University Of Science and Technology
Collage Of Dentistry
Department Of Biological and Preventive Sciences
Orthodontic Unite

Three-dimensional assessment for the synergistic effects of platelet-rich fibrin local injection combined with micro-osteoperforation versus MOPs alone on the rate of orthodontic tooth movement during canine retraction: a split-mouth randomized controlled clinical trial

A Research Proposal Submitted by

Hend Abulkarem Abdullah Nasher AL-Haifi

Supervisors

Dr. Maged Sultan Abdullah Al-Hammadi

Associate Professor of Orthodontics

Jazan University, Saudi Arabia

Dr. Ramy Abdulrahman Ali Ishaq

Assistant Professor of Orthodontics
Sana'a University, Yemen

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Introduction

1.1 Background

Orthodontic treatment is the restructuring of skeletal and/or dental tissues. Prolonged treatment duration is one of the main concerns of patients undergoing with fixed orthodontics. This extended orthodontic treatment in such particular cases has several drawbacks to the patients such as increased predisposition to root resorption, dental caries and gingival recession, etc. Consequently, researchers introduced few methods to accelerate the velocity of the tooth movement without any drawbacks. These kinds of methods used in orthodontics were popular as accelerated orthodontics.

Accelerated orthodontics could be possible by mechanical stimulation or device assisted therapy, surgical therapy and by the use of pharmacological agents. The movement of tooth orthodontically happens under mechanical forces depends upon the alteration of the tissues surrounding its radicular part. These mechanical forces create a response in cellular component of surrounding periodontal ligament (PDL), that creates resorption in bone on pressure side and deposition of bone on the either side (tension side) [1]. This is an inflammatory process and the rate limiting factor for tooth movement is bone resorption at the bone and periodontal ligament interface [2].

1.2 Statement of the problem:

Acceleration of tooth movement while orthodontic treatment is of increasing demand now a days because of patient's interest to get the treatment completed in less span of time and to decrease the number of visits. Also, adult orthodontics has more demand as the number of adult patients is getting increased.

Accelerating orthodontic techniques can be highly useful for fastening the treatment as in every technique being used; there is increased rate of tooth movement and hence decreasing the treatment time.

To our knowledge, no previous study has evaluated the effect of combined micro-osteoperforation and injectable plasma rich fibrin versus the effect of micro-osteoperforation alone on the orthodontic tooth movement during canine retraction.

1.3 Aim of the study :

1.3.1 General Objective:

The objective of this study is to evaluate the synergetic effect of micro-osteoperforation (MOPs) combined with injectable plasma rich fibrin (i-PRF) versus the effect of MOPs alone on the orthodontic tooth movement during canine retraction using cone beam computed tomography (CBCT).

1.3.2 Primary Objectives:

Evaluation the synergetic effect of (MOPs) and (i-PRF) versus the effect of (MOPs) alone on the rate of orthodontic tooth movement before canine retraction and after 6 months using (CBCT).

1.3.3 Secondary Objectives:

Evaluation the synergetic effect of (MOPs) and (i-PRF) versus the effect of (MOPs) alone on the bone fenestration, dehiscence and apical root resorption (ARR) of canine before canine retraction and after 6 months using (CBCT).

1.4 Hypothesis

1.4.1 Null Hypothesis:

The null hypothesis (H0) of this study is that, the combination of (MOPs) and (i-PRF) has no synergetic effect to accelerate orthodontic tooth movement and has no effect on the bone fenestration, dehiscence and apical root resorption during canine retraction.

1.4.2 Alternative Hypothesis:

The alternative hypothesis (H1) of this study is that, the combination of (MOPs) and (i-PRF) has a synergetic effect to accelerate orthodontic tooth movement and may affect the bone as fenestration or dehiscence and apical root resorption might occurred during canine retraction.

Chapter 2

Review of literature

Fixed orthodontics could last for 24 to 36 months which further poses the risk of complications associated with the treatment such as external root resorption, periodontal problems and patient compliance. Orthodontists are persistently motivated towards developing potential strategies to enhance the rate of orthodontic tooth movement [6-8].

Orthodontic tooth movement occurs under mechanical forces leading to remodeling changes in dental and paradental tissues. This force creates a response in cellular component of periodontal ligament, that leads to resorption of bone on the pressure side and apposition of bone on the tension side.[1] The activation of osteoblasts and osteoclasts results in remodeling of supporting structures to influence orthodontic tooth movement.[2] Application of orthodontic force leads to alteration of blood flow around the surrounding tissue, which reduces the oxygen level at the pressure side.[3] This event leads to release of different inflammatory mediators like colony stimulating factors, cytokines, growth factors, arachidonic acid metabolites and neurotransmitters as a result of which remodeling of bone occurs.[1,2]

In today's modern society, people are more aware regarding their looks. This has increased the demand of orthodontic treatment among young individuals. But the duration of treatment remains the major concern for them. The time required for completion of orthodontic treatment depends on various factors. These factors can broadly be categorized as patient factors, diagnostic characteristics, treatment modality factors and patient compliance. [4]

The amount of force delivered to a tooth and also the area of the periodontal ligament over which the force is distributed are important in determining the biologic effect. Long term comprehensive orthodontic treatment is dictated by biologic processes as well as mechanical principles and treatment approaches. The challenge for an

orthodontist is to determine an acceptable treatment option without compromising the outcome.

Orthodontic movement can be controlled by the size of the applied force and the biological responses from the periodontal ligament [3]. This orthodontic force would cause inflammation around the periodontal ligament due to changes in blood flow, leading to the secretion of different inflammatory mediators like colony-stimulating factors, cytokines, growth factor, arachidonic acid metabolites and neurotransmitters. As a result of these secretions, remodeling of the bone occurs [4, 5]. Macrophage colony stimulating factor (M-CSF), Receptor activator of nuclear factor kappa B ligand (RANKL), and osteoprotegerin (OPG) by osteoblasts play key roles in tooth movement. RANKL binds to its receptor, RANK (Receptor activator of nuclear factor kappa B), on the surface of osteoclastic cells at developmental stage. The RANKL/RANK binding is very critical for the function, differentiation, and survival of osteoclasts.

Microosteoperforations (MOPs):

this procedure was popularized as alveocentesis, which literally translates to puncturing bone utilizing many devices like TADs and Propel.

Propel, TM was launched by Propel Orthodontics to further reduce the invasive nature of surgical irritation of bone. The device has an adjustable depth at 0 mm, 3 mm, 5 mm, and 7 mm of tip depth and indicating arrow on the driver body. This device comes as ready-to-use sterile disposable device.

Kole[5] was the first to propose Cortectomy Assisted Orthodontic Treatment (CAOT) as a process of accelerating tooth movement. In CAOT, perforations of only the cortex are performed leaving the medulla intact and rapid tooth movement is due to increased bone turnover as a response to the surgical procedure.

A cascade of inflammation is initiated around the bone which is irritated surgically. This procedure causes increased osteoclast genesis thereby decreasing the mechanical resistance and causing faster tooth movement. This phenomenon is known as Regional Acceleratory Phenomenon (RAP).[5] A zone of high bone turnover with high osteoclastic and osteogenic activity is created that accelerates the speed of bone remodeling, thus accelerating the treatment.[6] The purpose of the present article is to narrate and outline the various methods of accelerating orthodontic treatment.

What is RAP or PAOO? How does it work?

• Regional Acceleratory Phenomena (RAP) is local response to a noxious stimulus, which describes a process by which tissue forms faster than the normal regional regeneration process. By enhancing the various healing stages, this phenomenon makes healing occur 2–10 times faster than normal physiologic healing (Frost, 1983).5

• Many studies have reported an increase in the activity of inflammatory markers such as chemokines and cytokines in response to orthodontic forces. Chemokines play an important role in the recruitment of osteoclast precursor cells, and cytokines, directly or indirectly, through the prostaglandin E2 pathway and the RANK/RANKL pathway, leading to the differentiation of osteoclasts from their precursor's cells into mature osteoclasts. Therefore, it is logical to assume that increasing the expression of these factors, by surgically irritating the bone should accelerate tooth movement.1-4

• A histological study showed that selective alveolar decortication induced increased turnover of alveolar spongiosa (Sebaoun et al 2008). Surgery results in a substantial increase in alveolar demineralization, a transient and reversible condition. This will result in osteopenia (temporary decrease in bone mineral density). The osteopenia enables rapid tooth movement because teeth are supported by and moved through trabecular bone. As long as tooth movement continues, there is prolongation of RAP. When RAP dissipates, the osteopenia disappears and the radiographic image of normal

spongiosa reappears. Then when orthodontic tooth movement is completed, an environment is created that favors alveolar re-mineralization.

• Simply stated, when bone is surgically irritated, a wound is created. This wound initiates a localised infl ammatory response. Due to the presence of the infl ammatory markers, osteoclasts migrate to the area and cause bone resorption. This effect, however, is temporary, and lasts for about 4 months,12 and the procedure needs to be repeated, in case faster tooth movement is still required.

1.1 Methods to Accelerate Tooth Movement:

Methods to accelerate orthodontic tooth movement can be broadly studied under the following categories:

1. Surgical Methods.

2. Physical/ Mechanical stimulation methods.

3. Drugs.

I. Surgical methods

a) Corticotomy

b) Periodontally Accelerated Osteogenic Orthodontics (PAOO)

c) Piezocision

d) Micro-osteoperforation

e) Interseptal alveolar surgery

f) Corticision

g) Surgery first approach

II. Physical/Mechanical methods

a) Low level laser therapy

b) Cyclic/ Resonance Vibration

c) Electric current

d) Electromagnetic field

e) LED device: Biolux

f) Therapeutic Ultrasound: Aevo system

g) Self ligating brackets

III. Drugs

a) Prostaglandin

b) Vitamin D3

c) Parathyroid hormone

d) Relaxin

Surgical techniques are more invasive and costly but are more beneficial with fewer side effects. Hence recent techniques such as piezocision, micro osteoperforations has the more demand in future. With increasing patient compliance, less invasive surgical techniques can be safely used to accelerate tooth movement.

Pharmacological methods have more side effects and hence most of them are still in experimental stage. Only limited human trails are available.

2.2 Micro-osteoperforation :

Also known as alveocentesis, it is the least invasive procedure in which micro-trauma is induced to the alveolar bone thus producing RAP, which in turn increases the rate of orthodontic tooth movement. [12] The procedure is very simple to perform with zero recovery time and significantly reduces the duration of orthodontic treatment.[13] The procedure can be performed with the help of Temporary Anchorage Devices (TADs) or PROPEL device (figure 1).

These methods were based on the principle that when the bone is irritated surgically, an inflammation cascade is initiated which caused increased osteoclastogenesis, hence causing faster tooth movement (Regional Acceleratory Phenomenon or Periodontally Accelerated Osteogenic Orthodontics).5 However, these were invasive and not well

accepted by the patients. Hence, newer surgical methods have arrived with the help of piezosurgery, fiberotomy, microosteoperforations etc. which achieve the same results as achieved by conventional corticotomy, but with reduced invasiveness and morbidity. These modalities have also been shown to reduce relapse, and pain and root resorption caused due to orthodontic forces.

The adjustable depth dial for microosteoperforations can be positioned to 0 mm, 3 mm, 5 mm, and 7 mm of tip depth, depending on the area of operation. Previous animal studies have shown that performing micro-osteoperforations (MOPs) on alveolar bone during orthodontic tooth movement can stimulate the expression of infl ammatory markers, leading to increases in osteoclast activity and the rate of tooth movement. Mani Alikhani et al (2013)15, performed a single center single blinded study to investigate this procedure on humans. They used a Ni-Ti closed coil spring, delivering a constant force of 100 g to distalize the maxillary canine after fi rst premolar extraction. The spring was anchored to a TAD distal to the second premolar, and attached to the canine using a power arm through the vertical slot of the canine bracket. Gingival crevicular fl uid (GCF) samples were collected from each subject to evaluate the level of infl ammatory response. GCF was collected before orthodontic treatment, immediately before the start of canine retraction, and at each subsequent visit, between 10 AM and 12 noon. These samples were taken from the distobuccal crevices of the maxillary canine. GCF samples were collected with fi lter-paper strips (Orafl ow, Smithtown, NY) inserted 1 mm below the gingival margin into the distobuccal crevices of the canine for 10 seconds. Cytokine levels were measured using a custom protein array for the following cytokines: CCL2 (MCP1), CCL-3, CCL-5(RANTES), IL-8 (CXCL8), IL-1a, IL-1b, IL-6, and TNF-a (Raybiotech, Norcross, Ga) according to the manufacturer's instructions. Alginate impressions were taken at the beginning of the study, immediately before canine retraction, and 28 days after canine retraction began to monitor the rate of

tooth movement. The impressions were immediately poured up with plaster (calcium sulfate). Vertical lines were drawn on the cast over the palatal surface of the canine and lateral incisor from the middle of the incisal edge to the middle of the cervical line. The distance between the canine and the lateral incisor was assessed before and after canine retraction at 3 points: incisal, middle, and cervical thirds of the crowns. All cast measurements were made using an electric digital caliper (Orthopli Corp, Philadelphia, Pa) with an accuracy of 0.01 mm. They concluded their study by stating that:

1. MOPs significantly increased the expression of cytokines and chemokines known to recruit osteoclast precursors and stimulate osteoclast differentiation.

2.MOPs increased the rate of canine retraction 2.3fold compared with the control group.

3. Patients reported only mild discomfort locally at the spot of the MOPs, at days 14 and 28, little to no pain was experienced.

4. MOPs are an effective, comfortable, and safe procedure to accelerate tooth movement during orthodontic treatment.

5. MOPs could reduce orthodontic treatment time by 62%.

However, this was the first study investigating this method, and certain issues were not addressed, such as, effect on root resorption, number of perforations required, long term effects (this study had a duration of only 28 days).

2.6 Study rationale:

The synergetic effect of the (MOPs) and (i-PRF) on the acceleration of orthodontic tooth movement during canine retraction requires to be investigated and evaluated.

Chapter 3

Subject and Methods

3.1 Trial Design:

The study will be a split mouth randomized controlled trial with a 1:1 allocation ratio.

3.2 Participants:

Female subjects requesting orthodontic treatment, aged 16-29 years with maxillary dentoalveolar protrusion and class II division 1 malocclusion full or half unit and mild crowding required the bilateral extraction of maxillary first premolars will be allocated in the study.

3.3 Eligibility criteria

3.3.1 Inclusion criteria:

- Age: 19- 38 years.
- Gender: females
- Participants requiring fixed orthodontic appliances in upper and lower archs.
- Treatment protocol: bilateral extraction of maxillary first premolars
- Medically: free of any medical disorders (diagnosed through proper, careful and detailed medical history that will be included in patient file).

3.3.2 Exclusion criteria:

- Chronic medication: antibiotic or anti-inflammatory.
- Systemic diseases: diabetes mellitus, kidney diseases and respiratory infection.
- Mouth breathing, xerostomia, hyposalivation
- Previous orthodontic treatment.
- History of unusual oral habits like tongue thrusting, finger sucking etc.

3.4 Study Settings and location for data collection:

The study will be performed in the Department of Orthodontics, University of Science and Technology (UST) and 2 private dental clinics in Sana'a, Yemen.

3.5 Ethical approval:

An approval from the Ethical Scientific Research Committee of the UST will be applied for the study. The researcher should be provided with a grant number for the clinical trial registration. All participants and their parents or guardians will receive written information about the aims and design of the study and will be requested to sign a written informed consent form.

3.6 Intervention:

3.6.1 Prepration of the patient :

At the first visit a case file will be opened for each participant, including patient information's, clinical examination, photograph's, plaster model and radiographs.

Based on the patientt dignostic decesion, If the individualized treatment plan is extraction protocol the patient will be recruted .

Before beginning of orthodontic treatment all participants will undergo a protocol of oral hygiene instruction and motivation that involve scaling and polishing for their teeth before placement of the orthodontic appliances, the instructions in the Orthodontic clinic for all the patients to brush their teeth minimum three times a day using the Bass modified technique with tooth paste containing fluoride after placement of the appliances.

The study will be explained to every subject in detail and an informed consent will be obtained by the patient herself and/ or the parent (in the situation that the subject was under 18 years old).

3.6.2 Fitting of FOA :

Fixed Orthodontic Appliance will be fitted to the teeth. 0.22-inch slot MBT bracket system (SIA, Italy) with straight wire appliance (SWA).Bands or buccal tubes will be placed on the first molars. The same adhesive material will be used (3M Unitek). Leveling and alignment will be initiated with (12 or 14 NiTi) and proceeded as per as the protocol require for each patient .

15 mL of whole unstimulating saliva (WUSS) samples will be taken from each participant at each assessment stages to test salivary pH .

3.6.3 Study groups :

According to the random allocation process, study groups will be categorized according to the intervention procedures into 2 groups:

A: micro-osteoperforations only (MOPs) / Control group

B: micro-osteoperforations (MOPs) with injectable rich plasma fibrine i-RPF/ Comparator or interventional group

3.7 Outcomes:

- Rate of canine retraction will be evaluated before and after retraction in 6 time points (T1 through T6) For the two groups of along 24 weeks.

3.8 Outcome Assessment :

Rate of en-mass retraction will be evaluated intraorally every 4 weeks for a total of 24 weeks (T1 through T6) using a digital caliper to measure the distance of space closure from the canine cusp tip to the 1st molar mesiobuccal cusp tip. Model cast will be taken in each re-call visit to verify the intraoral measurements Full field of view for maxilla and mandible cone beam computed tomography scans will be taken before and

after en-mass retraction to evaluate canine root length (indicative of external apical root resorption, EARR) and the presence of dehiscence or fenestration.

3.9 Protocol of micro- osteoperforation:

A randomly selected side of maxillary arch will receive PRF combined with MOPs. The contralateral side will receive only MOPs and served as the control. After the initial leveling and alignment phase reaching archwire 19x25 SS and immediately before en-mass retraction, i-PRF will be obtained from 20 ml of blood drawn from each patient's brachial vein, centrifuged at 700 rpm for 3 min. the injection of PRF will be performed under local anesthesia into the mucosa of the buccal and palatal aspects of the extraction sites for the intervention sides at three level distance along the 1st premolar socket. The application of MOPs for both sides will follow a systematic protocol. The MOPs will be placed at 5, 10 and 15 mm from the gingival margin and performed under local anesthesia using a mini-screw (1.8 mm diameter, 8 mm length) through a self-drilling method placed distal and mesial to the canine tooth. The procedures will be repeated 4 weeks later. En-mass retraction with absolute anchorage using mini-screws will be initiated in both sides utilizing a NiTi closed coil spring with 150g force. The TADs placed between roots of 2nd premolar and 1st molar.

Data collection:

CBCT images will be obtained for the participants before and after en-mass retraction. A Software will be used to perform the CBCT measurements as follow:

1. landmarks identification.
2. Reference lines and planes
3. Measurements.

3.12 Sample size:

Calculation of sample size will be based on previous studies.

3.13 Sample size calculation :

Sample size calculation will be calculated using G power software.

with a power of 80% and $\alpha = 0.05$, a minimum number of 35 participant will be required for each group.

3.14 Randomization:

After determination of the eligibility of participant as well as verification of their interest to participate in the trial, each will be invited to pick an envelope. The nurse or assistant will open the envelope.

3.14.1 Sequence generation:

A software randomization program (Research Randomizer) will be used to generate random allocation tables that include random number sequences for the participants. Two randomly sequencing numbered tables from 1 to 60 will be generate by the software. Each table represents a group of type method of tooth acceleration.

3.14.2 Allocation concealment

Sixty enclosed envelopes for both groups will be prepared before the study by orthodontist assistant. Each envelope containing the treatment allocation number which represent either the control or the interventional group for the left or right canine.

3.14.3 Implementation:

The orthodontist assistant is responsible for implementing the randomization process that include:

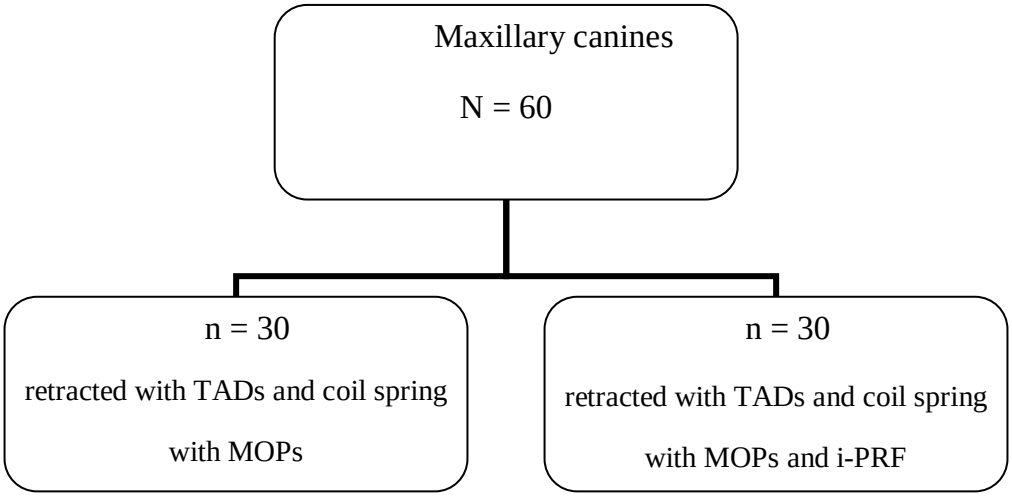
- Generate the allocation sequences and preparation of the enclosed envelopes in sequence numbers.
- Enrollment of the participants.
- Assignment of the participants into their groups.

3.15 Blinding (Masking):

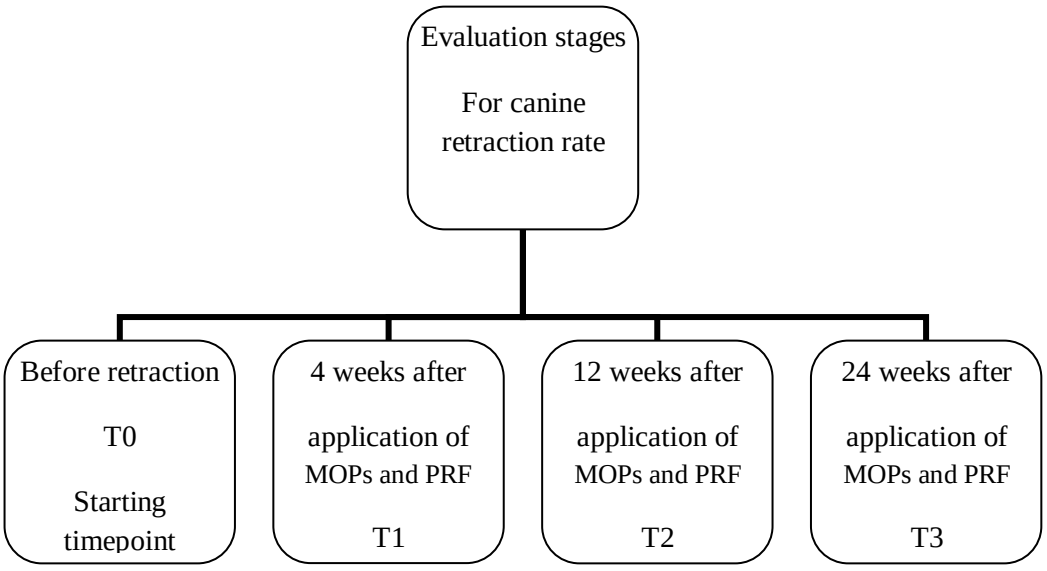
The data will be collected in coded tables without mention of any patients details to be analyzed by the statistician.

3.16 Enrollment :

(Consort follow diagram for patients participation)



- **Consort follow diagram for Evaluation stages of canine retraction**



3.17 Statistical Analysis:

The Shapiro-Wilk test will be applied to verify the normality of distribution of the examined variable on the whole sample.

The Chi^2-test will be used to establish whether a significant difference existed between the numbers of patients in each group. Deviations from baseline will be tested for significance with the Wilcoxon signed ranks test (one-tailed).

The t- test for independent samples will be applied for the comparison between two groups, while the comparison between T0 to T6 will carried out with the t-test for paired sample and repeated measure ANOVA.

The level of significance set at 0.05. Statistical analyses performed using the statistical software SPSS for Windows (version 25.0, SPSS Inc., Chicago,IL,USA).

3.18 Reserch Budget :

The research budget of the study will be supported by the University of Science and Technology (UST) Sana'a, Yemen.

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Appendix

List of abbreviations:

Abbreviation	word
MOPs	Micro- osteoperforations
i-PRF	Injectional plasma rich fibrin
ARP	Acceleration regional phenomena
WSL	White spot lesion
OT	Orthodontic treatment
UST	University of Science and Technology

List of figures:

(Figure 1) propel device

University of Science & Technology

College of Medical Sciences

Research Ethics Committee

For Committee Use Only
Consent form No.

Informed Consent Form

Screening Number [ ] Date:____

Purpose of the study:

This study is aimed to evaluate the synergistic effect of injectable plasma rich fibrine (i-PRF) and micro-osteoperforations (MOPs) on the acceleration of orthodontic tooth movement during canine retraction using intra-oral digital caliper and CBCT.

Study procedures:

You will be asked to answer some questions during clinical examination and give a sample of blood twice during canine retraction stage from orthodontic treatment.

Risk from the study:

As a result of participation in this study you will not be exposed to any serious risk. We are assuming in our study that the intervention will be minimal intervention with the using of endogenous plasma rich fibrin to be helpful for the acceleration of orthodontic tooth movement and closed the extracted in shorter time.

Benefits from the study:

The result of this study will be benefit for orthodontists and the patients to minimize or shortening the longevity course of fixed orthodontic treatment taking in consideration the safety interventional procedures of the study.

Complications anticipated (in case of clinical trials/ interventions):

No Complications may occasionally arise during the course of the study, rather than those tissue response during the course of fixed orthodontic treatment.

Compensation: No compensation will be paid for you.

Confidentiality:

All information collected in this study will be kept strictly confidential except as may be required by law or by the funding agency. You will not be identified by name when the results of the study are published.

Right of participants:

Participation in the study is voluntary. Refusal to participate will not influence the care of you in this institute in any way. Though we would like all study participants to co-operative with researcher. You are free to withdraw from the study anytime. If at any time during the course of the study, you have any questions or concerns related to the study, you can contact the following doctor:

Name: ---------- Contact information: ----------

Signature: ---------- Date: ----------

Name of witness one: ----------

Signature of witness one: ---------- Date: ----------

Name of witness two: ----------

Signature of witness two: ---------- Date: ----------

I, the undersigned have explained to the patient in a language he understands the procedures to be followed in the study and risks and benefits.

Name of the investigator: ----------

Signature of the investigator: ---------- Date: ----------

جامعة العلوم و التكنولوجيا

العلوم الطبية - كلية طب الأسنان

لجنة أخلاقيات البحث العلمي

For Committee Use Only
Consent form No.

إستمارة الموافقة المسبقة

فحص رقم : التاريخ :

الغرض من الدراسة:

تهدف هذه الدراسة إلى تقييم ومعرفة مدي التأثير التآزري للفيبرين الغني بالبلازما القابل للحقن (i-PRF) وفتحات العظام الدقيقة (MOPs) على تسريع حركة الأسنان التقويمية أثناء سحب الناب خلال المعالجة التقويمية باستخدام الفرجار الرقمي داخل الفم و باستخدام التصوير المقطعي المحوسب باستخدام الحزمة المخروطية CBCT.

إجراءات الدراسة:

سوف يكون عليك الإجابة علي بعض الأسئلة المرفقة للفحص السريري و إعطاء عينه من الدم وذلك مرتين خلال مرحلة سحب الناب أثناء المعالجة التقويمية .

فوائد من الدراسة:

سوف تفيد نتائج هذه الدراسة أطباء تقويم الأسنان و كذلك المرضى من خلال اثبات طرق متعددة و التي قد تساعد في تسريع و تقصير فترة المعالجة التقويمية الطويلة

الثقة و السرية الكاملة :

سيتم الاحتفاظ بجميع المعلومات التي يتم جمعها في هذه الدراسة بسرية تامة باستثناء ما قد يتطلبه القانون أو الجامعة ولن يتم التعرف عليك بالاسم عند نشر نتائج الدراسة.

حق المشاركين:

المشاركة في الدراسة تطوعية. رفض المشاركة لن يؤثر على رعايتك في المعالجة بأي شكل من الأشكال. على الرغم من أننا نود من جميع المشاركين في الدراسة أن يكملوا المشاركة ، فأنت / أنت حر في الانسحاب من الدراسة في أي وقت.

إذا كان لديك أي أسئلة أو استفسارات متعلقة بالدراسة في أي وقت أثناء الدراسة ، فيمكنك الاتصال بالطبيب:

اسم: د / هند عبد الكريم ناشرالحيفي معلومات الاتصال : جامعة العلوم و التكنولوجيا – صنعاء

أنا الموقعه أدناه قمت بالشرح الكامل لجميع المشاركين باللغة المفهومة لهم بتفاصيل الدراسة كاملة بما فيها من فوائد أ و أي مخاطر كامنه .

اسم الباحثة : هند عبد الكريم عبدالله ناشر الحيفي التوقيع: التاريخ: