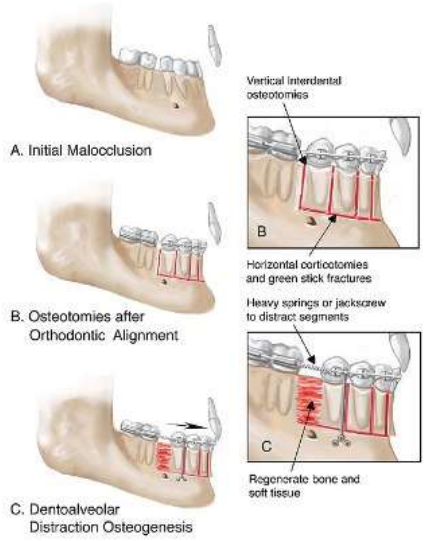

Figure 1.1 Corticotomy **Sacco (2018)**

People who take corticosteroids bisphosphonates and nonsteroidal anti-

inflammatory drugs or receive radiation therapy or have active periodontal disease, are the contraindications for corticotomy.

Clinical studies have shown that using corticotomy to help canine retraction can reduce the treatment time by 28 ~ 33%, and can increase the rate of tooth movement by 2 ~ 3 times. **(Unnam et al, 2018)**

1.1.1.1. **Advantage**

a. It has been proven successfully by many authors, to accelerate tooth movement.
b. Bone can be augmented, thereby preventing periodontal defects, which might arise, as a result of thin alveolar bone. **(Aboul-Ela et al, 2011)**

1.1.1.2. **Disadvantage**:

1. High morbidity associated with the procedure
2. Invasive procedure.
3. Chances of damage to adjacent vital structures.
4. Post-operative pain, swelling, chances of infection, avascular necrosis.
5. Low acceptance by the patient. **(Aboul-Ela et al, 2011)**

1.1.2. Periodontally accelerated osteogenic orthodontics (PAOO):

In **2001, Wilcko** developed a modified surgical method called PAOO.8,12 PAOO can be used in treating moderate to severe crowding, cases requiring expansion, reduced periodontal tissues, molar intrusion and open bite correction as well as to improve post-orthodontic stability. It can prevent the need of extraction and decrease the risk of dehiscence and fenestration.

The Wilcko brothers introduced the Periodontally Accelerated Osteogenic Orthodontics (PAOO) technique, in which orthodontic forces were applied 1 week before the procedure, and also added bone grafts after decortication. Both on the buccal and lingual sides of the selected area, intrasulcular incisions were made, a full-thickness flap was reflected and the corticotomies were performed. The

vertical incisions were located between the teeth and connected apically, and additional corticotomies were performed. Demineralized freeze-dried bone allograft (DFDBA) and bovine graft were placed and the flap was sutured. **(Wilcko et al, 2001).** Figure 1.2– shows surgical technique for undermining interseptal bone distal to canine. b. Mechanics and surgical technique involved in canine retraction.

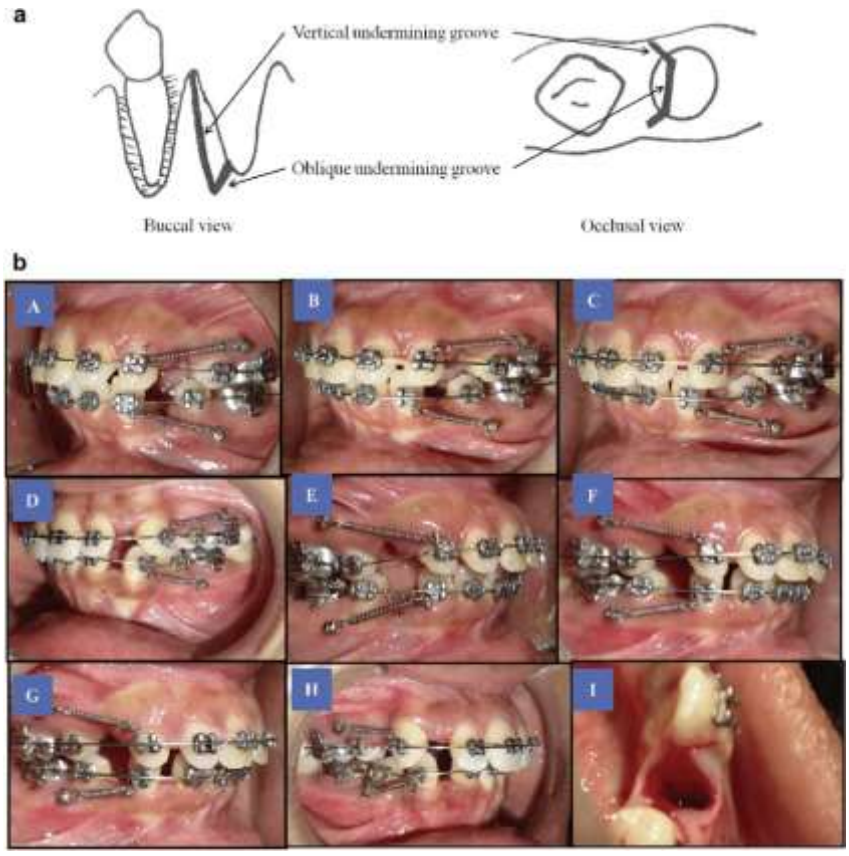

Figure 1.2 (A-D) Mechanics involved in canine retraction without periodontal distraction for Group I at time T0-T3; (E-H) Mechanics involved in canine retraction with periodontal distraction for Group II at time T0-T3; (I) Surgical technique for undermining interseptal bone distal to canine. (Khanna et al, 2014)

The surgical cuts created vertical grooves from 2 to 3 mm below the alveolar crest to 2 mm beyond the apices of the roots. And perform circular corticotomy to connect vertical cuts. Selective medullary penetration was performed to enhance

bleeding. Bone grafts was placed in most areas that have undergone corticotomies. The volume of the graft material could be decided by the alveolar bone thickness and the direction of tooth movement.

An immediate orthodontic force can be applied to the teeth. Initiation of the orthodontic force should not be delayed for more than 2 weeks after surgery. The duration of tooth acceleration is usually last for 4 to 6 months. **(Amit et al, 2012)**

1.1.2.1. **Advantage**: PAOO can decrease treatment time and increases alveolar bone width and volume. **(Amit et al, 2012)**

1.1.2.2. **Disadvantage**:

1. corticotomy might engender marginal interdental bone loss
2. induces loss of the attached gingiva
3. infection
4. unfavorable changes in the appearance of the gingiva
5. postoperative pain and swelling. **(Aboul-Ela et al, 2011)**

1.1.3. Interseptal alveolar surgery:

Interseptal alveolar surgery or distraction osteogenesis is divided into distraction of PDL or distraction of the dentoalveolar bone; example of both is the rapid canine distraction. The concept of distraction osteogenesis came from the early studies of limb lengthening. Also, from surgical treatments of craniofacial skeletal dysplasia, this concept was later adapted in relation to the rapid tooth movement. **(Ilizarov, 1988)**

In **2007, Ren** et al. conducted an animal experiment using the interseptal alveolar surgery and found that the speed of tooth movement was twice in the experiment side. **(Ren et al, 2007)**

Another human study found that the speed of tooth movement was about 1.6 times faster than the control side.

The surgical procedure was made at the time of tooth extraction, and performed vertical grooving and oblique grooving inside the tooth extraction socket. It reduced the interseptal bone by 1 to 1.5 mm. If the inter-radicular bone was present, it should be removed together.

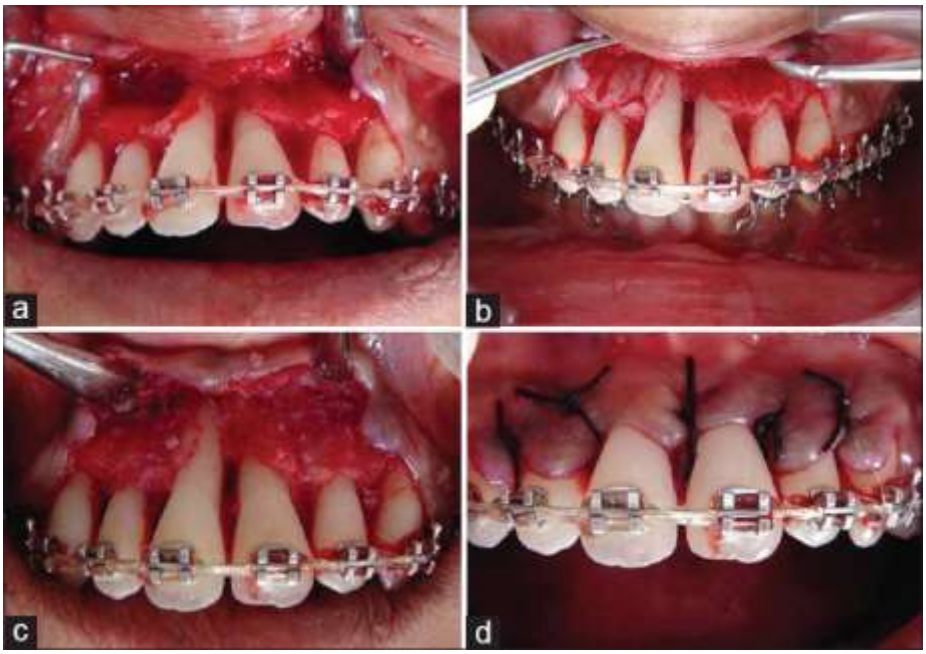

Figure 1.3 (a) Mucoperiosteal flap reflection, (b) Y-cut and vertical osteotomy, (c) demineralized freeze-dried bone graft material with nanohydroxyappetite bone particle, (d) interrupted sutures placed (Hosur et al, 2019)

This surgery can shorten the treatment time in extraction cases without flap reflection or another separate surgical procedure. **(Leethanakul et al, 2014)**

1.1.3.1. **Advantage**:

This surgery can shorten the treatment time in extraction cases without flap reflection or another separate surgical procedure. **(Leethanakul et al, 2014)**

1.1.3.2. **Disadvantage**:

If some anatomic structure was present, such as low maxillary sinus or narrowed ridge, that might be difficult to improve tooth movement by this

technique. **(Leethanakul et al, 2014)**

1.1.4. Piezocision:

In **2009, Dibart** used piezocision to accelerate tooth movement through trans-mucosal corticotomy without flap elevation. This method used a piezoelectric knife to cut bones from a small tissue opening. The knife can selectively cut the bone, thus preventing damage to adjacent soft tissue. **(Dibart et al, 2009)**
If hard and soft tissue grafts are required, they can be placed by using a tunneling procedure.

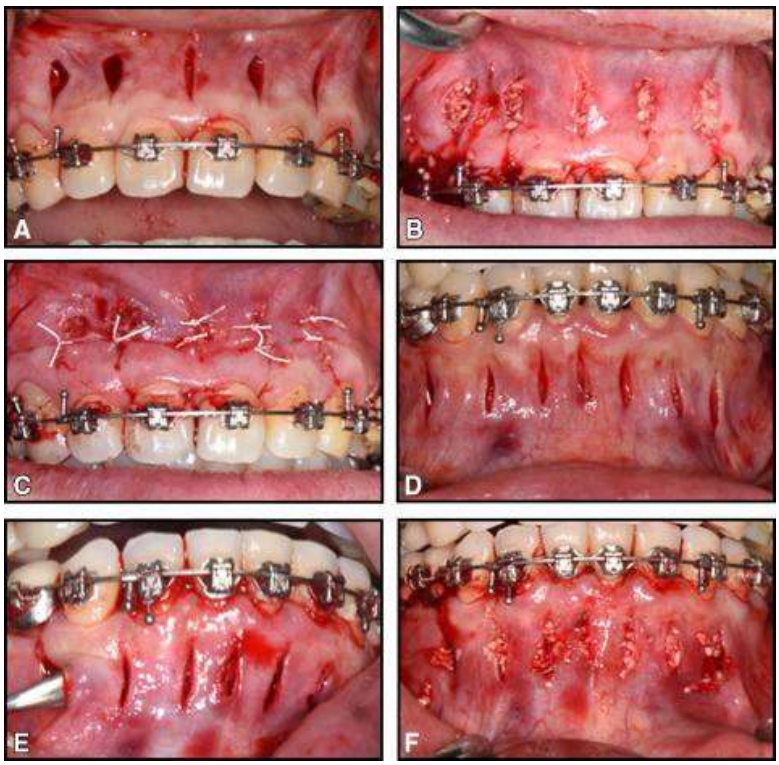

Figure 1.4 Peizocision (Sultana et al, 2022)

This technique can reduce about half of the total treatment time. The attachment level and pocket depth change minimally, but gingival scar tissue was observed and remained in most cases. **(Strippoli et al, 2019)**

In addition, the visibility of piezocision was inferior than corticotomy because the of the small soft tissue opening. Thus, risk of iatrogenic root damage, devitalization of teeth and invasive root resorption must be paid attention.

(Patterson et al, 2017)

Nowadays, using a 3D-printed computer-assisted piezocision to guide the surgery could reduce the risk of root damage. **(Hou et al, 2019)**

1.1.4.1. Indications:

- Class I malocclusions with moderate-to severe crowding (non-extraction)
- Correction of deep bite
- Selected class II malocclusions
- Rapid adult orthodontics
- Rapid intrusion/extrusion of teeth
- Simultaneous correction of osseous and mucogingival defects
- Prevention of mucogingival defects that may occur during or after orthodontic treatment
- Multidisciplinary comprehensive treatments (incorporating generalized or localized Piezocision). **(Kotrikova et al, 2006) (Kim et al, 2009)**

1.1.4.2. Contraindications:

- Active periodontal disease
- Ankylosed teeth
- Systemic conditions affecting bone metabolism • Medications affecting bone metabolism
- Noncompliant patient **(Kotrikova et al, 2006) (Kim et al, 2009)**

1.2 Non-surgical methods :

1.2.1 Low level laser therapy :

Photobiomodulation or low-level laser therapy (LLLT) is one of the most promising approaches today. Laser has a biostimulatory effect on bone regeneration, which has been shown in the midpalatal suture during rapid palatal expansion **(Saito et al, 1997)** and also stimulates bone regeneration after bone fractures and extraction site **(Trelles et al, 1987) (Takeda, 1988)**.It has been found

that laser light stimulates the proliferation of osteoclast, osteoblast, and fibroblasts, and thereby affects bone remodeling and accelerates tooth movement. The mechanism involved in the acceleration of tooth movement is by the production of ATP and activation of cytochrome C, as shown by **(Karu et al, 2008)** that low-energy laser irradiation enhanced the velocity of tooth movement via RANK/RANKL and the macrophage colony-stimulating factor and its receptor expression.

Animal experiments have shown that low-level laser can accelerate tooth movement. Furthermore, clinical trial attempts were made in which different intensities of laser were used and different results were obtained. **(Doshi-Mehta et al, 2012)**

Low-level laser therapy can be a very useful technique for acceleration of tooth movement since it increases bone remodeling without side effects to the periodontium. Laser wavelength of 800 nm and output power of 0.25 mW have indicated significant stimulation of bone metabolism, rapid ossification [39, 49], and also acceleration of tooth movement to 1.5-fold in rat experiments. **(Takeda, 1988) (Kawasaki et al, 2000)**

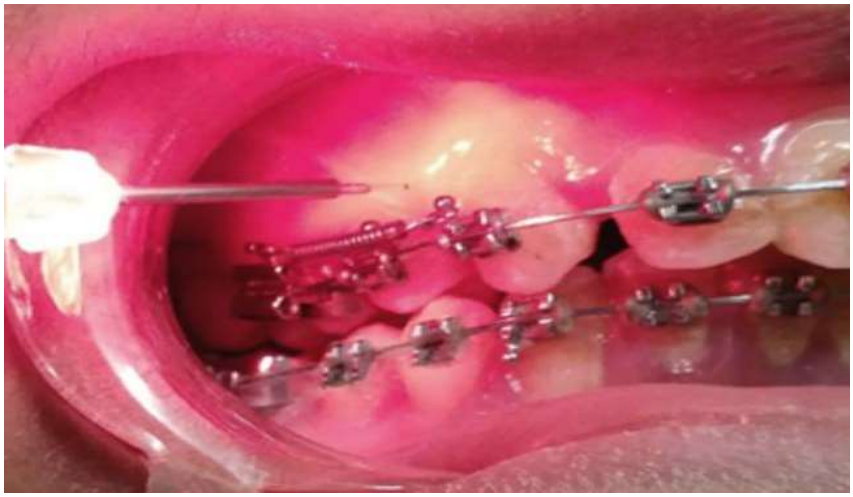

Figure 1.5 Low-level laser therapy (Qamruddin et al, 2021)

1.2.2 low intensity pulsed ultrasound:

Low intensity pulsed ultrasound [LIPUS] has been used widely in medical field for healing of fractures as well as bone regeneration. Xue., et al. **(Xue et al, 2013)** demonstrated that LIPUS promotes alveolar bone remodeling by stimulating the HGF/Runx2/BMP-2 signaling pathway and RANKL expression. He noted that LIPUS was able to accelerate orthodontic tooth movement by 45% after 14 days of treatment.

Figure 1.6 Low intensity pulsed ultrasound (Ildeu et al, 2014)

1.2.3 Micro-osteoperforations:

Also known as alveocentesis, micro-osteoperforations is a novel technique introduced to accelerate tooth movement, with minimal surgical intervention. It is a minimally invasive procedure, as there is no flap elevation or incisions prior to the osteoperforations. Propel (Propel Orthodontics, USA) is an example of a device that can be used to create MOPs. The effectiveness of the technique in accelerating tooth movement is theoretically the amplification in the expression of inflammatory markers that are normally expressed during orthodontic tooth movement. (**Alikhani et al, 2013) (Alikhani et al, 2015)**

Alikhani (2015) used MOPs (Propel) in a clinical trial in 20 adults with Class II division 1 malocclusions. Three flapless microperforations were performed under local anaesthesia distal to the canines, 6 months after the premolar extractions, in order to accelerate tooth movement.

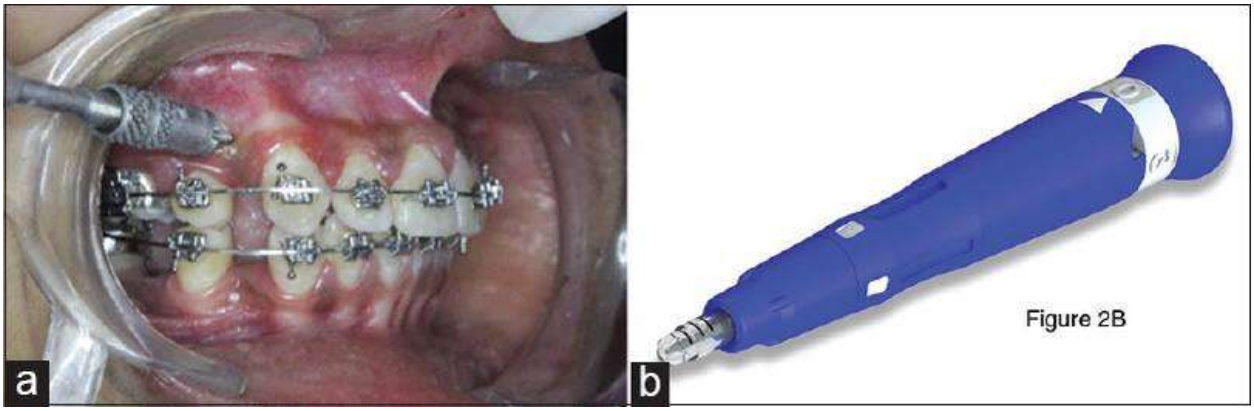

Figure 1.7 (a) Method of performing micro-osteo-perforations. (b) propel orthodontics (Ambashikar et al, 2021)

1.2.3.1 The disadvantage of the technique:

1. The extent of the injury created to the bone is minimal and therefore the RAP effect may not be as long as it is intended.
2. It is a blind technique and pre-planning of the position of the MOPs is crucial to avoid injury to the roots.
3. The inability to graft hard or soft tissues during the procedure to correct and reinforce the periodontium.
4. It is time consuming especially in the mandible because of the thick cortex and needs to be repeated frequently adding cost and chair time to treatment.

1.2.4 Fiberotomy:

Young., et al. (2013) conducted a study to investigate whether fiberotomy itself can accelerate tooth movement. In his study 34 Wistar rats, alveolar bone resorption and molar tooth movement were measured after fiberotomy, apical full-thickness flap without detachment of gingiva from the roots, or no surgery.

Orthodontic treatment was initiated at time of surgery and activated for 14 days, generating movement of the first maxillary molar buccal and then removed. He concluded by stating that fiberotomy solely ac- celerated orthodontic tooth movement and diminished relapse.

Figure 1.8 Fibrotomy procedure.

1.2.5 Resonance Vibration:

Recent studies have shown that mechanical vibration can enhance bone healing and bone strength, as well as reduce un- desirable effects of catabolic processes. A study conducted by **Nishimura., et al. (2008)** demonstrated that eight minutes of resonance vibrational activity applied weekly for three weeks increased the rate of tooth movement by 15%.

Another retrospective study con- ducted by **Bowman., et al. (2014)** stated that dental alignment using vibration device was faster than the control group.

1.3 Medications:

An analysis of forces and vectors does not completely explain the mechanism of orthodontic tooth movement. The complex interaction of different strain, gene expressions and activation of signaling pathways sets a new paradigm for explaining the mechanism of orthodontic tooth movement **(Masella and**

Meister, 2006). The effect of medications on signaling molecules such as eicosanoids or prostanoids is important to regulate pathways and pathological responses, which directly or indirectly affects orthodontic biological tooth movement **(Bartzela et al., 2009).**

Leukotrienes are the only eicosanoids that are formed independently from COX. Leukotrienes have an important role in inflammation and allergic diseases like asthma, however, based on an animal study done on rats, it also has some influence on OTM. The study demonstrated a significantly decrease in OTM after selective inhibition of leukotriene synthesis **(Mohammed et al., 1989).** Therefore, these findings suggest that the drugs which inhibit leukotrienes indirectly decrease OTM. The medications such as Zafirlukast and Montelukast block the leukotriene receptor which has the same effect as inhibition of leukotriene synthesis. Another approach to inhibit leukotriene synthesis is by selective blocking of lipoxygenase enzyme which helps in conversion of arachidonic acid to leukotrienes. This is achieved by drugs such as Zileuton. So, these drugs Zafirlukast, Montelukast and Zileuton which inhibit leukotrienes synthesis also decrease OTM **(Bartzela et al., 2009).**

1.3.1 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. 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. 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. **(Storey, 1973) (Tyrovola et al, 2001)**

1.3.2 Vitamin D3

Vitamin D3 (1,25 dihydroxycholecalciferol) is a hormone which regulates serum calcium and phosphate levels by promoting intestinal absorption and reabsorption. The deficiency of vitamin D3 can be due to low intake combined with inadequate exposure to sunlight, eventually leading to osteoporosis, and decreased bone mineralization. The effect of vitamin D3 on the rate of OTM has been studied in rats and the results suggested that Vitamin D3 can increase the rate tooth movement **(Al-Ansari et al., 2015).** These confounding effects of medication and drug abuse on tooth movement indicates that clinicians should enquire about the pre- scribed medication, over-the-counter drugs and dietary supplements taken by the orthodontic patients before initiation of treatment.

1.3.3 fluoride

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. **(Hellsing et al, 1991)**

1.3.4 Bisphosphonates

Another important group of drugs which affect orthodontic tooth movement are bisphosphonates, because of its direct effect on calcium homeostasis thereby affecting the bone metabolism, thus having an inhibitory effect on orthodontic treatment and tooth movement **(Adachi et al., 1997).** Bisphosphonates are used in the management of bone diseases such as osteoporosis, Paget's disease and bone metastasis. The half-life of Bisphosphonates is 10 years, therefore they continue to affect bone metabolism even after completion of therapeutic dose **(Bartzela et al.,**

2009).

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. **(Igar et al, 1996)**

1.3.5 **NSAID:**

NSAIDs (Non-Steroidal Anti-inflammatory Drug) are used by many patients for different conditions such as headache, migraine, gout, rheumatoid arthritis, osteoarthritis, post-operative pain, cardiovascular diseases and colorectal cancer. Although these drugs are used for different conditions, the doses vary from high to low dose, long term to short term prescriptions. NSAIDs can be divided into different groups depending on their chemical composition such as Salicylates, Arylalkanoic acids, Arylpropionic acids, Oxicams and Coxibs. The mechanism of action of these different NSAIDs are almost similar, they tend to suppress production of all prostanoids (thromboxanes, prostacyclines, and prostaglan- dins). Many animal studies have been done to know the effects of these NSAIDs on OTM but the effects were evaluated for short administrations. Based on these animal studies, the effect of different NSAIDs on OTM has been summarized in Table 1.

Table 1. The effects of NSAIDs on orthodontic tooth movement. **(Tyrovola et al, 2001)**

Non-steroidal anti-inflammatory drug	effect on bone metabolism	effect on tooth movement
aspirin	reduced resorption	reduced
diclofenac	reduced resorption	reduced
indomethacin	reduced resorption	reduced
ibuprofen	reduced resorption	reduced
flurbiprofen	reduced resorption	reduced
naproxen	reduced resorption	reduced
celecoxib	no effect	no effect
acetaminophen	no effect	no effect

The effect of these NSAIDs on OTM also depends on the dose and duration of these drugs which has to be considered during clinical application. The decrease in the rate of OTM may be related to the effect of these drugs on osteoclastic differentiation or in stimulating their activity **(Bartzela et al., 2009; Chumbley and Tuncay, 1986; Vayda et al., 2000; Zhou et al., 1997).** Many orthodontic patients take NSAIDs to overcome the initial discomfort caused by orthodontic tooth movement. Previous studies reported that NSAID's decrease the rate of tooth movement because of its effects on prostacyclines and thromboxanes **(Laudano et al., 2001; Bartzela et al., 2009; Seibert et al., 1994).** Further, inhibition of the inflammatory reaction produced by prostaglandins tends to slow orthodontic tooth movement **(Diravidamani et al., 2012).**

1.4 **Hormones**

1.4.1 Estrogens:

Estrogens are female sex hormones which are decreased after menopause in female patients leading to osteoporosis. Therefore, it can be suggested that Estrogens seems to reduce tooth movement rate **(Haruyama et al., 2002; Yamashiro and Takano- Yamamoto, 2001).**

1.4.2 Thyroid hormones:

Thyroid gland releases two hormones thyroxine and calcitonin which play an important role in calcium regulation and reabsorption. Although, there are no studies to show the effect of calcitonin on the rate of tooth movement, there are animal studies to show Thyroxin increases rate of tooth movement if injected locally by activating osteoclasts **(Shirazi et al., 1999; Verna et al., 2000).**

1.4.3 Relaxin:

Relaxin has been known as a pregnancy hormone. It is released just before child birth to loosen the public 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 remodeling of gingival tissue during extraction space closure, for orthopedic expansion in non – growing patients, by reducing the tension of the stretched soft tissue envelope, particularly the expanded palatal mucosa, after orthognathic surgery. **(Madan et al, 2007)**

1.4.4 Parathyroid hormone:

Parathyroid hormone (PTH) is secreted by parathyroid glands, which is released when there is low concentration of calcium in blood. The main effect of PTH is to increase the concentration of calcium by stimulating bone resorption. Therefore, PTH increases the rate of orthodontic tooth movement by stimulating bone resorption **(Soma et al., 1999, 2000).**

1.5 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. **(Kalia et al, 2004)**

Corticosteroids may increase orthodontic tooth movement but it depends on dosage and timing of steroids **(Verna et al., 2000)** in contrast to others **(Swanson**

et al., 2006) who claim that corticosteroids inhibit tooth movement by stimulating in vitro bone resorption (increased activity and/or formation of osteoclasts) which is also time and dose dependent.

1.6 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 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. **(Yamaski et al, 1984)**

1.7 Cytokines:

These short-range extracellular proteins modulate the activity of other cells. They are pro-inflammatory cells **(Proffit et al., 1999).** First it was thought that only lymphocytes produce these cells and named them as ‘‘lymphokines”. Later it was known that many different cells produce these proteins and hence renamed it as ‘‘cytokines” **(Sabane et al., 2016).** There are over 50 cytokines which are recognized. These proteins are seen in various stages of inflammation. Some of the cytokines which mediate the bone remodeling during orthodontic tooth movement are interleukin- 1, alpha1 beta, tumour necrosis factor (TNF), IL-6 **(Garlet et al., 2007).** The inflammatory cells which produce cytokines are osteo- blast, fibroblast, endothelial cells and macrophages **(Al-Ansari et al., 2015).**

1.8 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 remodeling process. **(Krishnan et al, 2006)**

1.9 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. **(Shdayfat, 2011)**

1.10 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

remodeling process, thereby complicating tooth movement. **(Krishnan et al, 2006)**

1.11 Anticonvulsants:

1.11.1 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. **(Karsten et al, 1997)**

1.12 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. **(Brezniak et al, 2002)** 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. **(Davidovitch et al, 1988)**

Chapter Two: Conclusion

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1- Medication use in orthodontics has the potential to enhance treatment outcomes and improve patient satisfaction, but should be used judiciously and with caution.

2- The effectiveness of accelerating/retarding medications depends on various factors such as the type and severity of malocclusion, the duration and frequency of medication use, patient's age and overall health.

3- While some medications have shown promising results in shortening the duration of orthodontic treatment or minimizing the need for extractions, their use may also be associated with potential side effects and risks. It is therefore important for orthodontic practitioners to carefully consider the potential benefits and risks of using medication in each individual case, and to monitor patients closely during treatment.

4- Future research in this area may focus on developing safer and more effective medications for accelerating or retarding orthodontic tooth movement, as well as identifying patient-specific factors that may influence the effectiveness and safety of these medications.

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