An evaluation of tooth root resorption associated with the use of photobiomodulation during orthodontic treatment with clear aligners

by

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ABSTRACT

INTRODUCTION

Photobiomodulation therapy has been reported to accelerate orthodontic tooth movement, which may also be contributing to an increase in orthodontically induced external root resorption (OIERR). The aim of this project is to evaluate the change in tooth root volume using cone-beam computed tomography (CBCT) in a group of orthodontic patients treated with clear aligners with or without the use of photobiomodulation as produced by the OrthoPulse® device.

METHODS

A semi-automated segmentation technique was used to obtain the tooth volume of maxillary and mandibular anterior teeth from CBCT imaging taken prior to the start of active aligner therapy (T0) and at the end of treatment or at least six months following the initiation of active aligner therapy (T1). The OrthoPulse group (n = 16) changed their clear aligners every 3-5 days and were instructed to use their OrthoPulse device once per day for 5 minutes per dental arch (10 minutes total). The clear aligner group (n = 16) served as a matched control and were instructed to change their aligners every 7-10 days. The individual's pre- and post-treatment teeth volumes were superimposed, and the crowns were virtually removed at the level of the cemento-enamel junction. The change in root volume between the two time points was then assessed.

RESULTS

There was no statistically significant difference between the pre-treatment and post-treatment root volumes of maxillary and mandibular central incisors, lateral incisors and canines, regardless of which intervention group the patient belonged to ($p = 0.840$). There was also no

statistically significant difference in the mean percentage change in root volume between clear aligner patients in this study who have been treated with photobiomodulation using the OrthoPulse device compared to a matched control group ($p = 0.310$).

CONCLUSIONS

Clear aligner patients in this study who changed their aligners every 3-5 days and used adjunctive photobiomodulation therapy did not experience clinically relevant OIERR. Due to the small sample size and the measurement error in the root segmentations, the presented results should be interpreted with caution.

PREFACE

This thesis is an original work by Dr. Antonio Rossi. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Evaluation of teeth root resorption associated with the use of photobiomodulation during orthodontic treatment", No. Pro00078048, February 6, 2018. No part of this thesis has been previously published.

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Conflict of Interest and Funding

The main author of this thesis received funding from Biolux Research Ltd. for a research assistantship to support this project and was responsible for the conception, design, data acquisition, analysis, and interpretation of data in all chapters. The terms of this arrangement were reviewed and approved by the University of Alberta in accordance with its policy on objectivity in research.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
ATP	Adenosine Triphosphate
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CBCT	Cone-Beam Computed Tomography
CCO	Cytochrome C Oxidase
CEJ	Cemento-Enamel Junction
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
ICC	Intraclass Correlation Coefficient
LED	Light-Emitting Diode
LLLT	Low-Level Light Therapy
MANOVA	Multivariate Analysis of Variance
NO	Nitric Oxide
OIERR	External Root Resorption
PDL	Periodontal Ligament
RoB	Risk of Bias
ROS	Reactive Oxygen Species
VTK	Visualization Toolkit

Chapter 1 – Introduction

1.1. Statement of Problem

Patient demand for shorter orthodontic treatment time has fueled recent interest in adjunctive modalities to accelerate tooth movement. Among these modalities, photobiomodulation is a technique that has been used to enhance biological processes around the teeth to allow for faster tooth movement. Importantly, these same biological processes are involved in orthodontically induced external root resorption (OIERR), a common undesirable side effect of orthodontic treatment with both fixed appliances and clear aligners.

With recent advances in Cone Beam Computed Tomography (CBCT) segmentation techniques which allow efficient determination of in-vivo tooth and root volumes, a three-dimensional investigation into the possible effect of photobiomodulation on OIERR is needed. This will allow the clinician to have confidence that they are not causing harm when using adjunctive therapy, like photobiomodulation, to accelerate tooth movement, and ultimately benefits the patient by allowing for shorter treatment times.

1.2. Objectives

The primary objective of this thesis is to evaluate changes in root volume using Cone Beam Computed Tomography (CBCT) in a group of orthodontic patients treated with clear aligners who had received adjunctive photobiomodulation therapy with the OrthoPulse device compared to a matched control group treated only with clear aligners.

The second objective is to determine the intra- and inter-rater reliability of a proposed dental root segmentation technique for the in-vivo quantification of OIERR in maxillary and mandibular anterior teeth.

1.3. Research Questions

The primary and secondary research questions, respectively, for this thesis are as follows:

1. Regardless of the intervention group, is there a difference between the pre-treatment and post-treatment root volumes of maxillary and mandibular central incisors, lateral incisors and canines?
2. Are there differences in the amount of root resorption experienced by the maxillary and mandibular anterior teeth between the patients treated with OrthoPulse compared to those treated without the device?

3. If there is a difference in the amount of root resorption between the patients treated with OrthoPulse compared to those treated without the device, are there differences in the amount of root resorption experienced between the twelve maxillary and mandibular anterior teeth within each group?

1.4. Hypothesis

The following null hypotheses (H_0) and alternative hypotheses (H_a) are proposed for the three research questions:

1. $H_{0:}$ There will be no difference between the pre-treatment and post-treatment root volumes of maxillary and mandibular central incisors, lateral incisors and canines regardless of the intervention group.
   $H_{a:}$ There will be a difference between the pre-treatment and post-treatment root volumes of maxillary and mandibular central incisors, lateral incisors and canines regardless of the intervention group.
2. $H_{0:}$ Orthodontic patients treated with clear aligners who had received adjunctive photobiomodulation therapy with the OrthoPulse device will not have a significantly different amount of OIERR compared to patients treated with clear aligners alone.
   $H_{a:}$ Orthodontic patients treated with clear aligners who had received adjunctive photobiomodulation therapy with the OrthoPulse device will have a significantly different amount of OIERR compared to patients treated with clear aligners alone.
3. $H_{0:}$ There will be no difference in the amount of root resorption experienced between the twelve maxillary and mandibular anterior teeth within each group.
   $H_{a:}$ There will be difference in the amount of root resorption experienced between the twelve maxillary and mandibular anterior teeth within each group.

Chapter 2 – Orthodontically induced inflammatory root resorption associated with the use of adjunctive interventions for accelerating tooth movement in patients undergoing orthodontic treatment: A systematic review

2.1. INTRODUCTION

2.1.1. Accelerated orthodontics

A recent trend in orthodontics has focused on developing novel approaches to accelerate tooth movement in an effort to decrease overall treatment time. Conventional orthodontic therapy with fixed orthodontic appliances has been shown to require, on average, 20 months to complete (1). A survey of adolescent patients and their parents as well as adult patients revealed that these groups would prefer if treatment was completed much sooner. Adult patients and parents would prefer if treatment would last from 6 to 18 months while adolescent patients prefer a treatment time of less than 6 months (2). While several factors can play a role in the overall length of treatment, it is an advantage for clinicians to complete their orthodontic treatments in a shorter time span to minimize unnecessarily increased overhead expenses and chair time. Longer orthodontic treatment times have been shown to increase the risk of external apical root resorption and enamel decalcification (3-5).

Multiple methods have been proposed to achieve accelerated tooth movement during orthodontic treatment. Non-surgical methods include limited orthodontics, novel bracket designs, customized fixed appliances, medications, microvibrations, low-intensity laser, photobiomodulation, electromagnetic fields and direct electrical currents (6). In addition, low intensity pulsed ultrasound has been shown to accelerate tooth movement in animals and humans (7, 8). Microvibration has been one of the most investigated amongst these interventions. A recent Cochrane review (2015) examined the effect of non-surgical interventions on orthodontic tooth movement (9). Only two articles were included for review and both studied the effects of microvibration on tooth movement. The authors concluded that both studies showed minor increases in the rate of tooth movement which may not be considered clinically significant. They also noted that the available evidence for these non-surgical interventions is of very low quality and therefore it is not possible to determine if there is a clinically relevant positive effect on orthodontic tooth movement (9).

Possible surgical interventions for accelerating tooth movement include micro-osteoperforations, piezocision, corticotomies, osteotomies, periodontal ligament distraction as well as a ‘surgery-first’ approach (6). Another Cochrane review, also from 2015, assessed the effects of surgically assisted orthodontics on the duration and outcome of orthodontic treatment (10). The authors included four studies which used corticotomies as their adjunctive intervention.

Relatively faster tooth movement, but not necessarily clinically relevant, was found with this surgical procedure. However, the evidence was also of low quality and the outcomes were measured over a short period in a small number of participants.

2.1.2. Photobiomodulation

Photobiomodulation is a general term which refers to biological alterations in organisms caused by photon interaction at the cellular level (11). Low-level laser or low-level light therapy (both referred to as LLLT) encompasses many different types of therapies based on the principles of photobiomodulation. Despite its name, the source of light used in LLLT can be from lasers, light-emitting diodes (LEDs), and lamp or sun light filtered by monochromators (11). Almost all LLLT treatments use red or near-infrared light with a wavelength between 600 and 1100 nm, output power of 1–1000 mW, a non-heating energy density between 0.1 and 100 J/cm2 and exposure time of a few minutes (11, 12). There is a large number of parameters that influence the delivery of LLLT (such as wavelength, power density, pulse structure, and timing) and these parameters must be adapted to each patient since skin color, age, gender, amount of hair and state of the soft tissue influence the light absorption and scattering (11). LLLTs are non-invasive, as light can penetrate through soft tissues to reach the target organ, and have varied clinical applications in medicine and dentistry, namely stimulating wound healing, reducing pain and controlling inflammation (13).

LLLT remains controversial among researchers and clinicians mainly due to the poor understanding about the biologic mechanisms behind the intervention. The most widely accepted theory is that mitochondrial chromophores, mainly cytochrome c oxidase (CCO), are activated by the absorption of photons produced by the light source in LLLT, which in turn increases its proton pumping activity in the electron transport chain. This results in an increase in adenosine triphosphate (ATP) production, which increases the energy available to the cell and increases its metabolism (14). Activation of CCO by light also initiates multiple intracellular signaling cascades which result in cellular changes, ultimately resulting in an increase in ATP production in the mitochondria. The secondary effects of photon absorption include an increase in reactive oxygen species (ROS) and nitric oxide (NO) and a modulation of calcium levels within a target cell (12). ROS production may stimulate or suppress transcription factors and DNA/RNA synthesis (11, 14).The production of NO through absorption of photons by nitric oxide synthase increases regional blood flow and osteoclastic activity (14). LLLT has been shown to

significantly increase periodontal ligament (PDL) cell proliferation, decrease PDL cell inflammation, and increase PDL osteoclastic activity in-vitro (15).

LLLT promotes both anti-inflammatory effects by decreasing inflammatory mediators such as prostaglandin E2, leukocytes, and TNFα , and pro-inflammatory effects, by increasing both mRNA expression and the protein concentration of anti-inflammatory mediators, such as IL-10 and HSP72 (11, 12). Lower doses of LLLT tend to produce biostimulatory effects (such as stimulation of fibroblasts or osteoblast), whereas higher doses will tend to result in bioinhibitory effects (such as the reduction of inflammatory mediators) (11, 12). A bioinhibitory dose modulates inflammation and decreases pain following orthodontic appointments. A biostimulatory dose improves healing by stimulating the osteoblast/osteoclast turnover, which ultimately increases the rate of orthodontic tooth movement and reduces treatment time (11, 12).

The OrthoPulse® (Biolux Research Ltd, Fremont, CA, USA) is a device which uses the principles of photobiomodulation (Figure 1). It produces light using LEDs with a near infrared wavelength of 850 nm and an intensity of less than 100 mW/cm^2 continuous wave (16). The LEDs are arranged in arrays to cover the target area of the alveolus of both the maxilla and mandible. The device is accompanied by a smartphone application that tracks the patient's compliance when the patient synchronizes their device with the application. The manufacturer's recommended regimen is 10 minutes per day while in active treatment. It has been reported to reduce pain and increase the rate of orthodontic tooth movement without a significant increase in orthodontically induced external root resorption (OIERR) (17-20).

Figure 1. *OrthoPulse Device*

2.1.3. Orthodontically induced external root resorption

Orthodontic tooth movement involves a dynamic process of bone breakdown and bone healing in response to external forces. Bone is resorbed on the pressure side by osteoclasts and deposited on the tension side of a tooth by osteoblasts (21). Compression of the PDL, especially when using heavier forces, leads to sterile necrosis of the PDL tissues which is referred to as hyalinization (22). Cementum adjacent to hyalinized areas of the PDL are targeted by clast cells when the PDL is repaired. When cementum and dentin are removed from the root surface, they are replaced once orthodontic movement stops in the same manner as alveolar bone during tooth movement. This phenomenon is referred to as root remodeling and is found in all orthodontic treatment (21).

Permanent root resorption only occurs when the repair process fails to replace the resorbed cementum/dentin. When the resorption process produces large defects at the apex, islands of dentin and cementum are formed that eventually become separated from the root surface. Hence, root resorption is most likely to occur in the apical portion of the tooth (21).

An individual's risk of developing orthodontically induced external root resorption (OIERR) during orthodontic treatment may be influenced by both orthodontic and patient-related factors. A systematic review by Weltman *et al.* (23) revealed that treatment duration, magnitude of applied force, direction of tooth movement, amount of apical displacement and method of force application (continuous vs intermittent), type of appliance and treatment technique technique do influence to different degrees the chances of OIERR. Among these factors, both the total apical displacement and treatment duration have been strongly correlated with mean apical root resorption (5). This review also found multiple patient-specific risk factors including: previous history of root resorption, tooth-root morphology, root length, and roots with developmental abnormalities, genetic background, systemic factors including medications, hormone deficiency, hypothyroidism, hypopituitarism, asthma, root proximity to cortical bone, alveolar bone density, chronic alcoholism, previous trauma, endodontic treatment, severity and type of malocclusion, patient age and sex (23). It has to be noted that these factors present significantly different risk degrees.

Orthodontic tooth movement occurs because of a sterile inflammatory process, which involves osteoclasts and osteoblasts to achieve bone remodeling. It has been proposed that surgical and some non-surgical interventions to accelerate orthodontic tooth movement can act as

a stimulus to increase the activity of these bone forming and bone resorbing cells (13). This increased bone remodeling rate could potentially increase the rate of tooth movement, which may lead to an overall reduction in the duration of orthodontic treatment. However, a proposed mechanism for OIERR has been an increase in the osteoclastic activity present in the apical third of tooth roots (24), which is likely to occur during accelerated tooth movement. Therefore, the increase in osteoclastic activity may also be contributing to OIERR in orthodontic patients treated with these adjunctive interventions to accelerate orthodontic treatment time.

2.1.4. Cone-Beam Computed Tomography and OIERR

Periapical radiographs, panoramic radiographs and Cone Beam Computed Tomography (CBCT) may be used to evaluate root resorption during orthodontic treatment (25, 26). Histological sections (27-32), light microscope (33, 34), scanning electron microscope (35-37), laser scans (38, 39) and micro-computed tomography (40-43) have also been used to assess changes in root morphology. However, these modalities have not been used clinically as they require the extraction of the affected tooth. In recent years, CBCT has become the preferred method to evaluate root resorption in a clinical setting. Flores-Mir *et al* (44) compared CBCT panoramic reconstructions and conventional panoramic radiographs to the tooth lengths measured with a digital caliper in orthodontic patients requiring premolar extractions. The study revealed that, in comparison to actual tooth lengths, conventional panoramic radiographs overestimated the lengths by 29%, while CBCT panoramic reconstructions underestimated the lengths by only 4% (44). A study by Dudic *et al* (26) showed that, when compared to CBCT, OIERR after orthodontic tooth movement is underestimated when evaluated on conventional panoramic radiographs. Ponder *el al* (45) suggested that the mean absolute difference in linear quantification of root lengths from periapical radiographs compared with quantification by using digital calipers was highly variable and greater than 1 mm. This variability may be considered clinically significant as it can change the diagnosed severity of the root resorption and may alter the orthodontic treatment plan. In contrast, both high- and low-resolution CBCT scans were accurate when compared with digital caliper measurements and were not significantly different from each other in terms of accuracy. Therefore, CBCT may be considered as a more accurate and effective tool to measure OIERR compared to conventional 2D radiographs.

2.1.5. Objective

The existing two Cochrane reviews (which were published in 2015) on surgical and non-surgical interventions for accelerating tooth movement have focused solely on patients receiving orthodontic treatment with fixed appliances and have evaluated apical root resorption as one of their secondary outcomes (9, 10). Neither study provided conclusions about the effect of these interventions on OIERR.

This review covers an additional 5 years of potentially new data. This review will also consider patients who have undergone orthodontic treatment with either fixed appliances or clear aligner therapy. Barbagallo *et al* (46) found that clear aligners had similar resorptive effects on root cementum as light (25 g) orthodontic forces with fixed appliances. In addition, Iglesias-Linares *et al* (47) also suggested that the predisposition to experience OIERR with clear aligner therapy is similar to that of using fixed appliances after adjusting for the response based on genotype and radiographic and clinical data.

Hence, the purpose of this systematic review was to investigate the available scientific literature that evaluates changes in root morphology in orthodontic patients treated with adjunctive surgical and non-surgical interventions for accelerating tooth movement. The secondary objective was to examine the effects of specific interventions on the rate and severity of root resorption.

2.2. METHODS

2.2.1. Protocol and registration

This systematic review was written in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (48). The protocol for this review has been submitted to PROSPERO for registration (CRD42018100132). No similar review protocols were found.

2.2.2. Eligibility criteria

Types of studies: Randomized controlled trials (RCTs) reporting on any changes in root morphology in conjunction with accelerated orthodontic tooth movement were included. Observational cohorts, *in vitro* studies, animal studies, case reports, case series, editorials, opinions, reviews, and technique description articles were excluded. No restrictions were placed on year or publication status.

Types of participants: Healthy subjects of any age receiving orthodontic treatment with fixed appliances or clear aligner therapy with adjunctive use of any intervention to increase the rate of tooth movement. Studies that included patients who were treated with orthognathic surgery, participants with cleft lip or palate, or with other craniofacial syndromes or deformities, patients receiving any kind of medication which can affect orthodontic treatment or with any systemic disease were excluded. Studies which included subjects with any history of trauma, prior root resorption or prior endodontic treatment were also excluded.

Types of interventions:

- Active interventions: Any intervention used to accelerate orthodontic tooth movement. Approaches that are considered refinements of conventional orthodontic treatment, such as selection of brackets, wires, biomechanical systems, digital treatment planning, indirect bonding, force levels, and anchorage systems were not considered. Pharmacological, periodontal distraction and distraction osteogenesis techniques were excluded from this study.

- Control: Any form of fixed appliance or clear aligner orthodontic treatment without the use of adjunctive interventions for accelerating orthodontic tooth movement. Studies which compared patients receiving an alternative accelerating intervention, different accelerating regimens or application techniques (i.e. laser irradiation regimens, corticotomy techniques etc.) were also considered.

Types of outcome measures: The primary collected outcome measure was the presence or absence of OIERR in the intervention group at the end of the treatment period. Secondary outcomes (severity and extent of the root resorption) between experimental and control groups assessed using any technique were also considered. This is usually determined in terms of the difference before and after orthodontic treatment in tooth root length in millimeters or volume in mm^3.

2.2.3. Information sources and search

Two independent reviewers performed electronic searches in the following databases: PubMed, MEDLINE via OvidSP, EMBASE via OvidSP, The Cochrane Library, Scopus, Web of Science and LILACS. A partial hand search of gray literature on OpenGrey, Google Scholar, ProQuest Central and the reference lists of selected articles were completed to add any references

that could have been missed during the electronic database searches. The following databases were searched to identify ongoing trials: US National Institutes of Health Register (ClinicalTrials.gov) and World Health Organization International Clinical Trials Registry Platform Search Portal (ICTRP) and metaRegister of Controlled Trials (mRCT). The search strategies are presented in Appendix 1. The database searches were updated until 15 February 2020. EndNote X9.3® (Thomson Reuters, New York, NY, USA) software was used to remove duplicates. Corresponding authors were contacted when additional or missing information on methods or results was needed.

2.2.4. Study selection

Two reviewers independently assessed the titles and abstracts of studies identified through the searches. All studies that did not meet the inclusion criteria were excluded. Full-text copies were then obtained for all studies which met the inclusion criteria and for those which there were insufficient data in the title and abstract. Two review authors assessed the full-text papers independently and selected the studies that fulfilled all inclusion criteria. Any discrepancies were reconciled by discussion between the two review authors or by the introduction of a third review author.

2.2.5. Data collection process and data items

Data extraction forms were created, and the following study characteristics were recorded independently by two review authors for all included studies: study characteristics, sample characteristics, observer's characteristics, characteristics of assessment methods (method used to determine root resorption) and main outcome data/results. Any discrepancies between both review authors were resolved by discussion or the introduction of a third review author.

2.2.6. Risk of bias in individual studies

The quality of all articles selected for inclusion was performed using the Cochrane Risk of bias tool for randomized controlled trials (RCTs) (49). The assessment was performed by two review authors independently. Any discrepancies between both review authors were resolved by discussion or the introduction of a third review author. The following domains were assessed as being at low, high or some concerns of risk of bias:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);

- blinding of outcome assessors (detection bias);
- incomplete outcome data addressed (attrition bias);
- selective outcome reporting (reporting bias);
- other bias.

The overall risk of bias of each included RCT was categorized and reported according to the following:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were assessed at low risk of bias;
- some concerns of risk of bias (plausible bias that raises some doubt about the results) if one or more domains were assessed as having some concerns of risk of bias; or
- high risk of bias (plausible bias that seriously weakens confidence in the results), if one or more domains were assessed at high risk of bias.

2.2.7. Summary measures

When possible for pooled data, mean differences with 95% confidence intervals were calculated for continuous data, and risk ratios (RR) with 95% CI for dichotomous data. In studies which reported a percentage of change and decrease in millimeters, a standardized mean difference (SMD) was used. In studies where data were unclear or missing, corresponding authors were contacted for original data.

2.2.8. Synthesis of results

Heterogeneity of included RCTs was evaluated by examining the characteristics of the studies and the similarity between the types of participants, the interventions, the outcomes, the data collection and the measurement techniques. A meta-analysis was not justified due to the wide variation in study methodology, study design outcome reporting and method used to measure root resorption.

2.2.9. Risk of bias across studies

Following the quality assessment of individual articles, each one was assigned to a group according to the adjunctive intervention used. For each intervention, the overall strength of the body of evidence was assessed using the GRADE approach (50).

2.2.10. Additional Analyses

Not applicable as a meta-analysis was not justified.

2.3. RESULTS

2.3.1. Study selection

A total of 4512 articles were initially identified through the search of electronic databases. A flowchart illustrating the selection of studies for this systematic review is presented in Figure 2. After removal of duplicate records and screening of title and available abstracts, 38 studies were considered for full-text reading. Three additional articles were included following hand search of the references of the full-text articles. After reading the full text of all selected articles, 20 articles (8, 17, 51-69) met the eligibility criteria and the characteristics of these studies can be found in Table 1. The 18 studies (29, 69-85) which were excluded during the last search phase can be found in Appendix 2. No articles were excluded based on language of publication.

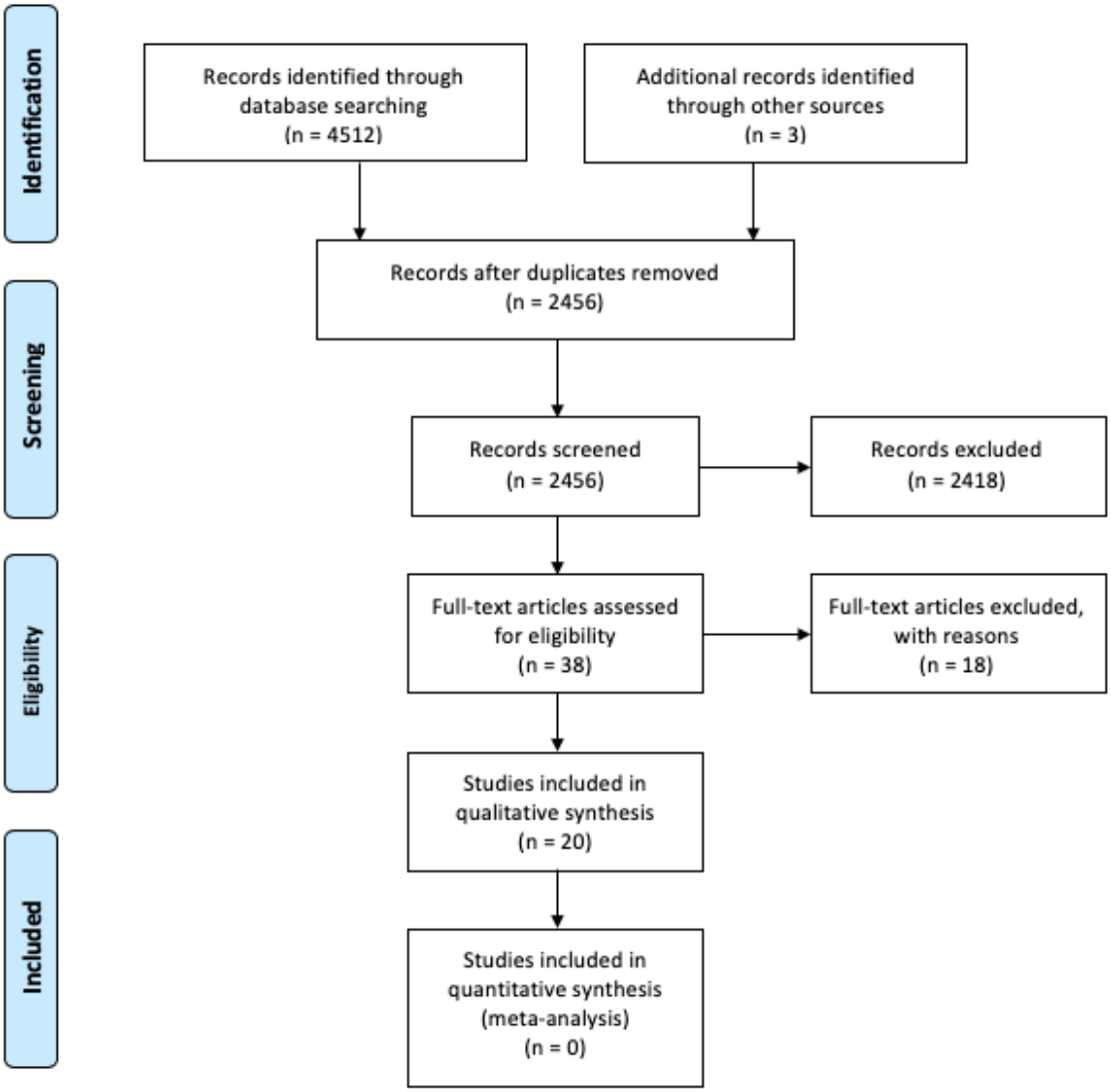

Figure 2. *PRISMA Flowchart of the study selection process*

2.3.2. Study characteristics

The characteristics of included and excluded studies can be found in Table 1 and Appendix 2, respectively. All included studies had a randomized controlled clinical trial (RCT) study design. Almost all studies took place in a university clinic setting. Ten of the included studies had a split-mouth study design (8, 52-56, 61-63, 66). Corticotomies by surgical bur (51, 58, 59, 86), corticotomies by piezocision (57, 65, 66, 86), microvibration (53, 60), low-level laser therapy (17, 54, 56, 63, 67), low intensity pulsed ultrasound (8, 55), micro-osteoperforations (52, 61, 62, 64, 66) and photobiomodulation (17, 67) were the adjunctive interventions which were discussed in the 20 studies included in this review. A total of 541 participants, including controls, were involved in the 20 studies. Five studies did not report the ratio between male and female participants (17, 62, 66, 68, 86). While most of the selected studies were composed of both adolescent and adult patients, six studies recruited only adult patients (51, 57-59, 65, 86). All studies which met the inclusion criteria only considered patients undergoing orthodontic treatment with fixed appliances.

2.3.3. Risk of bias within studies

As shown in Figure 3, all included studies were assessed for risk of bias using the Cochrane Risk of Bias Tool version 2.0 (87). From the 20 RCTs included, six studies were assessed as having an overall low risk of bias (52, 57, 63-65, 68). Eight studies were assessed as having some concerns about risk of bias (8, 53-55, 62, 66, 67, 86) and six as having an overall high risk of bias (17, 51, 58-61). Further details of these assessments are given in the risk of bias table corresponding to each study in Appendix 3.

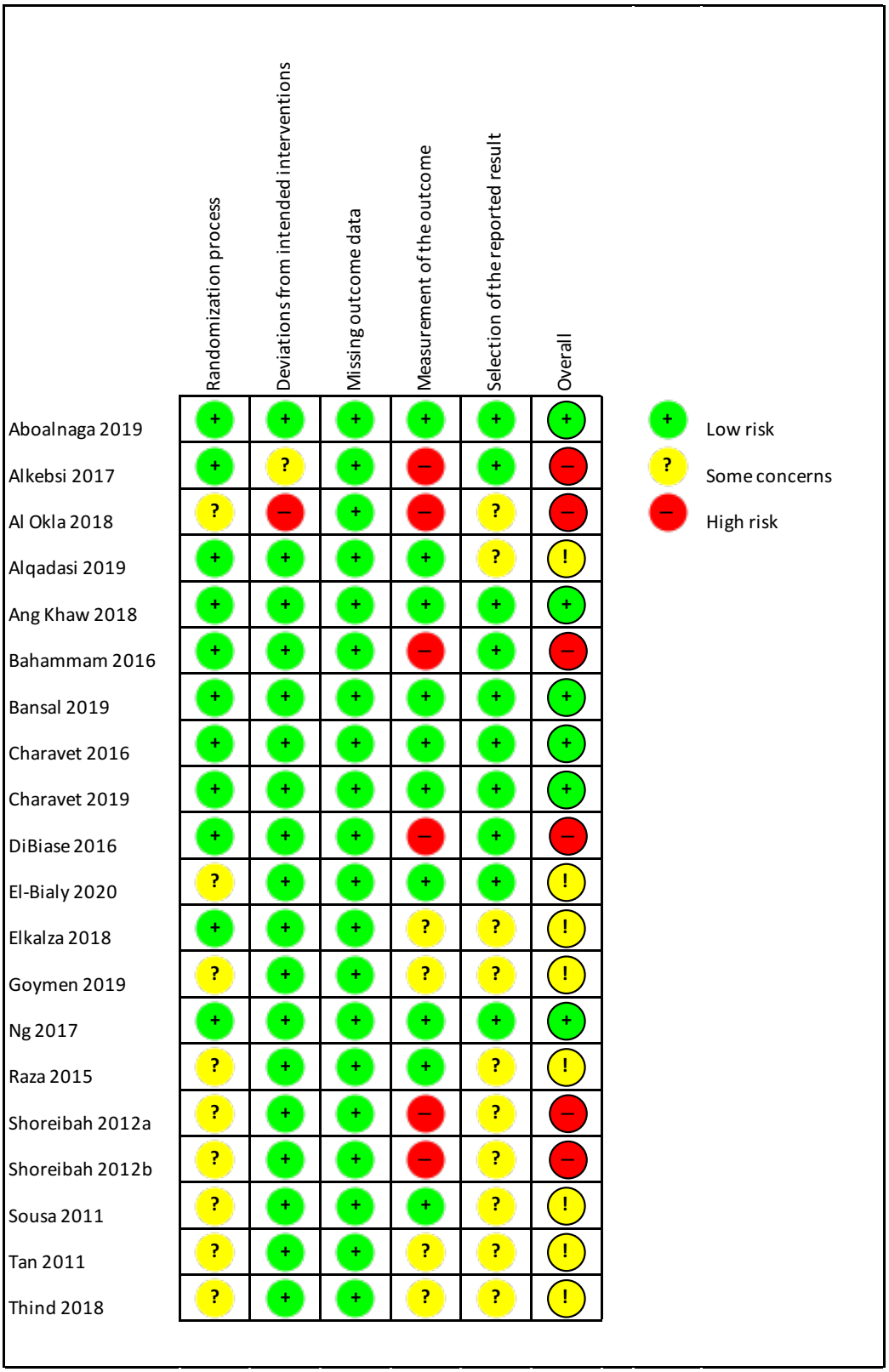

Figure 3. *Risk of bias summary: review authors' judgements about each risk of bias item for each included study*

2.3.4. Results of individual studies

A summary of the included studies and their findings is provided in Table 1.

Study	Intervention	Study Design	Study Setting, Country	No. of centers	Sample Size (M/F)	Patient Age (years)
Aboalnaga 2019	MOPs	RCT, Split mouth	University, Egypt	1	18 (0/18)	16-30
Alkebsi 2018	MOPs	RCT, Split mouth	University, Jordan	1	32 (8/24)	16-24
Al Okla 2018	LLLT	RCT	University, United Arab Emirates	1	Grp1: 17 (?/?) Grp2: 21 (?/?)	11-39
Alqadasi 2019	MOPs	RCT, Split mouth	University, China	1	8 (?/?)	15-40
Ang Khaw 2018	LLLT	RCT, Split mouth	University, Australia	1	20 (8/12)	15-18
Bahammam 2016	Corticotomy by surgical bur	RCT	University, Saudi Arabia	1	Grp1: 11 (4/7) Grp2: 11 (5/6) Grp3: 11 (4/7)	18-27
Bansal 2019	MOPs	RCT	University, India	1	Grp1: 15 (7/8) Grp2: 15 (7/8)	14-19
Charavet 2016	Corticotomy by piezocision	RCT	University, Belgium	1	Grp1: 12 (5/7) Grp2: 12 (4/8)	Grp1: 34 ± 8 Grp2: 27 ± 7 (mean ± SD)
Charavet 2019	Corticotomy by piezocision	RCT	University, Belgium	1	Grp1: 12 (5/7) Grp2: 12 (4/8)	Grp1: 29 ± 8 Grp2: 27 ± 7 (mean ± SD)
DiBiase 2016	Microvibration	RCT	University, United Kingdon	3	Grp1: 27 (14/13) Grp2: 22 (11/11) Grp3: 23 (11/12)	12-19
El-Bialy 2020	LIPUS	RCT, Split mouth	University and private clinic, Egypt/Canada	5	Grp1: 21 (5/16) Grp2: 10 (?/?)	12-37
Elkalza 2018	MOPs + corticotomy by piezocision	RCT, Split mouth	University, Egypt	1	Grp1: 8 (?/?) Grp2: 8 (?/?)	16-25
Goymen 2019	LLLT	RCT	University, Turkey	1	Grp1: 10 (4/6) Grp2: 10 (5/5) Grp3: 10 (5/5)	15-18
Ng 2017	LLLT	RCT, Split mouth	University, Australia	1	Grp1: 10 (?/?) Grp2: 10 (?/?) Grp3: 20 (?/?)	mean males 16.4 ± 1.3, females 16.7 ± 1.1
Raza 2015	LIPUS	RCT, Split mouth	University, Canada	1	10 (2/8)	Mean 15.5 ± 5.48
Shoreibah 2012a	Corticotomy by surgical bur	RCT	University, Egypt	1	Grp1: 10 (?/?) Grp2: 10 (?/?) Total: 20 (3/17)	18.4 to 25.6

Shoreibah 2012b	Corticotomy by surgical bur	RCT	University, Egypt	1	Grp1: 10 (?/?) Grp2: 10 (?/?) Total: 20 (4/16)	Mean 24.5
Sousa 2011	LLLT	RCT, Split mouth	University, Brazil	1	10 (6/4)	10.5–20.2
Tan 2011	Microvibration	RCT, Split mouth	University, Australia	1	15 (6/9)	Not reported
Thind 2018	Corticotomy by surgical bur + corticotomy by piezocision	RCT	University, India	1	Grp1: 20 (?/?) Grp2: 20 (?/?)	20-40

Study	Study Arms	Treatment Duration	Teeth Evaluated for OIERR	OIERR Assessment Method	OIERR Measurement Method (Outcome)	OIERR Findings
Aboalnaga 2019	Intervention Side: Miniscrew assisted Mx canine retraction with FA + MOPs Comparator side: Miniscrew assisted Mx canine retraction with FA	4 months	Maxillary canine	CBCT	Malmgren classification	No difference between groups
Alkebsi 2018	Intervention Side: Miniscrew assisted Mx canine retraction with FA + MOPs Comparator side: Miniscrew assisted Mx canine retraction with FA	3 months	Maxillary canine	PA	Root length (from midpoint of the cementoenamel junction to root apex)	No difference between groups
Al Okla 2018	Grp 1 (intervention): comprehensive treatment with FA + OrthoPulse device Grp 2 (comparator): comprehensive orthodontics with FA + sham OrthoPulse device	6 months ± 2 weeks	Maxillary central incisor	PA	Change in root length (from the gingival edge of the orthodontic bracket to root apex)	No difference between groups
Alqadasi 2019	Intervention Side: Miniscrew assisted Mx canine retraction with FA + MOPs	3 months	Maxillary canine	CBCT	Tooth length (from crown tip to root apex)	No difference between groups

	Comparator side: Miniscrew assisted Mx canine retraction with FA					
Ang Khaw 2018	Intervention Side: 4 weeks of buccal tipping force on Mx 1st premolar with FA, 6 weeks retention period with weekly sessions of laser and then extraction of 1st premolar Comparator side: 4 weeks of buccal tipping force on Mx 1st premolar with FA, 6 weeks retention period with weekly sham laser sessions and then extraction of 1st premolar	1 month	Maxillary First Premolar	micro-CT	Change in root volume (Root resorption craters)	No difference between groups
Bahammam 2016	Grp1 (comparator): Comprehensive orthodontic treatment with FA + modified technique of corticotomy alone Grp2 (intervention): Comprehensive orthodontic treatment with FA + corticotomy combined with a bovine-derived xenograft Grp3 (intervention): Comprehensive orthodontic treatment with FA + corticotomy combined with bioactive glass	3 to 5 months	Mandibular centrals and laterals	PA	Root length (from the cemento-enamel junction and root apex)	No difference between groups
Bansal 2019	Group 1 (intervention): COT with FA + MOPs in mandibular incisor	6 months	Mandibular centrals and laterals	CBCT	Root volume (from CEJ to root apex)	No difference between groups

	region Group 2 (comparator): COT with FA					
Charavet 2016	Group 1 (intervention): COT with FA + corticotomy by piezocision in maxillary and mandibular incisor region Group 2 (comparator): COT with FA	Grp1: mean ~310 days Grp2: mean ~540 days (Raw data not reported, only shown in figures)	Maxillary and mandibular central, lateral and canine	Medical CT	Malmgren classification	No difference between groups
Charavet 2019	Grp 1 (intervention): COT with customized FA + corticotomy by piezocision in maxillary and mandibular incisor region Grp 2 (comparator): COT with customized FA	Grp1: 278 ± 80.2 Grp2: 393 ± 55.7 (mean ± SD)	Maxillary and mandibular central, lateral and canine	CBCT	Malmgren classification	No difference between groups
DiBiase 2016	Grp1 (Intervention): COT (extraction plan) with adjunctive daily use of a functional Acceledent vibrational device Grp2 (Intervention): COT (extraction plan) with adjunctive use of a nonfunctional (sham) AcceleDent device Group 3 (Comparator): COT (extraction plan) alone	Mean 201.6 days (95% CI, 188.6-214.6 days)	maxillary right central incisor	PA	Change in root length (root length at T1 (R1) minus root length at T3 (R3), multiplied by the correction factor (C1/C3). A correction factor was calculated by dividing crown length at T1 (C1) by crown length at T3 (C3)	No difference between groups
El-Bialy 2020	Grp1 (Intervention): COT (premolar extraction plan) with T-loop space closure and adjunctive daily	Reported as "24 weeks or until the closure of the extraction space on	Maxillary and mandibular canine	CBCT	Weekly change in linear root length	Less OIERR in LIPUS group

	use of LIPUS device (Aevo) activated on one side (randomly selected) Grp2 (Comparator): COT (premolar extraction plan) with T-loop space closure	either side, whichever period was shorter"				
Elkalza 2018	Grp1 (Intervention): Miniscrew assisted Mx canine retraction with FA + MOPs on one side (randomly selected) Grp 2 (Comparator): Miniscrew assisted Mx canine retraction with FA + corticotomy by piezocision on one side (randomly selected)	Not reported	Maxillary canine	CBCT	Tooth length (from crown tip to root apex)	More OIERR in piezocision group compared to MOPs group and control group
Goymen 2019	Grp1 (Intervention 1): 4 weeks of buccal tipping force on Mx 1st premolar with FA then extraction + diode laser application at 0, 3, 7, 14, 21, and 28 days Grp2 (Intervention 2): 4 weeks of buccal tipping force on Mx 1st premolar with FA then extraction + daily LED light application Grp3 (Comparator): 4 weeks of buccal tipping force on Mx 1st premolar with FA then extraction + sham laser device	1 month	Maxillary First Premolar	Micro-CT	Total volume of resorption craters (change in root volume)	No difference between groups

Ng 2017	Grp1 (Intervention 1): 4 weeks of buccal tipping force on Mx 1st premolar with FA then extraction + LLLT continuous laser diode application Grp2 (Intervention 2): 4 weeks of buccal tipping force on Mx 1st premolar with FA then extraction + LLLT pulsed laser diode application Grp3 (Comparator): 4 weeks of buccal tipping force on Mx 1st premolar with FA then extraction + sham laser diode application	28 days	Maxillary First Premolar	Micro-CT	Total volume of resorption craters (change in root volume)	Less OIERR in LLLT groups compared to controls No difference between pulsed and continuous LLT groups
Raza 2015	Intervention Side: Mx canine retraction with FA + LIPUS on one side (randomly selected) Comparator Side : Mx canine retraction with FA only	28 days	Maxillary First Premolar	Micro-CT	Total volume of resorption craters (change in root volume)	Less OIERR in LIPUS group
Shoreibah 2012a	Grp1 (Invention): Non-extraction COT with FA + modified corticotomy technique with bone grafting Grp2 (Comparator): Non-extraction COT with FA alone	14-20 weeks	Mandibular centrals and laterals	PA	Change in root length (from the cemento-enamel junction and root apex)	Less OIERR in the corticotomy group
Shoreibah 2012b	Grp1 (Invention): Non-extraction COT with FA + modified corticotomy technique with bone grafting Grp2	14-20 weeks	Mandibular centrals and laterals	PA	Root length (from the cemento-enamel junction and root apex)	No difference between groups

	(Comparator): Non-extraction COT with FA + modified corticotomy technique (No grafting)					
Sousa 2011	Intervention Side: Segmental Mx or Md canine retraction with FA + LLT on one side (randomly selected) Comparator Side : Segmental Mx or Md canine retraction with FA only	4 months	Maxillary and Mandibular canines	PA	Malmgren classification	No difference between groups
Tan 2011	Intervention side: 4 weeks of buccal tipping force on Mx 1st premolar with FA then extraction + vibration device on one side of the mouth (randomly assigned) Comparator side: 4 weeks of buccal tipping force on Mx 1st premolar with FA then extraction	1 month	Maxillary first premolar	Micro-CT	Total volume of resorption craters (change in root volume)	No difference between groups
Thind 2018	Grp1 (Invention): COT with FA (premolar extraction plan) + corticotomy with surgical bur Grp2 (Comparator): COT with FA (premolar extraction plan) + corticotomy with piezocision	12 months	Maxillary and mandibular central incisor, lateral incisor and canine	CBCT	Tooth length (from crown tip to root apex)	No difference between groups

Table 1. *Characteristics and results of included studies*

2.3.5. Synthesis of results

Due to considerable heterogeneity in methodology used to quantify root resorption, variations in study design and duration of the included studies, a meta-analysis was not

considered appropriate. Instead, a qualitative synthesis of included studies was undertaken. The included studies were categorized according to the adjunctive intervention used for accelerating orthodontic tooth movement.

Corticotomy by surgical bur

Four studies investigated the effect of corticotomies by surgical bur on OIERR (51, 58, 59, 86). Bahammam *et al* (51) compared the effectiveness of corticotomies in conjunction with bovine-derived xenograft, bioactive glass or no grafting material for the treatment of 33 randomly assigned patients with moderate dental crowding. No control group was used in this study. Selective alveolar decortication was performed using a small round surgical bur in the form of vertical grooves through the labial cortical plate and orthodontic tooth movement was initiated 2 weeks after the corticotomy procedure. The authors measured root length with a standardized digital periapical radiograph of the mandibular right canine to the mandibular left canine. The root length was assessed by measuring the distance between the cemento-enamel junction and the apex of the root in millimeters. They showed that there was no significant difference in the mean root length pre-treatment, post-treatment, and 9 months post-treatment between the groups treated with no grafting material (group 1), bovine-derived xenograft (group 2) or bioactive glass (group 3). They also reported that the mean difference in root length, assumed to be root resorption, was not statistically significant at 9 months post-treatment when compared to pre-treatment values (-0.02 ± 0.02 mm in group 1, -0.03 ± 0.11 mm group 2, and -0.01 ± 0.01 mm in group 3).

Shoreibah *et al* performed two studies with similar protocols to one another but with different samples (58, 59). In both studies, selective alveolar decortication was performed by making vertical grooves through the labial cortical plate of bone between the roots of the mandibular incisors, laterals and mesial aspect of canines using a small round surgical bur. Orthodontic tooth movement was initiated immediately after the corticotomy was performed. Their results were recorded at three time points: on the day the corticotomy was performed, immediately post orthodontic treatment and six months post-treatment. Periapical radiographs were used to measure the distance between the cemento-enamel junction to the apex of the root. It is unclear if these were standardized radiographs. One study (59) consisted of a sample of 20 patients which were randomly assigned to receive a modified corticotomy technique with bone grafting or conventional orthodontic treatment. At 6 months post-orthodontic treatment, this

study found that the control group had a statistically significantly higher mean percent decrease in root length than the group which received corticotomies ($P < 0.001$) The corticotomy group experienced an average decrease in root length of 1.5 ± 0.9 mm, while the control group demonstrated an average net decrease in root length of 1.7 ± 9.5 mm. A second study (58) consisted of a sample of 20 patients which were randomly assigned to receive either a modified corticotomy technique (Group I) or a modified corticotomy technique with bone grafting (Group II). No control group was present in this study. At 6 months post-orthodontic treatment, Group I demonstrated an average net decrease in root length of -0.056 mm ± 0.025, while Group II demonstrated an average net decrease in root length of -0.050 mm ± 0.026 ($P=0.625$). This study found that there were no significant differences in the mean change in root length between time intervals in either group.

Thind *et al* (86) compared corticotomies by piezocision to corticotomies by surgical bur in patients treated with fixed appliances requiring extraction of all first premolars. In the group which received corticotomies with a surgical bur (group 1), a full thickness flap was reflected in both arches between the first premolar extraction sites and vertical grooves were placed in the interradicular area. In the group of patients which received corticotomies by piezocision (group 2), a similar protocol was used except the vertical grooves were performed with a piezo surgical knife. Each group had 20 patients assigned. OIERR was assessed by comparing measurements of whole tooth length obtained from CBCT at baseline and at 12 months following initiation of treatment. A statistically significant decrease in mean post-treatment tooth length was found in both the maxilla and mandible region in both groups ($P < 0.001$). The mean differences in root length were small (0.45 to 0.736mm) and not clinically significant. The authors did not perform a statistical analysis to compare the OIERR between the different interventions. However, the mean differences in root length in the maxilla and mandible in group 1 were both less than those found in group 2, indicating that there may be less OIERR with corticotomy by surgical bur. Nonetheless, the differences in OIERR between the interventions is small and unlikely to be clinically significant.

Corticotomy by piezocision

Four studies investigated the effect of corticotomies by piezocision on OIERR (57, 65, 66, 86). Charavet *et al* (57) evaluated the clinical outcomes of piezocision, which is a minimally invasive approach to corticotomy without bone grafting or sutures, in a group of 24 patients

presenting with mild dental crowding. Patients were randomly allocated to the piezocision group or a control group. The piezocision surgery was performed one week after orthodontic appliance placement and utilized a vertical piezoelectric device to make vertical corticotomies between each tooth in the maxilla and mandible. The authors used medical computed tomography to classify teeth based on the Malmgren classification (88), an index for qualitative assessment of root resorption. The number of teeth measured was unclear. However, they reported that there was no statistically significant increase in the Malmgren score observed in either group (0.91 ± 1.10 in the piezocision group and 0.46 ± 0.93 in the control group, $p = 0.21$). Given the Malmgren classification, these results indicate that almost all teeth experienced less than 2mm of root resorption in both groups. A second study by Charavet *et al* (65) used a very similar study protocol to compare patients treated with customized fixed appliances and corticotomies by piezocision to patients treated with customized fixed appliances alone. Corticotomies were performed in the interradicular area between the maxillary and mandibular teeth from canine to canine. The authors used CBCT imaging to assess OIERR in all teeth according to the Malmgren classification. Again, they reported that there was no statistically significant increase in the Malmgren score observed in either group (0.42 ± 1.0 in the piezocision group and 0.42 ± 1.2 in the control group, $p = 1.0$).

Elkalza *et al* (66) performed a split mouth study to compare OIERR following the application of micro-osteoperforations (MOPs) and corticotomy by piezocision in patients treated with fixed appliances and maxillary first premolar extractions. Canine retraction was undertaken with miniscrews for additional anchorage. 16 patients were randomized into two groups. In group 1, three MOPs were performed distal to the maxillary canine on the experimental side (randomly selected), while the control side received no intervention. In the second group, a piezo surgical knife was used to create vertical cortical bone incisions through a gingival opening mesial and distal to the maxillary canines on the experimental side while the canine on the opposite side served as control. The length of the maxillary canine was measured from CBCT taken before and after canine retraction. No significant differences in mean tooth length were found between the MOPs intervention group and the MOPs control group after canine retraction ($p = 0.422$). Mean canine root length in the piezocision intervention group was less than canine root length in the piezocision control group following canine retraction ($p = 0.033$). Given that this finding was statistically significant, piezocision may be responsible for an

increase in OIERR. Mean canine tooth length in the MOPs intervention group was significantly greater than the mean canine tooth length in the piezocision intervention group after canine retraction (P = 0.001). This further supports the notion that piezocision may have a deleterious effect on OIERR.

As described previously, Thind *et al* (86) compared corticotomies by piezocision to corticotomies by surgical bur and found that there was decrease in mean post-treatment tooth length in both groups. While this confirmed that some OIERR occurred during treatment, no evaluation of OIERR between the intervention groups was performed.

Microvibration

Two of the included studies examined the effect of microvibrations on OIERR (53, 60). DiBiase *et al* (60) investigated the effect of a vibrational device on orthodontically induced root resorption in 81 patients with mandibular incisor crowding undergoing extraction-based treatment. In this study, patients were randomly allocated to use of an intraoral vibrational device or an identical nonfunctional (sham) device for 20 minutes a day. They also included a control group of patients with fixed appliances only. The authors measured root resorption using non-standardized long-cone periapical radiographs taken at the start of treatment (T1) and at the end of alignment on insertion of a 0.019x0.025in stainless steel archwire (T3). Apical root resorption was measured in millimeters at the maxillary right central incisor using a formula which helps account for magnification differences between the radiographs at different time points. They reported that the use of a vibrational force device during the alignment phase of fixed appliance treatment did not have a significant effect on OIERR compared to either the sham or control groups. They also found that levels of OIERR were similar in each group. They noted that both the levels of OIERR and the proportion of patients with severe OIERR (>2mm) were in agreement with previously published studies. In addition, they reported that the OIERR measured at the maxillary central incisor was not significantly influenced by the patients' age or sex, initial root length, history of dentoalveolar trauma during treatment, relative duration of the alignment phase, or pain experienced during this phase.

Tan *et al* (53) explored the effects of the same vibrational device on OIERR. However, the authors employed a split-mouth study design by modifying the device in a way which it only vibrated on one side of the mouth. Fifteen patients requiring maxillary first premolar extractions were recruited. One side of their mouth was randomized to the use of the vibrational device for

20 minutes per day for 4 weeks. The other side served as a control. A buccally directed force was applied to the first premolars using brackets and wires throughout the study period. After four weeks, the upper first premolars were extracted, and volumetric measurements of the root resorption craters were obtained from micro-computer tomography (Micro-CT). The mean total amount of root resorption was 0.1085 mm^3 in the vibration group premolars and 0.095 mm^3 in the non-vibration group premolars. The difference in root resorption volume was not found to be statistically significant (p=0.67).

Low-level Laser Therapy (LLLT)

Four studies explored the effect of low-level laser therapy on OIERR (54, 56, 63, 67). Ang Khaw *et al* (63) performed a split-mouth study on 20 patients who required bilateral maxillary first premolar extractions during orthodontic treatment. The premolar on one side was randomly assigned to receive LLLT or placebo-laser (sham), while the other premolar was assigned to the other group. A 660-nm, 75-mW aluminum-gallium-indium-phosphorus laser was used with 8 points of contact application. A total of 6 weekly sessions of LLLT were performed on the premolar on the intervention side. All premolars were tipped buccally using fixed appliances to induce root resorption for 4 weeks, followed by 6 weeks of retention with a fixed retainer. The premolars were then extracted and scanned using Micro-CT. OIERR was measured by calculating the total volume of the resorption craters present on the tooth root. The LLLT group and the placebo-laser groups were found to have total crater volumes of 0.746 mm^3 and 0.779 mm^3, respectively. No statistically significant difference was found between the two groups (P = 0.705).

Goymen *et al* (67) randomly assigned 30 patients requiring orthodontic treatment with an indication for right maxillary first premolar extraction into 3 groups. Group 1 received laser application with an 810nm GaAlAs laser device at 0, 3, 7, 14, 21, and 28 days, Group 2 received LED light application with a wavelength of 850nm using a photobiomodulation device for 10 minutes per day during the study and Group 3 received a placebo laser treatment delivery by a laser device with a sham function. All premolars were tipped buccally using fixed appliances during the 28-day study period to induce root resorption and then subsequently extracted. The amount of OIERR was recorded using micro-CT by calculating the total volume of all resorption craters. The total crater volumes were 0.42 ± 0.07 mm^3 for Group 1, 0.25 ± 0.03 mm^3 for Group

2, and 0.40 ± 0.06 mm^3 for Group 3 (p = 0.099). Therefore, no significant difference in OIERR was found between the groups.

Ng *et al* (56) recruited a sample of 20 adolescent patients who required bilateral maxillary first premolar extractions during orthodontic treatment. Using a split mouth study design, they randomly assigned one premolar to receive LLLT and the other premolar received a placebo-laser (sham) treatment on days 0, 1, 2, 3, 7, 14, and 21 of orthodontic treatment. They also further subdivided the group which received LLLT into two groups: 10 premolars received LLLT by continuous delivery and 10 received pulsed delivery. An 808-nm diode laser was used in this study. All premolars were tipped buccally using fixed appliances during the 28-day study period to induce root resorption. The teeth were then extracted immediately and were individually scanned from the cementoenamel junction (CEJ) to the root apex by micro-CT. The total root resorption crater volume was recorded for each tooth. The mean total volume of root resorption craters per tooth was found to be 0.381 mm^3 for the LLLT teeth and 0.495 mm^3 for the placebo teeth. Therefore, the LLLT treatment produced an average of 0.114 mm^3 (23%) less root resorption than the placebo. This difference was statistically significant (P = 0.026). The pulsed laser group had 5% less root resorption than the continuous laser group, but this was not statistically significant (P = 0.823).

Sousa *et al* (54) also studied the effect of LLLT on OIERR. They used a split-mouth study design in the sample of 10 patients. They randomly assigned either maxillary or mandibular canine to the laser group, which was irradiated with a 780nm aluminum-gallium-arsenide (AsGaAl) laser for 3 days, or the control group (CG), which was not irradiated. In total, 26 mandibular or maxillary canines were evaluated, 13 laser irradiated and 13 non-irradiated (placebo). Patients were followed up for 4 months, and nine laser applications were performed (three each month). Periapical radiographs were used to assess root resorption according to the Malmgren classification (88). It is unclear if these radiographs were standardized. They found no statistically significant difference in the resorption of the canine roots between the laser-irradiated and non-irradiated groups (P=0.592).

Low-Intensity Pulsed Ultrasound (LIPUS)

Two studies investigated the effect of low intensity pulsed ultrasound on OIERR (8, 55). El-Bialy *et al* (8) evaluated a group of 31 patients who underwent conventional orthodontic treatment requiring extraction of all first premolars. A split-mouth study design was used, and 21

patients were given a LIPUS device that was randomly assigned to function on the right or left side of the corresponding arch. The contralateral premolar was used as a positive control. The device contained transducers that produce ultrasound with a pulse frequency of 1.5 MHz, a pulse repetition rate of 1 kHz, and average output intensity of 30 mW/cm. Ten additional patients were included to act as a negative control group with no use of the LIPUS device. Once the premolars were extracted, T-loop space closure was performed with adjunctive daily use of the LIPUS device. The rate of linear OIERR on the maxillary and mandibular canine was determined from CBCT images taken before and after approximately 24 weeks of treatment. The rate of OIERR was found to be similar between the positive and negative control groups ($p = 0.32$). Therefore, no crossover effects of the LIPUS were detected. The mean rate of OIERR for the LIPUS side was decreased compared to the positive control side (0.0092 ± 0.0226 mm/week and 0.0241 ± 0.0223 mm/week, respectively). This difference was considered statistically significant ($p < 0.05$).

Raza *et al* (55) also studied the effect of low-intensity pulsed ultrasound (LIPUS) on OIERR. The authors also used a split mouth design in a sample of 10 patients who required extraction of all four first premolars as part of their orthodontic treatment. One side of the arch received LIPUS for 20 minutes per day and the other side received a sham ultrasound transducer, serving as a self-control. Buccal root torque was applied to the premolars using fixed appliances. After 4 weeks, all first premolars were extracted and scanned using micro–CT. They found less total volume of resorption lacunae and percentage of root resorption in LIPUS-treated teeth compared to control teeth (mean differences of 0.54 ± 0.09 mm^3 and 0.33 ± 0.05 mm^3, respectively). These finding were statistically significant ($P < .001$). Significantly fewer resorption lacunae were also found on all root surfaces in the LIPUS group compared to the control except on the distal surfaces of the teeth.

Micro-osteoperforations (MOPs)

Five studies discussed the effect of micro-osteoperforations on OIERR (52, 61, 62, 64, 66). Aboalnaga *et al* (52) undertook a split-mouth study with 18 patients who required canine retraction with maximum anchorage following maxillary first premolar extraction as part of conventional orthodontic treatment with fixed appliances. Prior to canine retraction, three MOPs were randomly allocated to either the patient's right or left side, and the contralateral canine served as a control. Canine retraction lasted for 4 months. OIERR was described using the

Malmgren classification according to pre- and post-retraction CBCT imaging of the maxilla. No differences were found between the pre- and post-retraction canine root resorption scores in the control and MOP groups ($P > 0.05$).

Alkebsi *et al* (61) also used MOPS to accelerate orthodontic treatment in a group of 32 who required canine retraction with maximum anchorage following maxillary first premolar extraction as part of conventional orthodontic treatment with fixed appliances. Three MOPs were performed using miniscrews on the buccal bone distal to the maxillary canines on a randomly selected side. OIERR was measured from standardized periapical radiographs taken at baseline and after 3 months of canine retraction. OIERR was determined as the difference between root length from the root apex to the midpoint of the cementoenamel junction. A statistically significant amount of OIERR after 3 months of treatment was found in both the MOPs (0.61mm, $P = 0.013$) and the control groups (0.73 mm, $P = 0.004$), proving that OIERR occurred in both groups. However, there was no statistically significant difference between the control and MOP sides at baseline ($P = 0.59$) and after 3 months ($P = 0.48$).

Alqadasi *et al* (62) used a similar protocol to study MOPs in a group of 8 patients who required canine retraction with maximum anchorage supported by miniscrews following maxillary first premolar extraction. Three MOPs were randomly allocated to either the right or the left side and was performed on the buccal bone distal to the maxillary canine, with a perforation width of 1.5–2 mm width and depth of 5–7 mm. The contralateral premolar was used as a control. CBCT imaging was used to measure tooth length from crown tip to root apex at baseline and 3 months into canine retraction. Mean decreases in root length of 0.03 mm and 0.05 mm were found in the MOPs and control groups respectively. These findings were not statistically significant ($P= 0.934$ for MOPs and $P=0.929$ for control), indicating that no root resorption occurred during treatment. Measurements of root length after 3 months of treatment between the intervention groups were also not statistically significant ($P = 0.886$). Therefore, they concluded that MOPs does not produce more OIERR compared to conventional treatment.

Bansal *et al* (64) randomly allocation 30 patients with mild to moderate mandibular crowding to either an experimental group (conventional orthodontic treatment with fixed appliances assisted with MOPs in the lower incisors region) or a control group (conventional orthodontic treatment only). MOPs were performed before the initial archwire using a self-drilling 1.6 mm × 8 mm orthodontic mini-implant. The root volume from CEJ to root apex of the

mandibular incisors was measured from CBCT imaging taken pre-treatment and 6 months into treatment. A comparison of the mean volumetric OIERR experienced by each mandibular incisor showed no statistically significant difference between the MOPs and control groups (all $P > 0.05$).

As described previously, Elkalza *et al* (66) compared OIERR following the application of micro-osteoperforations (MOPs) and corticotomy by piezocision in patients treated with fixed appliances and maxillary first premolar extractions. The mean canine tooth length in the MOPs intervention group was found to be significantly greater than the mean canine tooth length in the piezocision intervention group after canine retraction ($P = 0.001$).

Photobiomodulation

Al Okla *et al* (17) randomly allocated 38 patients who required conventional orthodontic treatment into two groups: a treatment group, which used a LED device for LLLT delivery, and the control group, which used a placebo (sham) device. The LED device delivered light with a wavelength of 850 nm wavelength and was used for 10 minutes per day. Both groups were treated with fixed appliances in both arches for approximately 6 months, until initial alignment of maxillary and mandibular incisors were achieved. OIERR was then assessed by comparing the root length of the maxillary central incisors obtained from periapical radiographs taken pre-treatment and 6 months following the initiation of treatment. It is unclear if the radiographs were standardized. While the mean root length at the 6-month time point was significantly shorter in the LLLT group (19.63 ± 1.33 mm) compared to the control (20.85 ± 2.00 mm) group ($P = 0.021$), the mean change in root length from pre-treatment to the 6 month time point was not statistically significant between the two groups. Therefore, the amount of OIERR was similar in the LLLT and control groups.

As discussed previously, Goymen *et al* (67) found that there was no significant difference in OIERR in patients treated with fixed appliances who used either adjunctive laser, photobiomodulation or a place laser device.

2.3.6. Risk of bias across studies

Since no meta-analysis was performed, the overall strength of the body of evidence for the included studies was assessed using the GRADE approach (Appendix 4). The overall quality of evidence assessing the amount of OIERR when corticotomies by piezocision, microvibration,

and LIPUS were used was considered moderate while the quality of evidence for corticotomies by surgical bur and low-level laser therapy was considered low (Appendix 4).

2.4. DISCUSSION

Adjunctive interventions to accelerate orthodontic treatment have grown in popularity over the past decade. While decreased treatment times are favourable for both the clinician and the patient, caution must be used to ensure that no harm is being caused. For this reason, the present study summarizes the available literature focusing on OIERR, a potentially significant adverse event. Continuous orthodontic pressure stimulates the osteoclastic activity present in the apical third of tooth roots. This has been proposed as the mechanism for external apical root resorption (24). While an increase in PDL osteoclastic activity has been linked to accelerated orthodontic tooth movement (89), it may also be contributing to root resorption in orthodontic patients.

2.4.1. Summary of the evidence

Corticotomies by surgical bur

First popularized by the Wilcko brothers in 2001 (90), corticotomies have been promoted to increase the rate of orthodontic tooth movement by accelerating the normal physiologic processes involved in wound healing and bone remodelling (91). The localized noxious stimuli produced by injuring the interdental cortical bone causes the tissues to regenerate faster than normal. This mechanism is termed the Regional Acceleratory Phenomena (91). A recent systematic review performed a meta-analysis of two animal studies and found increased OIERR with this intervention (92). In contrast, one high risk of bias human study in this review showed that corticotomies using a surgical bur have a protective effect, although not clinically significant, on root resorption when compared to conventional orthodontic treatment (59). This is in agreement with the excluded clinical trials, which also suggest that corticotomies may have a mild protective effect or no effect on root resorption (70, 71, 74, 79, 80). The overall quality of evidence supporting this assessment is very low (Appendix 4). In addition, two high risk of bias studies found that the use of various bone grafting materials in conjunction with corticotomies did not significantly affect the amount of root resorption when compared to corticotomy alone (51, 58). However, the overall quality of evidence supporting this assessment is low to very low (Appendix 4). One study with some concerns of risk of bias found no difference in the effect of

corticotomy by surgical bur or piezocision on OIERR (86). The overall quality of evidence supporting this assessment is low (Appendix 4).

Corticotomies by piezocision

Corticotomies by piezocision are similar to those performed by surgical bur. Although they rely on the same biological mechanism, the use of a piezo surgical knife requires only a small incision in the buccal gingiva instead of a full mucoperiosteal flap (6). Therefore, this intervention is expected to have a similar influence on OIERR. Two low risk of bias studies (57, 65) and one study with some concerns of risk of bias (66) showed that corticotomy by piezocision does not significantly affect OIERR. The overall quality of evidence supporting this assessment is moderate to low (Appendix 4). While some excluded studies (69, 70, 81) have also suggested that piezocision does affect root resorption, one split-mouth study (85) reported a statistically significant 110% average increase in volumetric root loss in premolars treated with piezocision compared to the contralateral control premolar. However, the authors felt that some of this loss may be attributed to iatrogenic damage (85). As discussed previously, one study with some concerns of risk of bias revealed no difference in OIERR between groups treated with corticotomy by surgical bur or piezocision (86). The overall quality of evidence supporting this assessment is low (Appendix 4).

Microvibration

Based on the piezoelectric theory of tooth movement, vibrational forces are transferred to the dentition via a horseshoe shaped device. These forces deform the alveolar bone and generate piezoelectric charges. These charges induce microcurrents to flow through bone and soft tissue and may enhance tooth movement by stimulating osteoblastic and osteoclastic activity (93). A recent systematic review of animal studies found that mechanical vibration did not seem to have significant effect on OIERR in rats (92). One unclear risk of bias study (60) and one high risk bias study (53) both suggested that vibrational devices do not have a significant effect on OIERR. This is in agreement with an excluded prospective clinical trial which found no effect (75). The overall quality of evidence supporting these assessments is low (Appendix 4).

Low-level Laser Therapy

Low level laser therapy produces an increase in RANKL (Receptor Activator of Nuclear Factor Kappa B Ligand) in the periodontal ligament at the cellular level. This increases the differentiation of precursor cells into activated osteoclasts and may potentially increase the rate

of orthodontic tooth movement (6). In this review, two low risk of bias studies and two studies with some concerns of risk of bias showed that LLLT may reduce or have no effect on OIERR (54, 63, 67, 68). The overall quality of evidence supporting these assessments is low to very low (Appendix 4). This finding is comparable to a previous meta-analysis of the rat studies which found no overall differences between laser and non-laser treated rats (92). Two excluded non-randomized clinical trials also suggested that there is no difference in OIERR between laser vs non-laser treated teeth (73, 83). Furthermore, it appears that pulsed vs continuous laser application protocols have no effect on OIERR (56). The two included studies used different types of lasers and irradiation regimens; therefore, these factors may be influencing the results and further investigation is required to determine best practises.

Low-Intensity Pulsed Ultrasound

LIPUS uses acoustic pressure waves that promote cementogenesis and inhibit cementoclastogenesis by increasing the Alkaline phosphate (ALP) activity, collagen-I synthesis and Runx-2 protein in cementoblasts (55). Previous studies in humans (29) and animals (7) have reported a reduction in the severity of OIERR with the use of LIPUS. Two studies with some concerns of risk of bias (8, 55) were included in this review which suggested that LIPUS has a mild protective effect on OIERR. This is in agreement with another excluded study published by the same group which suggested an average of 76-97% reduction in resorption lacunae area in LIPUS treated teeth (29). The overall quality of evidence supporting this assessment is low (Appendix 4).

Micro-osteoperforations (MOPs)

The goal of MOPs is to elicit the same regional acceleratory phenomenon (RAP) as corticotomies in a less invasive procedure with less patient morbidity (52, 64). These surgical interventions stimulate bone remodeling which in turn accelerates orthodontic tooth movement (94). Two low risk of bias studies (52, 64), two studies with some concerns of risk of bias (62, 66) and one study with high risk of bias (61) suggested that MOPs likely result in little to no difference in OIERR. The overall quality of evidence supporting this assessment is moderate to very low (Appendix 4). This is consistent with one excluded study which reported that no OIERR was found when MOPs was used (82). One excluded study found that MOPs results in statistically significant OIERR in maxillary lateral incisors, although no control group was used (72).

Photobiomodulation

Photobiomodulation is considered as an alternative form of LLLT which is delivered by light emitting diodes (LEDs) and other visible light sources instead of lasers. Therefore, the same biological mechanisms as LLLT which potentially result in accelerated orthodontic tooth movement (11, 12). One study with some concerns of risk of bias and one study with high risk of bias revealed that PBM may reduce or have no effect on OIERR (17, 67). The overall quality of evidence supporting this assessment is low to very low (Appendix 4). These findings are in agreement with a scoping review published in 2019 which included non-randomised trials that found ten studies which reported a beneficial effect of photobiomodulation on OIERR and eight studies which showed no significant effect (95).

2.4.2. Limitations

The quality of evidence supporting adjunctive interventions for accelerating orthodontic tooth movement has been generally classified as poor (6). This is further evidenced by the fact that most of the studies included in this review were associated with some concerns or a high risk of bias (Figure 3) and none of the intervention outcomes had a high level of certainty of the provided evidence (Appendix 4). However, obtaining higher quality evidence may prove to be challenging. First, it is impossible to blind the investigator or the patient for some of the interventions, such as corticotomies. Secondly, randomization may be unethical for certain types of interventions. For example, if there is a lack of inter-radicular bone between adjacent teeth, then performing a corticotomy in this area may lead to iatrogenic root damage. This would also act as a confounder when evaluating OIERR if not taken into account. Finally, studies which use of a split-mouth study design also have certain limitations (96). There is a non-negligible risk of carry-across effects in all split-mouth studies of these adjunctive interventions, especially those studying microvibration. Despite its efficiency in terms of sample size (96), it is recommended that further research on this subject avoids the use of a split-mouth study design. It is also important to note that some of the included studies may have presented participant data from repeated or multiple site observations, or both, which may have led to unit of analysis errors (96).

Due to a wide variation in study methodology, study design outcome reporting and method used to measure root resorption, this systematic review was reported as a narrative review. The results presented must be interpreted with caution since study heterogeneity and data

weight were not considered due to the lack of data quality to justify a meta-analysis. Furthermore, eight excluded studies (69, 70, 73, 78, 79, 81-83) did not present quantitative data on root resorption and root resorption was only a secondary outcome in many of the included studies. This made the data extraction process difficult as the quality of reporting in most of the studies was poor.

Previous studies showed that root cementum undergoes a reparative process following orthodontic treatment. The reparative process is most significant over the first 4 weeks and then plateau after 6 weeks (28, 97). These adjunctive interventions may actually be producing more root resorption temporarily (98), but this may not be detected thereafter in studies due the reparative capability of the root cementum. Therefore, the follow-up period of some of the included studies may not have been long enough to allow for this repair to occur.

Studies which included subjects with any history of trauma, prior root resorption or prior endodontic treatment were excluded from this review. In addition, most of the included studies took place in a university clinic setting. Therefore, the results cannot be generalized to any potential orthodontic patient. This review also excluded pharmacological, periodontal distraction and distraction osteogenesis techniques because they are seldomly used in everyday clinical practice and some are only in preliminary stages of development. Future systematic reviews may consider the inclusion of these interventions as more high-quality evidence and clinical uses emerge.

2.4.3. Clinical implications

Given the best available evidence, clinicians can feel somewhat reassured that their decision to use these adjunctive interventions to accelerate orthodontic treatment will not likely produce harm to their patient in the form of root resorption above that which is expected from conventional orthodontic treatment. Although none of the studies included in this review showed an increase in the severity of root resorption, these findings are based on low-level evidence with high uncertainty levels and further research is likely to change the confidence in the effect estimate.

Orthodontically-induced inflammatory root resorption is a relatively rare adverse event. While some degree of OIERR occurs on all teeth following orthodontic treatment, severe OIERR is observed in only 1% – 5% of all orthodontically treated teeth (23). LIPUS showed some preventive effect. Nevertheless, the use of such adjunctive interventions to accelerate orthodontic

tooth movement for the purpose of preventing OIERR should not be supported by the findings of this review. This is unlikely to be good practice due to the large number of patients which need to be treated in order to produce a meaningful positive response. The clinician's management of other noted treatment and patient-related risk factors for OIERR are likely to have a greater impact.

Further well-designed and well-reported RCTs are required to better understand whether surgical and non-surgical adjunctive interventions to accelerate orthodontic treatment cause any clinically significant effect on tooth root morphology.

2.5. Conclusions

With a significant level of uncertainty (moderate to very low evidence level according to the GRADE tool) adjunctive interventions to accelerate orthodontic tooth movement do not appear to have a clinically significant effect on OIERR. Corticotomies by piezocision, micro-osteoperforations, microvibration and photobiomodulation may not have a significant effect on OIERR. Corticotomies by surgical bur, low-level laser therapy and low-intensity pulsed ultrasound may mildly reduce or have no effect on OIERR.

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Chapter 3 – Root Volume Measurement Protocol using 3D Cone Beam Computed Tomography

3.1. INTRODUCTION

Technological advances in 3D craniofacial imaging, such as cone-beam computed tomography (CBCT), are changing the way clinicians visualize and quantify orthodontically-induced external root resorption (OIERR). Multiple methods for evaluating changes in dental root morphology have been discussed extensively in the literature. Some of the most common *in-vitro* methods for detecting OIERR include histology sections (27-32), light microscope (33, 34), scanning electron microscope (35-37), laser scans (38, 39) and micro-computed tomography (40-43). The most common clinical assessment of OIERR is done using 2D imaging modalities, such panoramic (25, 44, 99, 100) or periapical radiographs (25, 41, 88, 101-106). More recently, 3D imaging modalities, such as CBCT, have become a popular method for evaluating root resorption (26, 101, 103, 107-111). The 3D visualization of root morphology provided by CBCT imaging is one of its main advantages over conventional 2D imaging.

Given that OIERR can occur anywhere along the tooth root surface, 2D imaging modalities are limited in their ability to only detect root resorption defects which either occur on the mesial or distal of the tooth, face in direct right angles to the focal beam of the X-rays or progress to a severe or advanced stage (112). These imaging modalities allow OIERR to be qualified based on root shape (25, 88) or to be quantified based on linear measurement between two different reference points (i.e. from the most incisal portion of the crown to the most apical portion of the root apex) (25, 45). A study comparing OIERR quantified by teeth lengths obtained from periapical and panoramic radiographs found that panoramic radiographs overestimated the amount of root loss by approximately 5–20% (25). This is likely due to the magnification caused by the relative position of the focal trough to the dental arch during panoramic imaging (112). To overcome these limitations, researchers have begun utilizing CBCT imaging to evaluate tooth and root lengths. It has been shown that CBCT images are far superior to periapical and panoramic radiographs for accurately establishing the degree of OIERR using linear measurements (44, 45, 107, 110, 113, 114). Therefore, the use of 2D imaging should be avoided when attempting to precisely quantify root resorption defects.

However, the quantification of OIERR using linear measurements is questionable since one would be ignoring resorption which occurs anywhere other than at the apical portion of the tooth. As a result, the use of CBCT imaging for the *in-vivo* volumetric assessment of changes in root morphology has now been the focus of many studies (32, 108, 115, 116). This method

allows root resorption defects to be analyzed anywhere they may occur on the root. The CBCT method for volumetric measurement of teeth *in-vivo* has been found to be comparable to both micro-CT (45, 108, 117) and water displacement (115) methods *in-vitro*, which are considered as the gold standards for volumetric assessment of hard tissues (118). One study revealed that CBCT measurements deviate slightly from the physical volumes of the teeth by as much as -4% to 7% (115). The resolution of the CBCT has also been found to influence the accuracy of quantification of OIERR. High-resolution CBCT imaging (0.2mm voxel) has been found to be significantly more accurate than low-resolution CBCT (0.4mm voxel) imaging for quantifying external lateral root resorption defects by volume compared to micro-CT images (0.018mm voxel) (45). Another study which compared the volumes of CBCT-scanned (at voxel sizes: 0.125, 0.20, 0.25, 0.30, and 0.40 mm) and laser-scanned teeth crowns and roots found that the volumes obtained for CBCT-scanned crowns were between 21.73% and 43.92% greater than laser-scanned crowns (39). Larger volume differences were correlated with increasing voxel sizes. Their results were similar for the CBCT-scanned roots, which were found to be between 18.27% to 41.58% greater than laser-scanned roots. The authors concluded that for applications which require high precision in volume measurements (such as identification of root resorption). voxels sizes of at least 0.25 mm or better must be used. However, better resolution results in a higher radiation dose and a longer scanning time for the patient, which are not desirable (39).

While advancements into 3D imaging have facilitated volumetric measurements of dental structures, there has also been a lack in homogeneity in the volume measurement protocols used. In order to calculate the volume of a tooth, it must first be isolated from surrounding structures. This process is called segmentation. Tooth segmentation protocols can be broadly divided into three categories: manual human segmentation, semi-automatic segmentation and fully automatic segmentation. The manual human segmentation technique involves the identification of tooth structure on a 2D slice-by-slice basis from the CBCT using specialized 3D software tools (119). Although very time consuming, this technique allows the greatest level of control. The most common fully automatic segmentation technique involves the selection of a ‘seed voxel’ of a tooth root or crown. Specialized 3D software then selects the largest connected area which contains the voxel itself and all voxels with gray values contained within a user-specified range (119). This segmentation method allows for more rapid identification of dental structures compared to manual segmentation but is prone to overestimating volume due to the inclusion of

non-dental structures which are similar in grey value to the seed voxel. The semi-automatic segmentation technique is a combination of manual and automatic techniques previously described. The tooth segmentation is first segmented using an automatic approach, followed by manual refinement by a human to ensure that an accurate representation of the tooth structure and anatomy is obtained (115, 119, 120). When all three methods were compared, it was found that the semi-automatic method showed excellent intra- and inter-observer reliability and precision when segmenting a maxillary first molar (119). The authors of this study did note that inter-observer reliability was rather poor while intra-observer reliability was excellent for volume measurements of tooth roots (119). However, they did not provide an explanation for this finding.

For this project, the maxillary and mandibular centrals, laterals, and canines were studied because these anterior teeth have been found to experience the most OIERR (121). The most resorbed tooth is the maxillary lateral incisor followed by the maxillary central incisor and the maxillary canine. In the mandible, the most resorbed tooth is the canine followed by the lateral and central incisors (121).

3.2 METHODS

3.2.1. Root volume segmentation

A semi-automatic segmentation technique was chosen for this project. ITK-SNAP (version 3.8; http://www.itksnap.org) is an open-source 3D medical imaging software which allows for the segmentation of structures from CBCT (122). It has been used in many studies in both medicine (122-124) and dentistry (125-128) for the volumetric analysis of structures of interest, including teeth (116, 125, 129-131). The main advantages of ITK-SNAP compared to other software are the reduced time required to segment a structure and its ease of use for clinical researchers (122). Segmentation of a child's caudate nucleus via ITK-SNAP was shown to have intra-observer and inter-observer reliability which is equivalent to manual segmentation by an expert in the domain (122). Other 3D software packages provide semi-automatic segmentation capability, but they are often too complex and overwhelming for clinical researchers. It was the opinion of the authors in one study that the choice of 3D software would not influence the volume measurements as long as voxel sizes were held constant and a proper segmentation protocol was used (119).

The CBCT images used for the volumetric analysis of teeth were previously acquired as part of pre-treatment (T0) and progress or post-treatment (T1) records for patients treated by one orthodontist in their private practice in Edmonton, Alberta, Canada. All CBCT images were acquired with the patient in centric occlusion using the i-CAT FLX (Imaging Sciences International, Hatfield, PA) with the following exposure parameters: scanning time 3.7s, 5 mA, 120 kVp, FOV: 13 cm × 16 cm, slice thickness 0.3mm. Images were converted to Digital Imaging and Communications in Medicine (DICOM) format by using the InVivo software (Anatomage, San Jose, CA). Shutter and panel calibration of the CBCT machine were performed on weekly basis according to manufacturer's recommendations. The DICOM data were then imported into the ITK- SNAP software.

Once the DICOM file is loaded into ITK-SNAP, the image contrast was adjusted to allow better visualization of the teeth and surrounding alveolar bone. The "Active Contour Segmentation Mode" (also called "Snake" function) was activated and the region of interest (either maxilla or mandible) was selected in all three planes of space (Figure 1). The maxillary and mandibular teeth were segmented separately due to the difficulty in separating the teeth in subsequent steps.

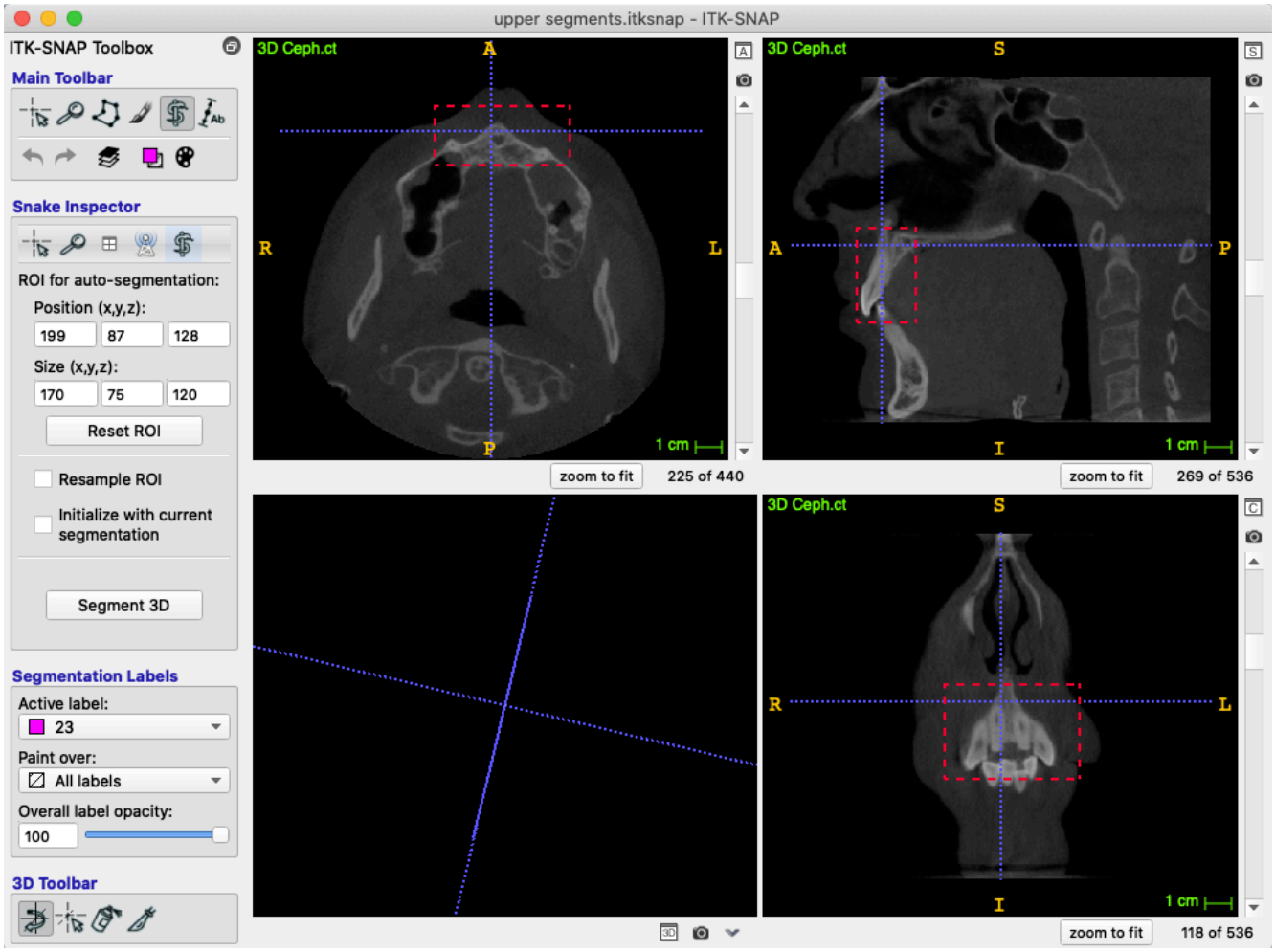


***Figure 1**: Selection of the region of interest for the segmentation procedure in ITK-SNAP*

In the following step, the "Thresholding" presegmentation mode was selected. Thresholding allows the software to select voxels for segmentation with an intensity inside of a specified range (132). The maximum grey value is selected for the upper threshold so that all radiopaque structures are selected. For the lower threshold of grey values, the operator chose a value which most clearly showed the full tooth anatomy while attempting to simultaneously minimize interference from the surrounding structures (Figure 2). Both the grey scale and blue/white filtered images are analyzed in all three planes of space to determine the ideal lower threshold value.

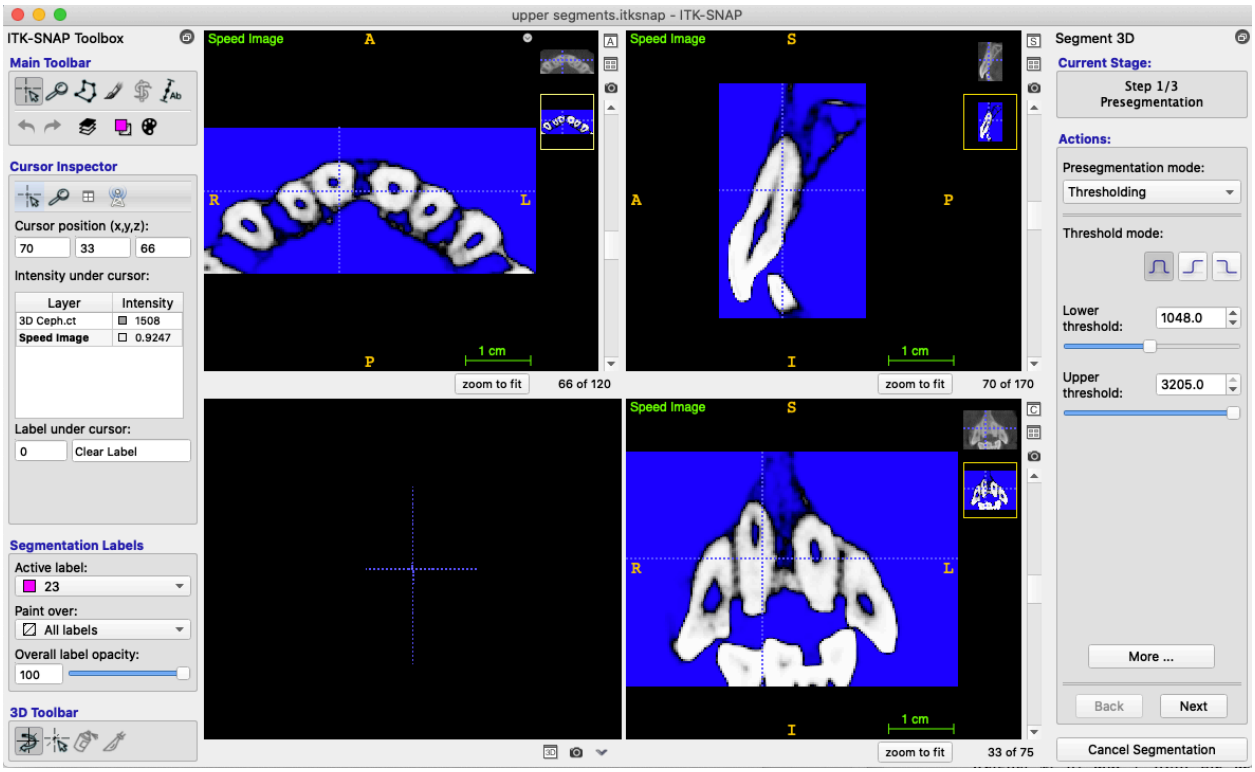


***Figure 2**: Selection of the threshold values for the segmentation procedure in ITK-SNAP*

The operator then places multiple spherical "seeds" on the teeth, from which the segmentation process will expand the color label to cover the entire tooth structure within the selected threshold range (Figure 3). The "seeds" were placed randomly within the tooth structure in all three planes of space while attempting to stay within the limits of each tooth. Their radius varied depending on the size and region of the tooth to be covered. Almost the entire tooth structure was covered with "seeds", as this was found to reduce the segmentation time in subsequent steps and resulted in less interference from the surrounding structures.

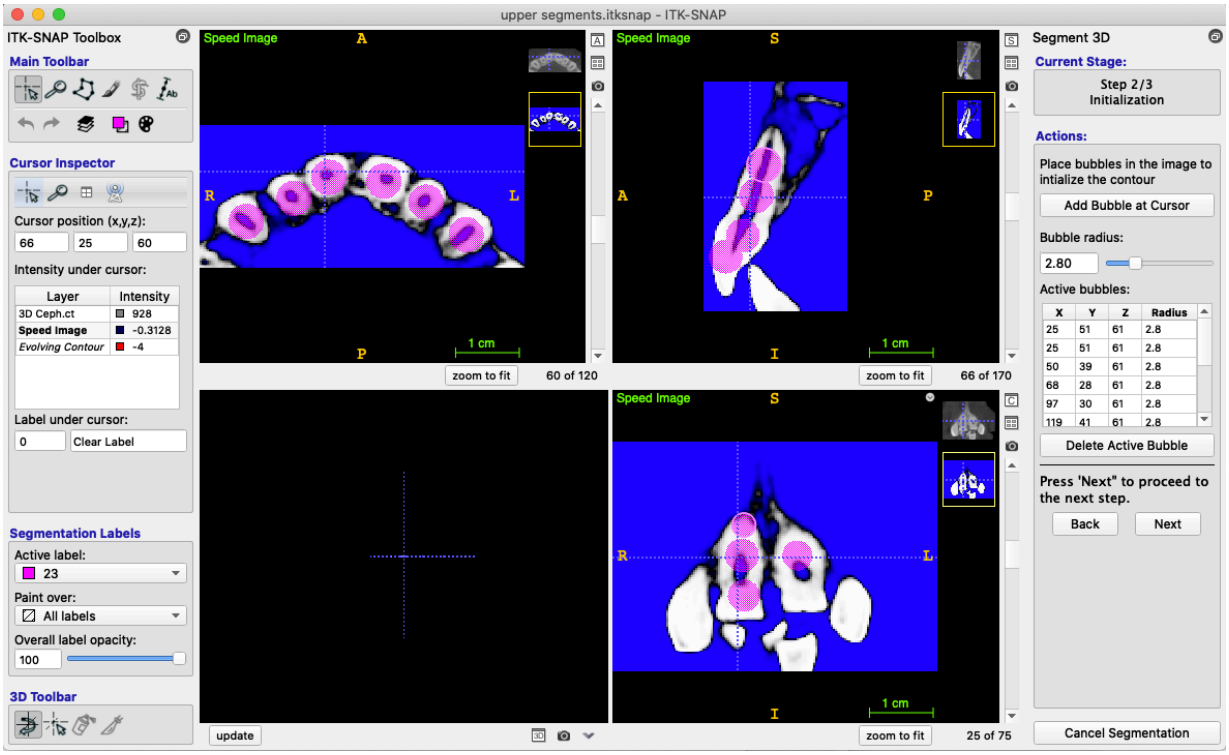


***Figure 3**: Placement of spherical "seeds" for the segmentation procedure in ITK-SNAP*

The actual contour segmentation was then initiated and proceeded automatically in a stepwise fashion. With each iteration, the multiple "seeds" grow and merge into a single color label which covers the entire tooth volume. The segmentation procedure may be rewound and advanced one step at a time. Once the operator felt that the entire tooth volume had been segmented, the segmentation procedure was terminated (Figure 4). No smoothing functions were used as these have been found to reduce volumetric measurements of teeth by 3% to 12% (115).

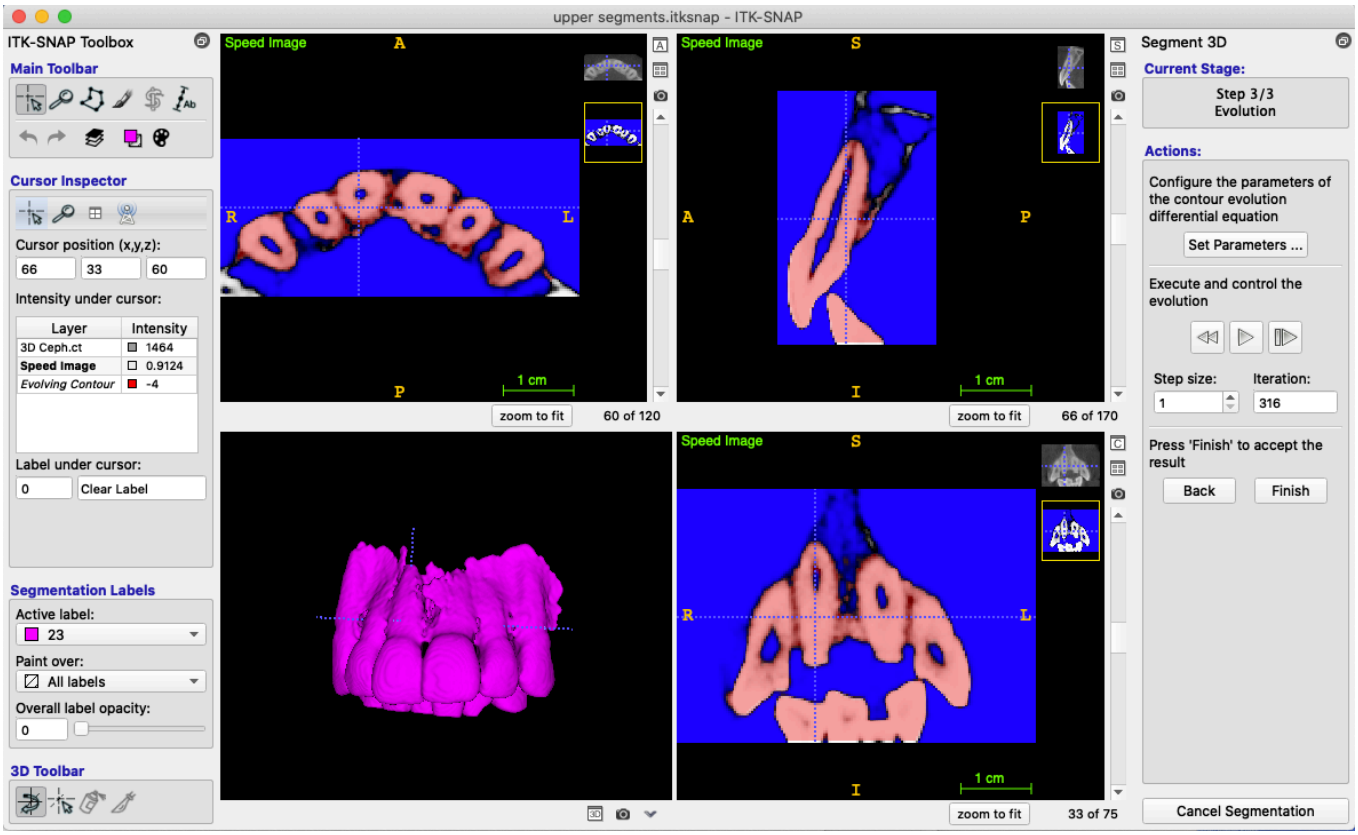
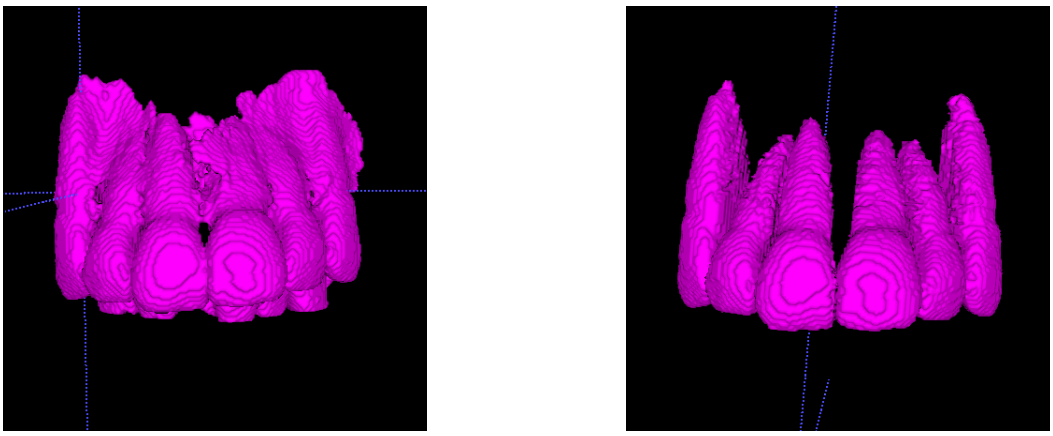


***Figure 4**: Results of the segmentation procedure in ITK-SNAP*

Manual refinement was then undertaken using the Paintbrush mode on a 2D slice-by-slice basis to remove any voxels which represented surrounding structures and add any voxels which had been inadvertently omitted from the tooth volume during the segmentation process. All refinements were performed in all three planes of space. The 3D view was used to verify that proper tooth anatomy had been obtained and to ensure that there was no obvious misidentification of dental structures (Figure 5).



(A) **(B)**

Figure 5*: 3D view of the segmented maxillary teeth in ITK-SNAP (a) before manual refinement and (b) after manual refinement*

The cut-plane tool (also called “Scalpel”) was used in the 3D view window to divide the segmentation into individual teeth and to remove any non-dental structures. A vertical cut-plane was first defined between teeth #2.2 and 2.3. and the color label to the left of the cut-plane was replaced with the color label for tooth #2.2 This process was repeated for all teeth from right to left (Figure 6). The color label for each tooth was chosen at random but was consistent for all CBCTs. Further manual refinement was performed at the end of this step to ensure the no errors were made when dividing the teeth.

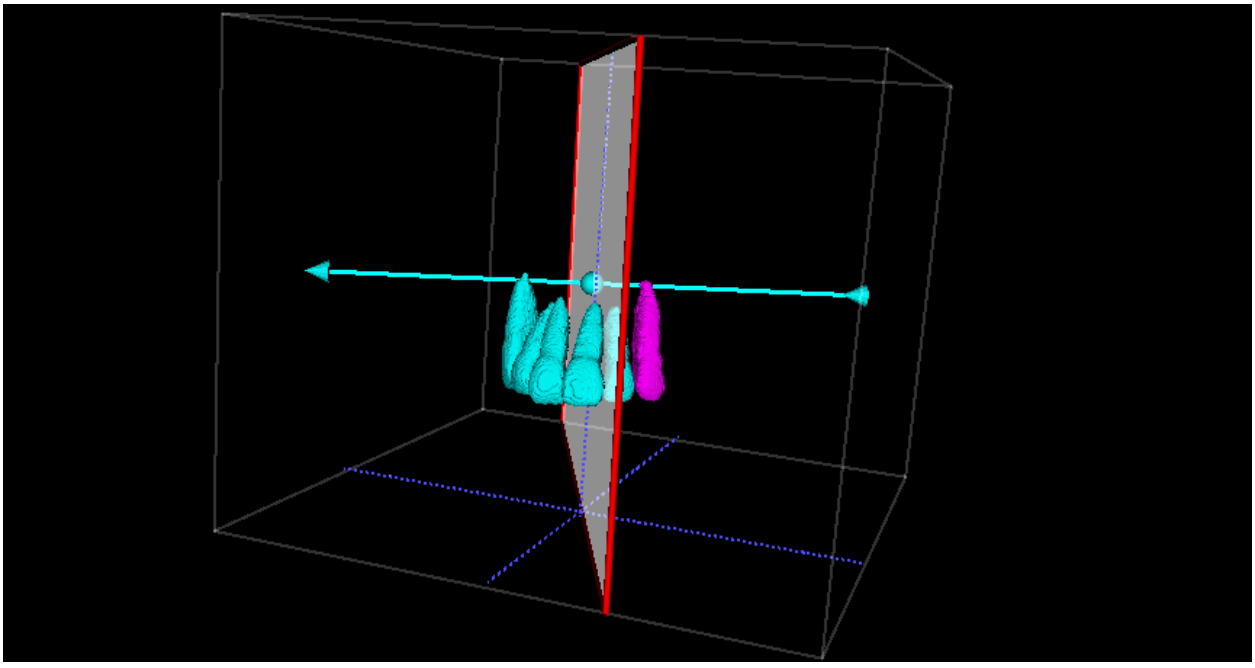


Figure 6*: Use of cut-plane tool to divide segmentation into individual teeth in ITK-SNAP*

Once partitioning was completed, the individual teeth were exported as a surface mesh in the Visualization Toolkit (VTK) file format. The entire process was repeated in the mandibular arch in the same manner (Figure 7). The volume of the whole tooth for each time point was recorded.

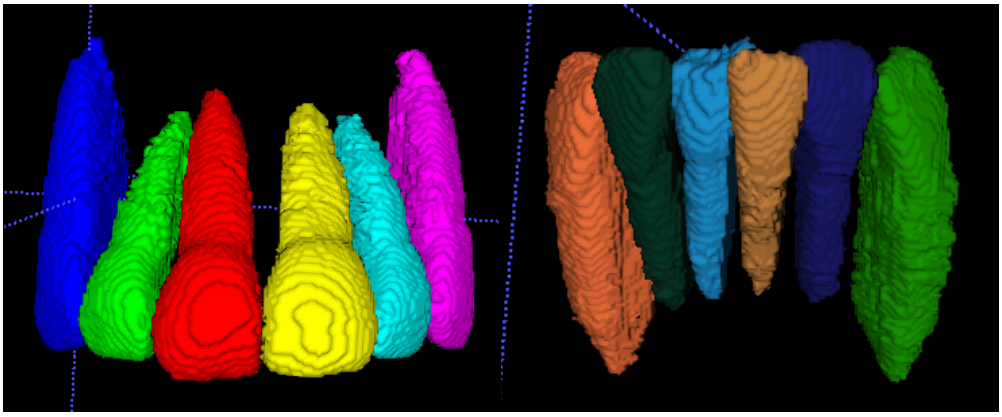
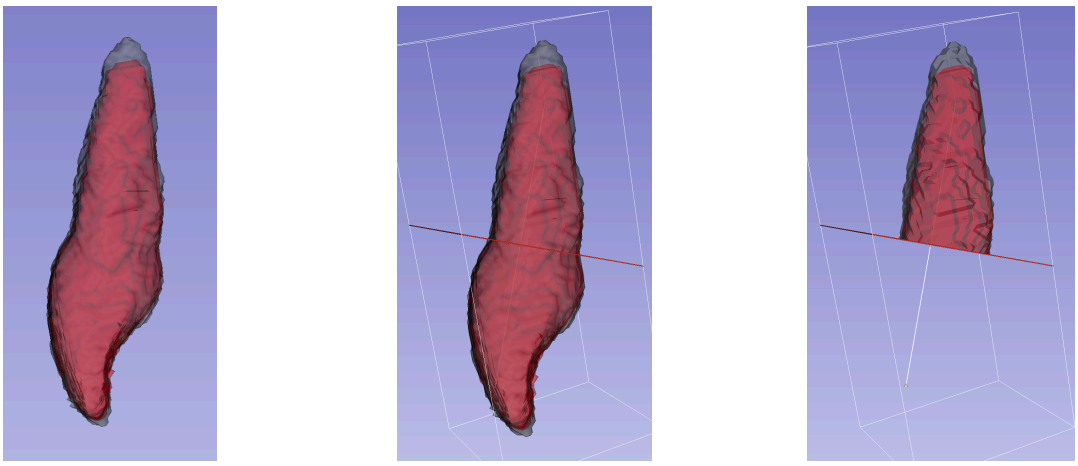


***Figure 7**: Completed segmentation of all maxillary and mandibular teeth in ITK-SNAP*

The VTK files for all maxillary and mandibular teeth for both time points were imported into 3DSlicer software (version 4.10.2, https://www.slicer.org/.) (133). Corresponding teeth volumes from T0 and T1 were superimposed by the best fit alignment using an iterative closest point algorithm (Figure 8A) (134). A reference plane was constructed using the highest point of the labial and palatal cemento-enamel junction and a perpendicular line drawn through the long axis of the tooth (Figure 8B). The superimposed VTK images were segmented immediately below reference plane and the crowns of the teeth were removed. Only the volume of the root portion for each time point was computed (Figure 8C). This protocol is similar to ones which have been previously described in the literature (116, 135, 136).



(A) **(B)** **(C)**

Figure 8. *(A) Superimposition of T0 (grey) and T1 (red) (B) Reference plane (red line) (C) Superimposed root images at T0 and T1-mesial palatal color map view.*

In clinical practice, it is more meaningful to report root resorption in terms of a percentage change in root volume. Therefore, the root volume change was calculated from pre- and post-treatment root volumes for each tooth using the following formula:

$$\%\Delta\, root\ volume = \frac{root\ volume_{post-treatment} - root\ volume_{pre-treatment}}{root\ length_{pre-treatment}} x100.$$

3.2.2. Reliability analysis

To assess intra-rater reliability, the principal investigator (A.R.) performed the entire segmentation protocol three times for twelve teeth. Each set of measurements was taken one week apart from each other. The teeth were pseudo-randomly selected using Microsoft Excel® (Microsoft Corp., Redmond, W.A., USA). The patient and the tooth number were randomized, while ensuring that each type of tooth (maxillary central, maxillary lateral, maxillary canines, mandibular central, mandibular lateral or mandibular canine) was selected at least twice. This was done to allow reliability to be assessed for all six different types of teeth simultaneously. Intraclass Correlation Coefficient (ICC) was used to measure agreement between the measurements. A two-way mixed model with measures of consistency was chosen, given that the patients/teeth were chosen at random while the rater remained fixed and the rater's variability was considered irrelevant

To assess inter-rater reliability, two orthodontic residents (K.C. and G.M.) with the same background dental knowledge and experience were trained in each step of the described segmentation protocol. Both investigators measured the same twelve randomly selected teeth as

measured by the principal investigator. Interclass Correlation Coefficient (ICC) was used to measure agreement between the principal investigator's second measurement (determined randomly) and the additional investigator's single measurement. A two-way mixed model with measures of absolute agreement was chosen given that the patients/teeth were chosen at random while the raters remained fixed and the rater's variability was considered to be relevant.

The statistical analyses were performed using IBM SPSS Statistics for Mac, version 23 (IBM Corp., Armonk, N.Y., USA). A significance level of $\alpha=0.05$ was chosen for all statistical analyses. As a guideline, ICC values less than 0.50, between 0.50 and 0.75, between 0.75 and 0.90, and greater than 0.90 were considered indicative of poor, moderate, good, and excellent reliability, respectively (137).

3.3. RESULTS

3.3.1. Intra-rater reliability

The raw data for segmentations of whole tooth volume at T0 and T1 obtained by the principal investigator is presented in Table 1 and 2, respectively. The ICC (Single Measures) value of 0.995 with 95% CI [0.986, 0.998] demonstrates excellent intra-rater reliability for the measurements of tooth volume at T0 (Appendix, Table 1). A similar result was found for the intra-rater reliability of measurements of tooth volume at T1, with ICC (Single Measures) value of 0.999 with 95% CI [0.997, 1.000] (Appendix, Table 3). The results of the corresponding ANOVA corroborate the ICC values obtained and showed high variance in the patients' measurements and relatively low variance attributable to the observer unreliability (Appendix, Table 2 and 4, Figure 1 and 2). The measurement error was obtained by calculating the mean and standard deviation of the individual differences between the three measurements for tooth volume. Overall, a measurement error of 10.4 ± 6.6 mm^3 and 5.3 ± 62.9 mm^3 was found for tooth volume measurements at T0 and T1, respectively (Table 1 and 2).

Patient	Tooth Number	Rater #1 1st Measurement	Rater #1 2nd Measurement	Rater #1 3rd Measurement	Rater #1 Mean Measurement	Mean difference between measurements (error)	Standard deviation of error
1	1.3	931.2	861.3	866.1	886.2	46.6	36.3
2	1.1	523.0	528.7	524.4	525.4	3.8	2.2
3	1.3	667.6	680.5	654.2	667.4	17.5	7.6
4	1.2	297.0	303.9	300.2	300.4	4.6	2.0
5	1.1	673.3	683.5	688.3	681.7	10.0	5.1

6	4.1	342.9	349.4	348.6	347.0	4.3	3.1
7	4.1	316.5	300.9	299.8	305.7	11.1	8.7
8	4.3	510.9	525.2	538.3	524.8	18.3	7.9
9	4.2	263.5	263.7	260.6	262.6	2.1	1.6
10	4.3	390.5	390.4	393.3	391.4	1.9	1.6
11	4.2	400.4	397.6	397.9	398.6	1.9	1.4
12	1.2	392.3	395.8	395.2	394.4	2.3	1.5

Table 1: *Measurements obtained during intra-rater reliability assessment of whole tooth volume at T0 (all units in mm^3)*

Patient	Tooth Number	Rater #1 1st Measurement	Rater #1 2nd Measurement	Rater #1 3rd Measurement	Rater #1 Mean Measurement	Mean difference between measurements (error)	Standard deviation of error
1	1.3	882.6	857.7	848.7	863.0	22.6	12.6
2	1.1	511.1	513.9	511.9	512.3	1.9	1.0
3	1.3	636.7	642.9	649.9	643.2	8.8	3.8
4	1.2	284.5	281.3	284.5	283.4	2.1	1.8
5	1.1	638.1	633.3	634.7	635.4	3.2	1.7
6	4.1	365.2	373.6	372.9	370.6	5.6	4.3
7	4.1	277.2	277.5	278.9	277.9	1.1	0.7
8	4.3	499.4	500.3	501.3	500.3	1.3	0.6
9	4.2	277.2	281.5	273.9	277.5	5.1	2.3
10	4.3	357.2	345.0	349.4	350.5	8.1	3.9
11	4.2	368.3	366.3	367.6	367.4	1.3	0.7
12	1.2	387.7	385.6	389.7	387.7	2.7	1.2

Table 2: *Measurements obtained during intra-rater reliability assessment of whole tooth volume at T1 (all units in mm^3)*

The measurements obtained by the principal investigator of root volume at T0 and T1 following the removal of the crown (as seen in Figure 3C) were compared (Table 3 and 4). The ICC (Single Measures) value of 0.992 with 95% CI [0.978, 0.997] demonstrates excellent intra-rater reliability for the measurements of root volume at T0 (Appendix, Table 5). Excellent intra-rater reliability of measurements of tooth volume at T1 was also found, with ICC (Single Measures) value of 0.993 with 95% CI [0.980, 0.998] (Appendix, Table 7). There was high variance in the patients' measurements and relatively low variance attributable to the observer unreliability (Appendix, Table 6 and 8, Figure 3 and 4). Overall, a measurement error of 7.9 ±

5.1 mm^3 and 7.1 ± 4.1 mm^3 was found for root volume measurements at T0 and T1, respectively (Table 3 and 4).

Patient	Tooth Number	Rater #1 1st Measurement	Rater #1 2nd Measurement	Rater #1 3rd Measurement	Rater #1 Mean Measurement	Mean difference between measurements (error)	Standard deviation of error
1	1.3	520.3	478.6	475.2	491.4	30.1	23.2
2	1.1	193.8	199.5	195.0	196.1	3.8	2.3
3	1.3	337.7	342.9	333.1	337.9	6.5	2.9
4	1.2	121.5	120.6	119.6	120.6	1.3	0.6
5	1.1	270.5	285.5	288.9	281.6	12.3	7.9
6	4.1	159.5	175.5	171.1	168.7	10.6	5.8
7	4.1	161.3	160.8	159.3	160.5	1.4	0.7
8	4.3	234.9	239.7	243.8	239.5	6.0	2.6
9	4.2	144.9	147.0	143.0	144.9	2.7	1.2
10	4.3	186.3	194.5	196.1	192.3	6.5	4.3
11	4.2	205.9	205.4	210.1	207.1	3.2	2.3
12	1.2	202.7	187.7	188.6	193.0	10.0	7.9

Table 3: *Measurements obtained during intra-rater reliability assessment of root volume at T0 (all units in mm^3)*

Patient	Tooth Number	Rater #1 1st Measurement	Rater #1 2nd Measurement	Rater #1 3rd Measurement	Rater #1 Mean Measurement	Mean difference between measurements (error)	Standard deviation of error
1	1.3	489.8	464.8	441.3	465.3	32.3	14.0
2	1.1	185.7	189.9	184.4	186.7	3.7	2.2
3	1.3	312.8	319.2	319.9	317.3	4.7	3.5
4	1.2	113.9	109.7	108.6	110.7	3.5	2.2
5	1.1	239.0	243.3	244.9	242.4	3.9	2.2
6	4.1	182.0	188.2	182.6	184.3	4.1	3.1
7	4.1	146.7	144.8	146.9	146.2	1.4	1.0
8	4.3	217.1	226.7	230.4	224.7	8.9	4.8
9	4.2	157.7	159.4	151.3	156.1	5.4	3.3
10	4.3	153.6	161.0	161.1	158.6	5.0	4.3
11	4.2	177.8	173.8	179.6	177.1	3.8	2.0
12	1.2	192.5	179.3	180.9	184.2	8.8	6.3

Table 4: *Measurements obtained during intra-rater reliability assessment of root volume at T1 (all units in mm^3)*

The percentage change in root volume from T0 to T1 for the three assessments obtained by the principal investigator is presented in Table 5. The ICC (Single Measures) value of 0.953 with 95% CI [0.881, 0.985] demonstrates excellent intra-rater reliability for the semi-automatic segmentation technique used in this project (Appendix, Table 9). The results of the corresponding ANOVA corroborate the ICC values obtained and showed high variance in the patients' measurements and relatively low variance attributable to the observer unreliability (Appendix, Table 10 and Figure 5). An overall measurement error of 1.9 ± 1.2 % was found for change in root volume measurements (Table 1).

Patient	Tooth Number	Rater #1 1st Measurement	Rater #1 2nd Measurement	Rater #1 3rd Measurement	Rater #1 Mean Measurement	Standard error	Percentage uncertainty
1	1.3	-5.9	-2.9	-7.1	-5.3	1.3	-23.7
2	1.1	-4.2	-4.8	-5.4	-4.8	0.4	-7.6
3	1.3	-7.3	-6.9	-4.0	-6.1	1.1	-17.5
4	1.2	-6.3	-9.0	-9.2	-8.2	0.9	-11.5
5	1.1	-11.6	-14.8	-15.2	-13.9	1.1	-8.1
6	4.1	14.1	7.2	6.7	9.3	2.4	25.4
7	4.1	-9.1	-9.9	-7.8	-8.9	0.6	-7.0
8	4.3	-7.6	-5.4	-5.5	-6.2	0.7	-11.3
9	4.2	8.8	8.5	5.8	7.7	1.0	12.4
10	4.3	-17.6	-17.2	-17.9	-17.5	0.2	-1.1
11	4.2	-13.6	-15.4	-14.5	-14.5	0.5	-3.4
12	1.2	-5.0	-4.5	-4.1	-4.5	0.3	-6.1

Table 5: *Measurements obtained during intra-rater reliability assessment of root segmentation (all units in %)*

3.3.2. Inter-rater Reliability

The raw data obtained by the principal investigator's second set of measurements (selected at random) and the two additional investigators are compared in Table 6 and 7. The ICC (Single Measures) values of 0.966 with 95% CI [0.911, 0.989] and 0.962 with 95% CI [0.732, 0.991] demonstrate excellent inter-rater reliability for the whole tooth volume measurements at T0 and T1, respectively (Appendix, Table 11 and 13). The results of the corresponding ANOVAs showed evidence to reject the null hypothesis ($p = 0.063$ and $p<0.0005$ for tooth volume at T0 and T1, respectively). Therefore, the mean tooth volume obtained by at least one observer may be different than the others (Appendix, Table 12 and 14). Nonetheless, high variance in the patient measurements and relatively low variance attributable to the observer

unreliability was found. This finding is further confirmed by visual inspection of the line graphs of all measurements at T0 and T1, which show fairly good agreement between observers. (Appendix, Figure 6 and 7). Overall, a measurement error of 40.4 ± 23.1 mm^3 and 44.7 ± 27.9 mm^3 was found for tooth volume measurements at T0 and T1, respectively (Table 6 and 7).

Patient	Tooth Number	Rater #1 Measurement	Rater #2 Measurement	Rater #3 Measurement	Mean Measurement (All raters)	Mean difference between raters (error)	Standard deviation of error
1	1.3	931.2	970.51	1011.17	947.7	99.9	55.2
2	1.1	523.0	589.61	508.25	542.2	54.2	31.0
3	1.3	667.6	638.47	590.32	636.4	60.1	26.2
4	1.2	297.0	310.37	288.05	300.8	14.9	8.0
5	1.1	673.3	698.81	686.84	689.7	10.2	6.2
6	4.1	342.9	369.45	349.59	356.1	13.4	11.4
7	4.1	316.5	281.03	258.85	280.3	28.0	12.2
8	4.3	510.9	586.59	520.87	544.2	43.8	34.3
9	4.2	263.5	269.07	278.51	270.4	9.9	4.7
10	4.3	390.5	427.81	334.63	384.3	62.1	28.4
11	4.2	400.4	363.27	346.06	369.0	34.4	17.2
12	1.2	392.3	472.04	390.68	419.5	54.2	42.6

Table 6: *Measurements obtained during inter-rater reliability assessment of whole tooth volume at T0 (all units in mm^3)*

Patient	Tooth Number	Rater #1 Measurement	Rater #2 Measurement	Rater #3 Measurement	Mean Measurement (All raters)	Mean difference between raters (error)	Standard deviation of error
1	1.3	857.7	1011.63	890.25	919.9	102.6	62.8
2	1.1	513.9	575.11	517.61	535.5	40.8	32.2
3	1.3	642.9	655.45	588.11	628.8	44.9	28.7
4	1.2	281.3	322.62	281.74	295.2	27.5	23.5
5	1.1	633.3	704.11	633.42	656.9	47.2	40.8
6	4.1	373.6	384.34	341.76	366.6	28.4	16.2
7	4.1	277.5	302.88	253.49	278.0	32.9	14.3
8	4.3	500.3	576.57	529.76	535.5	50.8	23.7
9	4.2	281.5	287.73	239.96	269.7	31.8	22.4
10	4.3	345.0	416.03	353.94	371.7	47.4	33.6
11	4.2	366.3	398.15	343.86	369.4	36.2	16.4
12	1.2	385.6	424.56	355.74	388.6	45.9	20.4

Table 7: *Measurements obtained during inter-rater reliability assessment of whole tooth volume at T1 (all units in mm^3)*

The measurements obtained by the principal investigator and the two additional observers of root volume at T0 and T1 following the removal of the tooth crown (as seen in Figure 3C) were compared (Table 8 and 9). The ICC (Single Measures) values of 0.931with 95% CI [0.822, 0.978] and 0.933 with 95% CI [0.817, 0.979] demonstrate excellent inter-rater reliability for the root volume measurements at T0 and T1, respectively (Appendix, Table 15 and 17). Just as with the whole tooth volume measurements, the results of the corresponding ANOVAs showed evidence to reject the null hypothesis ($p = 0.046$ and $p = 0.019$ for root volume at T0 and T1, respectively). Hence, the mean root volume obtained by at least one observer may be different than the others (Appendix, Table 16 and 18). Visual inspection of the line graphs of all measurements at T0 and T1 revealed fairly good agreement between observers on all teeth except #1.2, 4.2 and 4.3. There was still high variance in the patients' measurements and relatively low variance attributable to the observer unreliability (Appendix, Table 16 and 18, Figure 8 and 9). Overall, a measurement error of 32.8 ± 20.9 mm^3 and 31.1 ± 20.3 mm^3 was found for root volume measurements at T0 and T1, respectively (Table 8 and 9).

Patient	Tooth Number	Rater #1 Measurement	Rater #2 Measurement	Rater #3 Measurement	Mean Measurement (All raters)	Mean difference between raters (error)	Standard deviation of error
1	1.3	931.2	970.51	1011.17	947.7	99.9	55.2
2	1.1	523.0	589.61	508.25	542.2	54.2	31.0
3	1.3	667.6	638.47	590.32	636.4	60.1	26.2
4	1.2	297.0	310.37	288.05	300.8	14.9	8.0
5	1.1	673.3	698.81	686.84	689.7	10.2	6.2
6	4.1	342.9	369.45	349.59	356.1	13.4	11.4
7	4.1	316.5	281.03	258.85	280.3	28.0	12.2
8	4.3	510.9	586.59	520.87	544.2	43.8	34.3
9	4.2	263.5	269.07	278.51	270.4	9.9	4.7
10	4.3	390.5	427.81	334.63	384.3	62.1	28.4
11	4.2	400.4	363.27	346.06	369.0	34.4	17.2
12	1.2	392.3	472.04	390.68	419.5	54.2	42.6

Table 8: *Measurements obtained during inter-rater reliability assessment of root volume at T0 (all units in mm^3)*

Patient	Tooth Number	Rater #1 Measurement	Rater #2 Measurement	Rater #3 Measurement	Mean Measurement (All raters)	Mean difference between raters (error)	Standard deviation of error
1	1.3	857.7	1011.63	890.25	919.9	102.6	62.8
2	1.1	513.9	575.11	517.61	535.5	40.8	32.2
3	1.3	642.9	655.45	588.11	628.8	44.9	28.7
4	1.2	281.3	322.62	281.74	295.2	27.5	23.5
5	1.1	633.3	704.11	633.42	656.9	47.2	40.8
6	4.1	373.6	384.34	341.76	366.6	28.4	16.2
7	4.1	277.5	302.88	253.49	278.0	32.9	14.3
8	4.3	500.3	576.57	529.76	535.5	50.8	23.7
9	4.2	281.5	287.73	239.96	269.7	31.8	22.4
10	4.3	345.0	416.03	353.94	371.7	47.4	33.6
11	4.2	366.3	398.15	343.86	369.4	36.2	16.4
12	1.2	385.6	424.56	355.74	388.6	45.9	20.4

Table 9: *Measurements obtained during inter-rater reliability assessment of root volume at T1 (all units in mm^3)*

The raw data obtained for change in root volume by the principal investigator and the two additional investigators is presented in Table 10. The ICC (Single Measures) value of 0.386 with 95% CI [0.052, 0.797] demonstrates poor inter-rater reliability for the semi-automatic segmentation technique used in this study (Appendix, Table 1). The results of the corresponding ANOVA corroborate the ICC values obtained and showed high variance in the both the patient and observer measurements (Appendix, Table 20 and Figure 10). Visual inspection of the line graph of all measurements revealed that teeth #1.2, 4.1, 4.2 and 4.3 appear to be the sources of unreliability (Appendix, Figure 10). An overall measurement error of 5.5 ± 3.0 % was found for change in root volume measurements (Table 10).

Patient	Tooth Number	Rater #1 Measurement	Rater #2 Measurement	Rater #3 Measurement	Mean Measurement (All raters)	Mean difference between raters (error)	Standard deviation of error
1	1.3	-2.9	0.8	0.2	-0.6	2.5	1.6
2	1.1	-4.8	-8.1	-0.8	-4.6	4.9	2.1
3	1.3	-6.9	-0.2	-2.9	-3.3	4.5	2.0
4	1.2	-9.0	-7.0	-4.9	-7.0	2.8	1.2
5	1.1	-14.8	-7.6	-12.6	-11.7	4.8	2.5
6	4.1	7.2	0.2	-3.5	1.3	7.1	3.5

7	4.1	-9.9	-5.1	-4.7	-6.6	3.5	2.6
8	4.3	-5.4	-6.0	-4.0	-5.1	1.4	0.7
9	4.2	8.5	8.6	10.0	9.0	1.1	0.8
10	4.3	-17.2	-1.0	2.6	-5.2	13.2	8.5
11	4.2	-15.4	7.8	-6.3	-4.6	15.4	7.2
12	1.2	-4.5	-11.3	-5.9	-7.2	4.6	2.8

Table 10: *Measurements obtained during inter-rater reliability assessment of change in root volume (all units in %)*

3.4. DISCUSSION

The segmentation protocol to assess root volume which was used in this project showed excellent intra-rater reliability but poor inter-rater reliability as determined via the ICC values. These results are consistent with previous studies which used a similar protocol (119, 138). The authors of one study found that their root segmentation protocol resulted in an inter-rater ICC value of 0.728 with 95% CI (0.198,0.926) (119). It is important to note that this study also found that there was excellent agreement between observers for measurements of whole tooth volume. Given that our results also highlighted that volumes obtained from whole tooth segmentation were significantly more reliable than root segmentation, it is likely that one source of error is the identification of the CEJ. Once the segmented teeth are imported into the 3D Slicer software, the models appear grey by default and the observer can only rely on exterior anatomical landmarks to identify the CEJ. Some teeth did not have a distinct border between the tooth enamel and cementum, which can make it challenging for the observer to assess where to place the cut-plane tool to isolate the root. This is unlike on the CBCT, where the grey value differences between the enamel and cementum is very obvious. The poor inter-observer reproducibility may also be due to the propagation of error, since each step of the segmentation protocol is dependent upon the previous one.

Despite the poor inter-rater reliability, this segmentation protocol was selected for this thesis since the main research question involves the comparison of OIERR between two groups of patients having undergone different interventions. Therefore, only good intra-observer repeatability was required. This segmentation protocol also eliminated the effect of changes in crown volume during treatment, such as interproximal reduction and the addition of attachments for clear aligners.

The greatest percentage error in intra-rater measurements was found on tooth #4.1, followed by teeth #1.3 and 4.2. The similarity in grey values between tooth cementum and surrounding PDL and bone made it challenging to distinguish between the tooth and surrounding tissues. This is especially true in the mandibular incisors and maxillary canines, since their roots lie in proximity to the buccal and lingual cortices of bone in the apical region. For this reason, it was noted subjectively by the investigators that post-treatment roots were easier to segment than pre-treatment roots due to the presence of an enlarged PDL. Another area which proved difficult to segment was the interproximal region, where the similarity in grey values between the adjacent enamel made it difficult to assess the boundary between teeth. This could have led to the over-contouring of one tooth and the under-contouring of the adjacent tooth. This error may be compounded by the fact that each tooth has two contact points which are susceptible to misidentification. The presence of normal anatomical variation in root morphology, such as dilacerations and bifid root canals, also influenced the segmentation of the apical region. The level of mineralization of the tooth and the presence of metallic restorations also need to be considered (138). Finally, there are a variety of CBCT-related factors, such as scanning parameters (138, 139), which affect the volume measurements obtained. CBCT machines reproduce tissue density as a grey scale in a relative fashion which is machine-specific, unlike the absolute grey density values (Hounsfield units) obtained by medical CT machines (140, 141). Therefore, machine calibration may also influence the grey scale values used to determine the upper and lower thresholds during segmentation. Patient-related factors, such as movement during imaging (45, 138), also appear to play a role. The observer's experience with the software, their knowledge of dental anatomy, and their level of fatigue are additional factors which may affect root volume measurements (138).

In this segmentation protocol, the tooth pulp was included in the root volume measurement. Identification and further segmentation of the pulp chambers would have been labor intensive and unreliable given that the root canal diameter is often smaller than the voxel size used for image acquisition in this project. In addition, changes in the volume of the pulp chamber during treatment would not affect the assessment of external root resorption. Therefore, it was decided to include the volume of all internal dental soft tissues (the pulp chamber and root canal system) when measuring root volume.

Validation of the proposed segmentation protocol was not performed since the main objective of this project is to compare root resorption between two groups of patients having undergone different interventions. Precision is defined as the degree to which a measurement obtained by a person on one occasion is repeated on a subsequent occasion, whereas accuracy is defined as the closeness of a measured value to the "true" or known value (142). This project only requires a protocol with a high degree of precision, not accuracy. Furthermore, an *in-vitro* validation study for the quantification of root resorption using this protocol cannot be accomplished as this would require the researcher to assess the root volume *in-vitro* prior to orthodontic treatment. The extraction of a tooth and its subsequent handling, storage and imaging for an *in-vitro* study, even if done with extreme care and caution, will almost always result in some damage to the tooth, which will subsequently reduce its total volume. Nonetheless, a recent study using a similar *in-vivo* segmentation protocol and CBCT scanning parameters found that whole tooth volume measurements obtained were not significantly different from tooth volumes obtained by laser scan once the teeth were extracted (138).

An important limitation of this study is the use of full FOV CBCT imaging with a voxel size of 0.3mm in determining the volume of a tooth. The authors of one study which compared the volumes of CBCT-scanned at different voxel sizes to laser-scanned teeth crowns and roots concluded that the quantification of root resorption require voxels sizes of at least 0.25 mm or better (39). However, the CBCT imaging analyzed was the best available given the retrospective nature of this study. A larger voxel size of 0.3mm makes the imaging more susceptible to a phenomenon called the "partial volume effect" (143), which occurs when a voxel is larger than the object or the densities it represents, such as at the boundary between bone, PDL and tooth. Since the voxel can display only one gray value at a time, the voxel displays a grey value which is an average of the densities of the adjacent structures. This can make it difficult to identify the boundaries between the tooth and the surrounding tissues and also results in lower spatial resolution (143). The larger FOV used in this project also reduced the spatial resolution due to increased scatter levels of the x-ray beams (143). Smaller FOV CBCT scans focusing only on the maxillary and mandibular teeth would have been preferred. However, these are rarely taken on a repeated basis on the same patient during routine orthodontic treatment.

As CBCT technology continues to improve, future studies should focus on evaluating different tooth and root segmentation protocols using higher resolution CBCTs with smaller

FOVs. Recent attempts at performing fully automated segmentations using mathematical algorithms and artificial intelligence appear promising and should be explored further so that these algorithms may be incorporated into software which clinicians use on a daily basis (144-147).

3.5. CONCLUSION

The proposed protocol for obtaining root volume using *in-vivo* segmentation of a tooth from CBCT imaging was found to have excellent intra-observer repeatability but poor inter-observer reproducibility. Measurement error in repeated measures of root volume of the same tooth by one observer was found to be between -23.7% and 25.4%.

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Chapter 4 – An evaluation of root resorption associated with the use of photobiomodulation during orthodontic treatment with clear aligners: A retrospective cohort study

4.1. INTRODUCTION

Orthodontically induced external root resorption (OIERR) is a common undesirable side effect of conventional orthodontic treatment. Some degree of OIERR occurs on all teeth which is not clinically significant (23). Severe OIERR (defined as root shortening greater than 6mm) is observed in approximately 1.5% of patients (24, 148). This root shortening may affect the long-term prognosis of a tooth, leading to the possible loss of the tooth and a compromised orthodontic result. An individual's risk of developing external root resorption during orthodontic treatment may be influenced by both orthodontic and patient-related factors (23). Orthodontic treatment-related risk factors include treatment duration, magnitude of applied force, direction of tooth movement, amount of apical displacement and method of force application, type of appliance, and treatment technique (5, 23). Multiple patient-specific risk factors have also been reported in the literature, including: previous history of root resorption, tooth-root morphology, length, and roots with developmental abnormalities, genetic influences, systemic factors including drugs, hormone deficiency, hypothyroidism, hypopituitarism, asthma, root proximity to cortical bone, alveolar bone density, chronic alcoholism, previous trauma, endodontic treatment, severity and type of malocclusion, patient age and sex (23). The extent to which any one of these factors influence the severity of OIERR remains a source of debate.

There has been a growing interest among orthodontists in using adjunctive therapies to help accelerate orthodontic tooth movement, fueled by the need to find practice differentiators in an increasingly competitive marketplace for orthodontic patients. In addition, orthodontic patients, both young and old, are demanding shorter treatment times than the average 20 months which is required for conventional orthodontic treatment (2). While several factors can play a role in the length of treatment, it is an advantage for clinicians to complete their orthodontic treatments in a shorter time span. Longer treatment times have been shown to increase the risk of tooth root resorption, enamel decalcification, caries and periodontal disease (3, 4).

There exists both surgical and non-surgical modalities which may be used to accelerate orthodontic treatment (6). Among the non-surgical adjunctive interventions for accelerating tooth movement, the OrthoPulse® (Biolux Research Ltd, Fremont, CA, USA), a device which uses the principles of photobiomodulation, will be investigated in this study (Figure 1). Photobiomodulation, also known as low-level light therapy (LLLT), uses light in the red-to-near infrared range (600–950 nm) generated by low energy laser or light-emitting diode (LED) arrays

(149). Specifically, the OrthoPulse® produces light using LEDs with a near infrared wavelength of 850 nm and an intensity of 60 mW/cm^2 continuous wave (16). The LEDs are arranged in arrays to cover the target area of the alveolus of both the maxilla and mandible. The device is accompanied by a smartphone application, which tracks the patients' compliance. The manufacturer's recommended regimen is 10 minutes per day while in active orthodontic treatment. The biological mechanism of photobiomodulation has yet to be fully elucidated. Studies have shown that mitochondrial cytochrome c oxidase, the terminal enzyme in the mitochondrial oxidative respiration chain, becomes activated when it absorbs photons in this wavelength range, which in turns leads to an increase in adenosine triphosphate (ATP) production and cell metabolism (14, 150, 151). LLLT has been shown to significantly increase periodontal ligament (PDL) cell proliferation, decrease PDL cell inflammation, and increase PDL osteoclastic activity in-vitro (15). Continuous orthodontic pressure stimulates the osteoclastic activity present in the apical third of tooth roots. This has been proposed as the mechanism for external apical root resorption (24). While the increase in PDL osteoclastic activity by LLLT has been linked to enhanced orthodontic tooth movement (89), it may also be contributing to root resorption in orthodontic patients treated with this adjunctive therapy.

Figure 1. *OrthoPulse Device*

In recent years, three-dimensional Cone-Beam Computed Tomography (CBCT) has become widely used in orthodontics. Orthodontic practitioners use this technology to obtain orthodontic diagnostic records and evaluate for impacted teeth, pathology, skeletal asymmetries, airway morphology and orthognathic surgery. Compared to two-dimensional imaging, the use of CBCT imaging has been shown to be a more accurate and precise way of quantifying OIERR (44, 45, 107, 110, 113). Furthermore, the *in-vivo* volumetric assessment of changes in root morphology using CBCT has been the focus of many studies (32, 108, 115, 116). The main advantage of this method compared to linear quantification of root resorption is that it allows resorption defects to be analyzed anywhere they may occur on the root surface. It has been

suggested that both high and low resolution CBCT scans can be used to accurately quantify root resorption defects (45).

This study will focus on patients who have undergone orthodontic treatment with Invisalign® clear aligners (Align Technology Inc, San Jose, CA). It has been reported that clear aligners and light orthodontic forces with fixed appliances had similar effects on OIERR (46, 152). A more recent study using CBCT imaging found that the prevalence and severity of OIERR in patients with clear aligners may be in fact less than those in patients with fixed appliances (153). Therefore, it appears that the light, intermittent forces delivered by the clear aligners may provide a protective effect on root resorption.

While a previous study has already investigated the effect of photobiomodulation therapy on tooth root morphology following orthodontic treatment, the study did not contain a control group, was lacking appropriate and complete reporting and focused only on fixed orthodontic appliances (77). Therefore, the aim of this study is to evaluate volumetric changes in root morphology using CBCT in a group of orthodontic patients treated with clear aligners who had received adjunctive photobiomodulation therapy with the OrthoPulse device. More specifically, the primary and secondary research questions, respectively, for this project are as follows:

1. Regardless of the intervention group, is there a difference between the pre-treatment and post-treatment root volumes of maxillary and mandibular central incisors, lateral incisors and canines?
2. Are there differences in the amount of root resorption experienced by the maxillary and mandibular anterior teeth between the patients treated with OrthoPulse compared to those treated without the device?
3. If there is a difference in the amount of root resorption between the patients treated with OrthoPulse compared to those treated without the device, are there differences in the amount of root resorption experienced between the twelve maxillary and mandibular anterior teeth within each group?

4.2 METHODS

This retrospective non-randomized cohort study was approved by the University of Alberta research ethics committee (Pro00078048).

CBCT imaging from 32 subjects who received comprehensive orthodontic treatment with clear aligners (16 consecutively treated OrthoPulse® patients who met the inclusion/exclusion

and 16 matched control patients) were retrospectively compared for this study. Written informed consent was obtained from each participant. All patients began treatment between January 1st, 2015 and July 1st, 2019 and data was collected up to January 1st, 2020. Both treatment and control groups were treated by one orthodontist in his private practice. All new patients in this orthodontic office were offered acceleration of orthodontic treatment using the OrthoPulse device during the study period. Patients were given the choice whether or not to use the device following a discussion of possible risks and benefits. All new patients in this orthodontic office also receive a full field-of-view CBCT prior to the start of active aligner therapy (T0) and at least six months following the initiation of active aligner therapy as prescribed by the treating orthodontist or at the end of treatment (T1).

Subjects were selected based on the following criteria:

- Inclusion criteria:
    - Full permanent dentition
    - Non-extraction treatment plan
    - Little's irregularity score of greater than 1 mm in either the maxilla or mandible
    - Good compliance with clear aligner treatment as assessed by the treating orthodontist
    - Use of photobiomodulation device at least 50% of total recommended time
    - Treatment time more than 6months but less than 3 years
    - Availability of two CBCTs with acceptable quality and at least 6 months but no more than 4 years apart
    - Time from end of treatment to final CBCT (T1) no more than 30 days
    - Aligner changes every 3-5 days for OrthoPulse group and 7-10 days for control group

- Exclusion criteria:
    - History of trauma
    - History of root resorption
    - History of endodontic treatment
    - Use of other orthodontic accelerating modalities
    - Use of any investigational drugs
    - Use of non-steroidal anti-inflammatory drugs
    - Use of bisphosphonate drugs
    - Hormone deficiency
    - Pregnancy
    - Hypothyroidism
    - Hypopituitarism
    - Asthma

- Chronic alcoholism
- Relocated or moved during the study

The exclusion criteria were obtained based on risk factors for root resorption previously reported (23, 92).

The OrthoPulse group (n = 16) received treatment with Invisalign clear aligners (Align Technology, San Jose, CA) and changed their clear aligners every 3-5 days. They were instructed to use their OrthoPulse device for 10 minutes once per day (5 minutes to each dental arch per day) at any time during the day (16). Compliance was monitored using an application on the patient's mobile phone which is synced to the OrthoPulse device. The clear aligner group (n = 16) served as a control and received treatment with Invisalign clear aligners. They were instructed to change their aligners every 7-10 days, as determined by the treating orthodontist. Little's irregularity index (154) was calculated for both maxillary and mandibular arches from pre-treatment digital casts using OrthoCAD software (Align Technology, San Jose, CA, USA). To ensure that both groups were similar, patients in the control group were matched to those in the OrthoPulse group based on the following variables: the type of malocclusion based on molar classification (Class I, Class II or Class III), the total number of aligners used between the two time points , case difficulty as determined by the irregularity index of both arches, age and finally gender. These variables are among some of the patient-related factors which are possibly linked to increased root resorption for which data was available to allow for matching (23, 155).

A multivariate analysis of variance (MANOVA) was used to determine if the baseline characteristics of both intervention groups were similar a priori. The model assumptions for MANOVA were investigated prior to carrying out the overall test (Appendix, Table 1). As shown in Appendix, Table 2, the results of the MANOVA show that there was a statistically significant difference between the intervention groups in at least one of the baseline characteristics (Wilks' $\Lambda = 0.141$, $F(19, 12) = 3.836$, $p = 0.011$).

To understand which baseline characteristic was different between the two intervention groups, follow-up univariate ANOVAs were performed (Appendix, Table 3). They confirmed that baseline characteristics of the participants in the two groups were similar for all continuous variables, except total treatment time for which there was strong evidence to reject the null hypothesis ($P < 0.0005$) (Appendix, Table 3). This is expected given that both groups were matched for total number of aligners. Since the patients in the OrthoPulse group were changing

their aligners almost twice as often as the control group, it is expected that the total treatment time in the control group would also be approximately twice as long. Gender and type of malocclusion were similar in both groups (Appendix, Table 4).

All CBCT images were acquired with the patient in centric occlusion using the i-CAT FLX (Imaging Sciences International, Hatfield, PA, USA) with the following exposure parameters: scanning time 3.7s, 5 mA, 120 kVp, FOV: 16 cm × 13 cm, slice thickness 0.3mm. Images were converted to Digital Imaging and Communications in Medicine (DICOM) format by using the InVivo software (Anatomage, San Jose, CA, USA). The resulting DICOM folders were randomized. CBCT data was imported into ITK-Snap software (version 3.8, http://www.itksnap.org) in DICOM format. A semi-automatic segmentation technique was used to generate volumes for all 12 teeth (Figure 2). This protocol is similar to ones which have been previously described in the literature (116, 135, 136) and described in detail in Chapter 3 of this thesis. Measurements were performed by the same blinded investigator in a dark room. The volume datasets for T0 and T1 were exported as the Visualization Toolkit (VTK) file format and imported into 3DSlicer software (version 4.10.2, https://www.slicer.org/.). T0 to T1 images were superimposed by the best fit alignment using an iterative closest point algorithm (Figure 3A). A reference plane was constructed using the highest point of the labial and palatal cemento-enamel junction and a perpendicular line drawn through the long axis of the tooth (Figure 3B). The superimposed teeth were cut immediately below the reference plane, the crowns of the teeth were removed, and only the volume of the root portion was computed (Figure 3C). In clinical practice, it is more meaningful to report root resorption in terms of percentage change in root volume. Therefore, the root volume change was calculated from pre- and post-treatment root volumes for each tooth using the following formula:

$$\%\Delta\, root\ volume = \frac{root\ volume_{post-treatment} - root\ volume_{pre-treatment}}{root\ length_{pre-treatment}} x100.$$

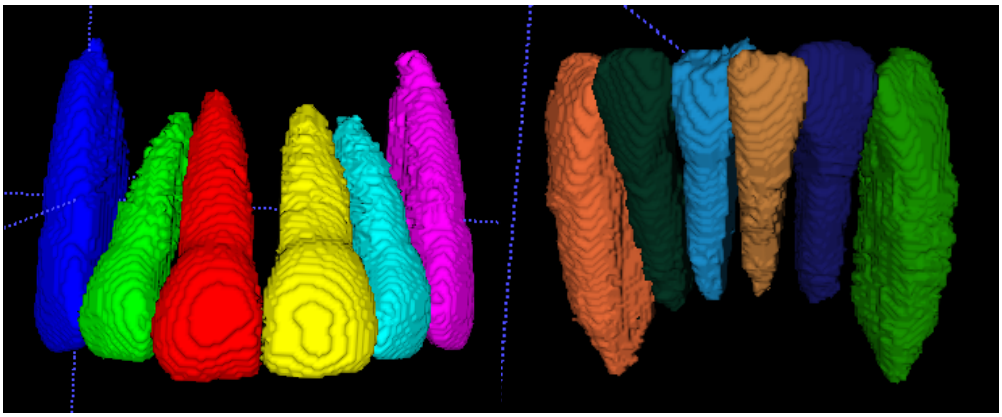
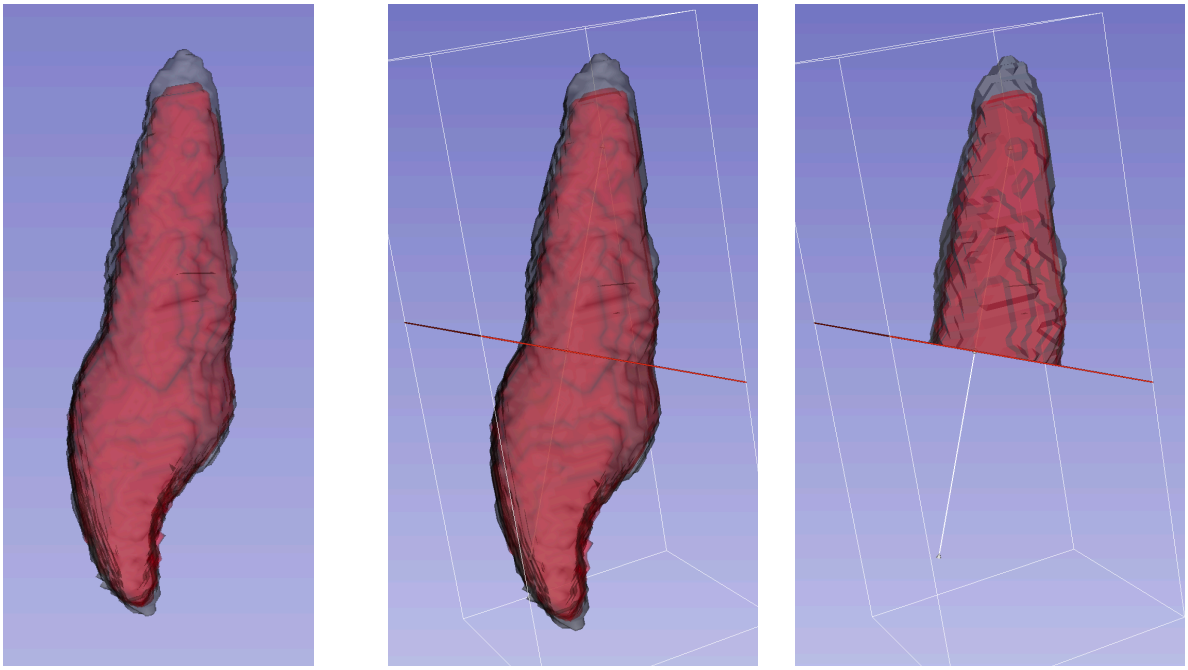


***Figure 2**: Completed segmentation of all maxillary and mandibular teeth in ITK-SNAP*



(A) **(B)** **(C)**

***Figure 3.** (A) Superimposition of T0 (grey) and T1 (red) (B) Reference plane (red line) (C) Superimposed root images at T0 and T1-mesial palatal color map view.*

A modified Little's irregularity index (154) was used to measure the crowding of the anterior portion of the maxillary or mandibular arches. The index measures the horizontal linear displacement of anatomic contact points of each maxillary and mandibular incisor from the adjacent anatomic point and sums the five displacements together. Once summed, the value represents the severity of anterior crowding. This measure was used as a proxy to determine the severity of the malocclusion and the amount of displacement experienced by each group of teeth.

Lateral cephalograms were obtained from the CBCT images from both time points (T0 and T1). Tracing was performed and values for maxillary and mandibular incisor inclination were recorded for each patient (U1-PP and IMPA, respectively). U1-PP is the angle formed between the maxillary central incisor and the palatal plane (formed by the landmarks for anterior nasal spine and posterior nasal spine). IMPA represents the angle formed between the mandibular central incisor and the mandibular plane (formed by the landmarks for gonion and gnathion). These angles were selected due to their high reliability (156). The change in inclination of the incisors was used as a proxy for the amount of apical displacement experienced by the teeth, which has been shown to be a strong risk factor for root resorption (5).

Sample size was calculated using data from a pilot study which evaluated the volume of tooth root present at 2mm coronal from the tooth apex. This length was chosen since identification of root resorption greater than 2mm using linear measurements is widely considered as being clinically significant (157). The study used the same protocol as above with the exception of placing the cut at 2mm from the pre-treatment tooth apex. In summary, linear root resorption of 2mm represented between 0.84 and 9.23% of total root volume with a mean of 3.75% (Appendix, Table 12). Using the method described by Chow *et al* (158), the minimum sample size required was calculated to be 98 patients per group with a significance of $\alpha = 0.05$ and 80% power.

The statistical analyses were performed using IBM SPSS Statistics for Mac, version 23 (IBM Corp., Armonk, N.Y., USA). A significance level of $\alpha = 0.05$ was chosen for all statistical analyses.

4.3. RESULTS

4.3.1. Descriptive statistics

Complete descriptive statistics can be found in Table 1. Data are expressed as mean ± standard deviation. When considering both groups combined, the greatest mean decrease in root volume was found to be 1.54 ± 10.66 % on tooth #1.1 followed by 1.41 ± 10.55 % for tooth #2.1. For the OrthoPulse group, the greatest mean decrease in root volume was found to be 4.14 ± 13.21 % on tooth #1.3 followed by 2.87 ± 12.42 % for tooth #1.1. For the control group, the greatest mean decrease in root volume was found to be 0.68 ± 10.22 % on tooth #2.1 followed by 0.22 ± 8.76 % for tooth #1.1. It is interesting to note that multiple teeth exhibited mean increases in root volume. The greatest mean increase in root volume was found to be 5.33 ± 13.34 % tooth

#4.3 in the control group. Overall, the OrthoPulse group was found to have a mean decrease in root volume of 1.05 ± 2.14 % when all teeth were considered, whereas the control group was found to have a mean increase in root volume of 2.07 ± 2.14 %. Mean compliance for the OrthoPulse group was 88.1 ± 16.3%. No adverse events were reported by any of the patients in either intervention groups.

	INTERVENTION	MEAN CHANGE IN ROOT VOLUME (MM^3)	STANDARD DEVIATION	MEAN CHANGE IN ROOT VOLUME (%)	STANDARD DEVIATION
TOOTH #1.3	Control	2.94	22.74	2.42	9.96
	OrthoPulse	-18.49	38.83	-4.14	13.21
	Combined	-7.78	33.14	-0.86	11.98
TOOTH #1.2	Control	-1.84	19.53	1.64	14.75
	OrthoPulse	-6.89	22.84	-1.96	16.04
	Combined	-4.36	21.06	-0.16	15.27
TOOTH #1.1	Control	-1.43	15.41	-0.22	8.76
	OrthoPulse	-9.64	27.61	-2.87	12.42
	Combined	-5.53	22.39	-1.54	10.66
TOOTH #2.1	Control	-2.11	16.95	-0.68	10.22
	OrthoPulse	-7.19	26.44	-2.13	11.16
	Combined	-4.65	22.00	-1.41	10.55
TOOTH #2.2	Control	-2.03	18.93	1.30	16.38
	OrthoPulse	-3.88	23.90	-0.26	16.13
	Combined	-2.95	21.23	0.52	16.01
TOOTH #2.3	Control	7.23	21.84	2.63	9.94
	OrthoPulse	-14.96	39.43	-3.28	14.25
	Combined	-3.87	33.32	-0.33	12.45
TOOTH #3.3	Control	9.36	23.36	4.88	9.80
	OrthoPulse	-12.06	42.69	-0.93	14.32
	Combined	-1.35	35.55	1.98	12.43
TOOTH #3.2	Control	3.42	14.45	3.85	10.37
	OrthoPulse	-0.23	19.53	2.38	17.53
	Combined	1.60	17.00	3.12	14.19
TOOTH #3.1	Control	1.16	10.23	2.21	12.57
	OrthoPulse	2.64	17.99	3.51	16.92
	Combined	1.90	14.42	2.86	14.68
TOOTH #4.1	Control	0.28	11.08	1.26	11.88
	OrthoPulse	0.13	15.06	1.47	14.51
	Combined	0.20	13.00	1.36	13.05

TOOTH #4.2	Control	4.91	15.24	5.33	13.34
	OrthoPulse	-7.41	25.29	-2.75	18.71
	Combined	-1.25	21.47	1.29	16.50
TOOTH #4.3	Control	-0.45	33.21	0.19	11.84
	OrthoPulse	-9.00	30.79	-1.64	13.34
	Combined	-4.73	31.80	-0.72	12.44

Table 1*: Descriptive statistics of change in root volume data in OrthoPulse patients, Control patients and combined for all teeth*

4.3.2. Presence of root resorption

A multivariate analysis of variance (MANOVA) was used to determine if any root resorption occurred during orthodontic treatment, regardless of intervention. The model assumptions for MANOVA were investigated prior to carrying out the overall test (Appendix, Table 5).

As shown in Appendix, Table 6, the results of the MANOVA show that there was no evidence to reject the null hypothesis (Wilks' $\Lambda = 0.745$, $F(11, 20) = 0.571$, $p = 0.840$). In other words, none of the teeth experienced a statistically significant amount of root resorption during treatment when all teeth were considered jointly.

4.3.3. Changes in root volume

The effect of the OrthoPulse device on OIERR was explored, while controlling for the confounding variables (treatment time, total number of aligners, change in incisor inclination and irregularity index). A repeated-measures analysis of covariance (ANCOVA) was chosen as the most appropriate statistical analysis.

The model assumptions were investigated prior to carrying out the ANCOVA (Appendix, Table 7). Due to its correlation with intervention and total number of aligners (Appendix, Table 9), it was decided to omit treatment time from the final statistical model. Multicollinearity was also found between the change in upper and lower incisor inclination. However, both variables were maintained in the model. Hypotheses for the ANCOVA can be found in Appendix, Table 11. The results of the ANCOVA can be found in Appendix, Table 12. Once all non-significant covariates were removed from the model, only one dependent variable was maintained: intervention (OrthoPulse vs control). Although the main effect for intervention was not significant, it was maintained in our model due since it answers our main research question.

As seen in Appendix Table 12, the main effect of tooth number showed no statistically significant difference in mean percentage change in root volume among the different teeth ($F(11, 2.153) = 0.683$, $p = 0.519$). Hence, there was no difference in the mean percentage change in volume in any of the teeth analyzed. From this finding, it follows that maxillary and mandibular teeth experienced similar amounts of OIERR. In addition, the teeth experienced changes in root symmetrically when comparing the patient's right and left sides. This finding can be explained by the presence of both positive and negative values for change in root volume measurements found in each tooth (Appendix, Figure 4).

As seen in Appendix Table 13, the main effect of intervention showed that there was no statistically significant difference in mean percentage change in root volume between intervention groups ($F(1, 30) = 1.065$, $p = 0.310$). Therefore, there does not exist a difference in mean percentage change in root volume among OrthoPulse and control patients.

There was no statistically significant interaction between the intervention and tooth number on change in root volume ($F(2.153, 64.600) = 0.558$, $p = 0.588$). Therefore, the differences in mean percentage change in root volume between intervention groups are independent of the tooth being analyzed. In other words, the mean percentage change in root volume does not change differently between the different teeth depending on whether or not the patient was treated with the OrthoPulse device.

4.4. DISCUSSION

The amount of root resorption considered clinically significant tends to vary among different dental professionals. One study found that orthodontists consider a 32% loss in root length to be significant and they are only concerned about the long-term prognosis of a tooth when it loses more than 43% of the initial root length (159). However, it is not possible to draw conclusions about changes in root volume from linear measurements. The magnitude of the changes in root volume in this study are comparable to those stated previously in the literature (109). The results showed that the teeth which experienced the most OIERR were the maxillary central incisors (Table 1). This is contrary to what has been found in previous studies which showed that the most resorbed teeth are the maxillary lateral incisors (121, 160). This is likely an incidental finding in this group of patients.

It is also interesting to note that approximately 41.6% of all the teeth in OrthoPulse group and 57.9% of all teeth in the control group in this study demonstrated mean increases in root

volume, which were not statistically significant (Table 1). This can first be explained by observer error as well as measurement error due to the partial volume effect in low resolution CBCT imaging, which is the main limitation of this study (161). Although one study (45) suggests that volumes obtained from low resolution CBCT scans are only on average 0.10 mm^3 smaller than the gold standard micro-CT measurements, the authors only quantified root resorption defects which ranged from 0.82 to 3.93 mm^3. Therefore, this error is compounded when much larger volumes, such as the entire root, are evaluated. Some increase in root volume may be attributable to the repair of the root by new cementum which is formed shortly after the application of an orthodontic force (97). The similarity in grey values on a CBCT between tooth and surrounding tissue makes the segmentation procedure quite challenging, especially in the mandibular incisor and maxillary canine regions, where the roots of these teeth are in close proximity to the cortical plate of bone. The interproximal region between teeth was equally problematic, since similarities in grey values between the adjacent enamel made it difficult to assess the boundary between teeth. The presence of normal anatomical variation in root morphology, such as dilacerations and bifid root canals, also influenced the segmentation of the apical region. The level of mineralization of the tooth and the presence of metallic restorations also need to be considered (138). There are a variety of CBCT-related factors, such as scanning parameters and machine calibration (138, 139), which affect the volume measurements obtained. However, these factors may not be contributing significantly to the measurement error, since all scans in this study were taken by the same machine using the same scanning parameters. Patient-related factors, such as movement during imaging (45, 138), also appear to play a role. The observer's experience with the software, their knowledge of dental anatomy, and their level of fatigue from repeated segmentations are other factors which may influence root volume measurements (138). The overall measurement error in change in root volume measurements was found to be 1.9 ± 1.2 % for the segmentation technique used in this study. Given the results of the pilot study which indicated that a clinically meaningful amount of root resorption may represent between 0.84 and 9.23% of total root volume depending the type of tooth, the amount of root volume change due to measurement error may be falsely interpreted as clinically significant root resorption.

The patients in the control group in this study were asked to change their aligners every 7-10 days, which is considered the standard of care according to the manufacturer's most recent clinical protocols (162). The patients in the OrthoPulse group instructed to change their aligners

every 3-5 days, which is almost double the rate compared to the control group. Therefore, it follows that, for the same number of aligners, the total treatment time in the OrthoPulse group is almost half compared to the control group. More frequent aligner changes may lead to more sustained forces on the teeth over a greater period of time, which increases the risk of a patient developing root resorption. However, this phenomenon was not found in our study. The inclusion of another control group with patients who used clear aligners and who changed their aligners every 3-5 days is essential to determining whether the similarity in OIERR between the two groups in this study was due to the anti-resorptive effects of the OrthoPulse device in the treatment group. An alternative explanation to this finding is that, regardless of how often the aligners are changed, the lighter forces delivered to the teeth by the thermoplastic material used in clear aligners may lead to less risk of developing OIERR compared to the use of fixed appliances (153). One study reported that clear aligners may have similar resorptive effects on root cementum as light orthodontic forces with fixed appliances (46), whereas another study reported that clear aligners produced less OIERR than fixed appliances (153). Therefore, the magnitude of OIERR to be expected during orthodontic treatment with clear aligners compared to fixed appliances remains unclear.

Two intervention groups in this study were matched based on the following characteristics: the type of malocclusion, the total number of aligners used between the two time points, change in incisors inclination in both arches and case difficulty as determined by the irregularity index of both arches. This was done to minimize their effect on the results obtained since they have been identified as possible confounding variables in previous studies (5, 23, 155) The baseline characteristics of the participants in the two groups were similar for all these variables (Appendix, Table 3 and 4). The change in incisor inclination obtained from the CBCT-reconstructed lateral cephalograms was used as a proxy for the amount of apical displacement, which has been shown to have a direct relationship with OIERR (5). The limitation of this measurement is that it only reflects the change of the inclination of the maxillary and mandibular central incisors, whereas all anterior teeth are changing inclination by variable amounts. In addition, bodily displacement of the tooth may not imply changes in tooth inclination but will result in apical displacement. It is theoretically possible to accurately quantify apical displacement using a superimposition of sequential CBCT imaging, but no clear protocol has yet to be established in the literature. There have also been studies that have used 2D lateral

cephalogram superimposition techniques for quantifying apical displacement (5, 116). However, these suffer from the same limitation described previously and do not provide significantly better information compared to the use of change in inclination alone.

Since this was a retrospective study, the allocation to the intervention (OrthoPulse) was not randomized and the patient and the treating orthodontist were not blinded. Therefore, there exists many sources of bias which have not been accounted for. There may exist a selection bias in the patients who chose to use the OrthoPulse, as it was only given to those who could afford to pay a nominal fee for the device. The treating orthodontist may have also influenced the results by their role in the development of the digital treatment plan for the clear aligners or their decision about when to discontinue a patient's treatment. However, given the retrospective nature of the study, it was not possible for the treating orthodontist to know which patients would ultimately be included in this study, especially among those in the control group. Finally, observer bias may also be present, given that they may have been able to identify during segmentation which CBCT images were taken at the second time point since the teeth were often well aligned and enlarged PDL spaces were present.

The effectiveness and penetration of light from the OrthoPulse device was another important aspect not evaluated in this study. The "effective" penetration of light through soft tissue is about 3.5-4 cm and depends on the wavelengths and power of the light used (11). Given that the average gingival thickness is between 1.25 to 1.56 mm depending on the location (163), it is likely that the light was able to penetrate into the bone. Once the light reaches bone, it must travel through bone to exert an effect on the root. One study showed that for each millimeter of increased bone thickness that light penetrates through, there is 6.81% loss of energy (164). In this study, the thickness of the gingival tissue was found to have some weakening effect that was not clinically significant. Wavelengths in the range 690 nm to 860 nm have been found to allow light penetration into soft tissue most efficiently (11). In this study, the OrthoPulse device provided light in the 850 nm, which falls into this effective range. Nevertheless, the wide variation in soft tissue and bone morphology present around teeth roots makes it difficult to quantify exactly how much light was absorbed by each cell in the target area. Compliance data recorded on the application on the patient's mobile phone proved to be unreliable as well, given that some patients reported using the device without connecting it to their mobile phone. Therefore, it is likely that the compliance data obtained is the lower bound of the measure of a patient's true

compliance. Nonetheless, patients with less than 50% compliance of the recommended wear were excluded to take into account this phenomenon.

For this retrospective cohort study, a causal inference cannot be drawn as there was a lack of random allocation. Furthermore, there may be a number of other confounding orthodontic and patient-related factors that are also contributing to the measured root volume changes. A randomized controlled clinical trial would be a better study design to answer the main research questions. The study included only patients who presented to one orthodontist's private clinic, therefore random sampling of the patients from the population was not done. As a result, inference to the population is not possible with the results of this study. Further randomized studies which use higher resolution CBCT imaging are needed to determine a true cause and effect relationship between OIRR and photobiomodulation devices.

4.4. CONCLUSION

None of the maxillary and mandibular anterior teeth in this study experienced a statistically significant amount of root resorption during treatment when all teeth were considered jointly. When controlling for the total treatment time, total number of aligners, change in incisor inclination and irregularity index, clear aligner patients in this study who changed their aligners every 3-5 days and used adjunctive photobiomodulation therapy did not experience statistically significant amount of OIERR compared to matched control patients. Due to the small sample size and the measurement error in the root segmentations, the presented results should be interpreted with caution.

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Chapter 5 – General Discussion and Conclusion

5.1 General Discussion

As orthodontists adopt new digital innovations, the role of the orthodontist will continue to evolve in order to enhance patient care. The use of photobiomodulation during orthodontic treatment with clear aligners has been marketed as an effective method to accelerate orthodontic tooth movement. It may allow patients to complete their treatment faster with less in-office visits, which satisfies one of the major demands of the current generation of parents and patients. It is also a potential advantage to the clinician by decreasing the risk of root resorption, caries, periodontal disease associated with longer treatment times.

In-office 3D imaging using Cone beam Computed Tomography (CBCT) is another innovation which is rapidly gaining popularity as it provides the orthodontist with a tremendous amount of 3D diagnostic information inaccessible to previous generations of orthodontists. Conventional 2D imaging modalities are limited due to the presence of magnification, distortion, superimposition and misrepresentation of structures (165). Instead, CBCT images have allowed the orthodontist to better understand the "third dimension" of orthodontics, the skeletal, dental and soft tissues structures in the transverse plane. In addition, it has become an invaluable tool for the detection of impacted teeth and pathology (such as root resorption), placement of temporary anchorage device, analysis of temporomandibular joint and airway, identification of skeletal asymmetries and planning of orthognathic surgery (165). CBCT imaging has been demonstrated to aid in altering treatment planning for impacted maxillary canines, unerupted teeth, severe root resorption, and severe skeletal discrepancies (166). CBCT is also now heavily used for research purposes, as it allows the investigator to analyze and measure any area of interest in the craniofacial complex in all three planes of space. In addition to pre-treatment diagnosis and treatment planning, CBCT may also be used to assess the effects of different interventions during treatment and to monitor stability and outcome post-treatment (166).

While CBCT requires a much lower ionizing radiation dose than traditional medical computed tomography (166), there is nonetheless an increased risk of radiation-induced carcinogenesis from low levels of radiation which a person is exposed to throughout their lifetime, known as stochastic effects (166). Given the relatively young age of the typical orthodontic patient, the effective radiation dose for CBCT imaging in orthodontics is particularly of concern due to their increased rate of cellular growth and organ development, longer life expectancies, higher specific organ and effective doses, and possibly higher radiation doses than

adults unless pediatric exposure reduction techniques are employed (166). There remains a debate about whether CBCT should be considered the standard of care for the diagnosis and treatment planning of all orthodontic patients. The position statement by the American Academy of Oral and Maxillofacial Radiology (AAOMR) regarding the use of CBCT in orthodontics emphasizes that it should only be used to answer clinical questions for which lower-dose conventional imaging is unable to adequately answer (166). This follows the principle of "as low as reasonably achievable" (ALARA), which encourages the orthodontist to address the patient's imaging needs to effectively diagnose and treat their malocclusion with as low a radiation dose as possible. (167). The use of CBCT imaging and resulting increase in radiation dose to the patient in this study is largely justified by the large number of studies which have shown the benefit of 3D CBCT imaging compared to conventional imaging when assessing root resorption (44, 45, 107, 110, 113, 114). It may be argued that a small or medium FOV CBCT would have been preferable for this research. However, the retrospective nature of this thesis ensured that the patients were not exposed to any additional radiation beyond what would normally have occurred during their treatment with the treating orthodontist. In addition, separate written and verbal informed consent was obtained from all patients following education on the specific risks, benefits, and alternatives to CBCT imaging. This is in accordance with the guidelines published by the AAOMR (168).

In Chapter 2, a systematic review of the literature surrounding OIERR and accelerated orthodontics was performed. The findings suggest that corticotomies by piezocision, micro-osteoperforations, microvibration and photobiomodulation may not have a significant effect on OIERR. It was also found that corticotomies by surgical bur, low-level laser therapy and low-intensity pulsed ultrasound may mildly reduce or have no effect on OIERR. However, this effect did not seem clinically significant. Overall, the quality of evidence supporting these findings is moderate to very low according to the GRADE approach. The decision was made prior to starting the literature search to only include randomized controlled trials (RCTs) as non-randomized clinical trials on this specific topic have been known to suffer from significant flaws in their methodology. Nonetheless, among the 20 randomized controlled trials included, eight were assessed as having some concerns of risk of bias and six as having an overall high risk of bias. Hence, there was a high level of uncertainty in the included studies, despite attempts to include higher quality research. The two included articles on photobiomodulation used the

OrthoPulse device. A recent scoping review published in 2019 on the effects of photobiomodulation on OIERR employed a more lenient inclusion criteria found 18 articles which addressed this topic. The authors found that ten studies reported a beneficial effect of photobiomodulation on OIERR while eight studies showed no significant effect (95). None of the articles found showed that photobiomodulation potentially increases OIERR. Therefore, the clinician may be reassured that the use of these devices in patients is unlikely to produce more OIERR than would be expected with conventional orthodontic treatment without adjunctive photobiomodulation therapy.

In Chapter 3, a protocol for the in-vivo volumetric assessment of OIERR using a semi-automatic segmentation technique for all maxillary and mandibular teeth was outlined. Similar protocols have been used successfully in the past to evaluate changes in root volume (116, 135, 136). The intra-observer reliability was found to be excellent, whereas the inter-observer reliability was poor. When the inter-observer reliability for the whole tooth volume was compared to that of the root volume, it was found that segmentations of the whole tooth were more reliable than those of the root only. Other studies have found similar results (119, 138). Therefore, it was concluded that it was likely the identification and placement of a cut plane at the CEJ in the segmentation process, which was causing this discrepancy. More training of the observers was unlikely to improve inter-observer reliability as all observers had extensive knowledge of dental anatomy. The identification of the CEJ occurs after the teeth have been superimposed, where they are displayed as greyscale models and does not provide the observer with any visual clue as to the boundary between these two dental structures. Other landmarks may be considered in future studies, such as choosing the cut plane to be a predefined distance from the most apical aspect of the tooth. However, given the variability in tooth length and morphology, this approach may be missing some resorption which occurs more coronal to the cut plane. Given the full coronal coverage provided by the clear aligners, the use of whole tooth volume was considered. However, a root only approach was needed in this project since enameloplasty and interproximal reduction was done on most patients, which would result in an artificial reduction in whole tooth volume. Furthermore, the main research question was to determine the relative difference in OIERR between two intervention groups, therefore the proposed protocol was adequate for this purpose.

Chapter 4 of this thesis used the segmentation protocol developed in Chapter 3 to retrospectively compare OIERR in a group of patients treated with clear aligners to a group of matched control patients treated with clear aligners alone. Only 16 patients were found to satisfy the strict inclusion criteria used in this study. First, it was found that the matching process was successful, resulting in the two groups having similar baseline characteristics. The presence of OIERR regardless of intervention was then explored. None of the maxillary and mandibular anterior teeth in this study were found to a statistically significant amount of root resorption during treatment. Since the risk of developing OIERR is multi-factorial (5, 23, 155), an effort was made to control for the effect of the total treatment time, total number of aligners, change in incisor inclination and irregularity index, when comparing the two intervention groups. It was found that clear aligner patients in this study who changed their aligners every 3-5 days and used adjunctive photobiomodulation therapy did not experience a statistically significant amount of OIERR compared to matched control patients. However, the range of the data for OIERR for each tooth was wide, as teeth were found to have both an increase and decrease in root volume. Therefore, when these values were statistically analyzed, they resulted in no difference between the groups. While some of this variation may be attributable to individual variability and the reparative process in root cementum, the magnitude of the changes in root volume observed indicates that other factors are likely at play. Therefore, due to the small sample size and the measurement error in the root segmentations, the clinician should take great care in interpreting the presented results. The findings of this study add to the body of evidence that indicates that photobiomodulation does not have a deleterious effect of root resorption and may in fact have a protective effect.

5.2. Main limitations

A large measurement error was noted in the segmentation technique due to the use of low-resolution CBCT imaging with a voxel size of 0.3 mm. The main indication for taking the full FOV CBCT images which were analyzed in this study was for diagnosis and treatment planning, which requires lower resolutions be used in order to ensure that the ALARA principle is respected. Therefore, the treating orthodontist's objective was not originally to quantify root resorption. While this resolution may be acceptable for their original purpose, a voxel size of at least 0.25 mm has been recommended for the visualization and quantification of OIERR (39). Multiple studies have reported that even 0.25 mm voxel size may not be adequate to accurately

quantify root resorption defects (119, 169). Therefore, it is likely that voxel sizes even smaller than 0.25 mm are required for the in-vivo assessment. However, this comes at a significant cost of increased radiation to the patient, which may not be justifiable given the lack of knowledge about the correlation between tooth volume loss and the long-term prognosis of a tooth.

There exist many CBCT related factors, such as voxel size, artifacts, tube current, tube voltage, fields of view and imaging software all play a role in the quality of the CBCT obtained (138, 139). A factor which is of particular concern is the partial volume effect (143). In a scan with a voxel size of 0.3mm, the PDL cannot be distinguished clearly since it is usually approximately 0.18 mm to 0.21mm wide (170). Since the voxel can display only one gray value at a time, the voxel displays a grey value which is an average of the densities of the alveolar bone, PDL and root. Therefore, this difficulty in identification of the root may be responsible for the measurement error for root volume measurements. There exist many patient related factors that affect the quantification accuracy of root volume measurements obtained, most notably patient movement during the scan and thickness of the soft tissues overlying the maxilla and mandible (45, 138).

The segmentation technique used in Chapter 3 was not validated compared to a gold standard such as micro-CT or laser scan of the teeth. However, given its similarity to other validated studies (116, 135, 136), it is not unreasonable to believe that it satisfied its main purpose which was to determine the relative difference in OIERR between two groups of patients. Finally, while the study controlled for the effects of total treatment time, total number of aligners, change in incisor inclination and irregularity index, it is impossible to rule out the influence of other unknown factors on the results obtained. The ideal study design to answer the research questions would be a randomized double-blinded prospective controlled clinical trial. However, given the very small changes in root volume that would be considered clinically significant, the sample size required may be too large to make this study design feasible. A control group which only used clear aligners with aligner changes every 3-5 days and a control group with no orthodontic intervention would have been important additions to the project to better understand if the findings are truly a result of the protective effect of photobiomodulation on OIERR. However, a sufficient number of these patients were not available at the time of publication.

5.3. Future research

High-quality RCTs using better resolution and smaller FOV CBCT scans are required to understand the true cause and effect relationship of photobiomodulation on OIERR. However, patient radiation exposure and the needs of the researchers must be balanced. A possible approach to reduce the radiation dose would be to obtain a conventional panoramic and cephalometric radiograph, followed by a higher resolution small FOV CBCT scan to assess root volumes during the diagnosis and treatment planning stage. Depending on the type of CBCT machine, this protocol has been found to result in less effective radiation dose than obtaining two full FOV scans during treatment (166).

Future research projects should focus on correlating the amount of OIERR assessed using volumetric measurements to the long-term prognosis of teeth. While there is a good understanding of the relationship between length of a tooth and its prognosis, it may also be interesting to consider how root surface area influences the survival of a tooth now that this data is available from the segmented teeth.

A better understanding of the penetrance of the photons from the LEDs in the OrthoPulse device are required. With higher resolution CBCT scans and a better understanding of this phenomenon, one could theoretically investigate the relationship between the amount of light energy received by the root to the amount of OIERR measured at different sections on the root surface (i.e. apical, mid-root and coronal), depending on the thickness of alveolar bone and soft tissues between the root and the light source. Future studies may also explore how changing the parameters of the light source (such as wavelength, intensity, pulse structure, and timing) may affect OIERR.

5.4 General Conclusions

- With a significant level of uncertainty, adjunctive interventions to accelerate orthodontic tooth movement did not appear to have a clinically significant effect on OIERR.
- The protocol used for the semi-automated segmentation and dental root measurement of maxillary and mandibular anterior teeth from full FOV CBCT scans possessed excellent intra-rater but poor inter-rater reliability.
- In response to the primary and secondary research questions of this thesis, the following conclusion were drawn:
    - There was no statistically significant difference between the pre-treatment and post-treatment root volumes of maxillary and mandibular central incisors, lateral

incisors and canines. regardless of which intervention group the patient belonged to. Hence, there was no statistically significant amount of OIERR found during treatment when comparing pre- and post-treatment root volumes in this group of patients.

- There was no statistically significant difference in the mean percentage change in root volume between clear aligner patients in this study treated with photobiomodulation using the OrthoPulse device compared to a matched control group, while controlling for the effect of total treatment time, total number of aligners, change in incisor inclination and irregularity index.
- There was no statistically significant difference in the amount of root resorption experienced between the twelve maxillary and mandibular anterior teeth within each group.

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Appendices

Chapter 2, Appendix 1. Description of the search performed in various databases and number of hits

PubMed search (759)

((((((("Orthodontics"[Mesh] OR orthodontic*)) AND ("Tooth Movement Techniques"[Mesh] OR tooth mov* OR teeth mov* OR root mov* OR apex mov* OR apical mov* OR tooth retract* OR teeth retract* OR root retract* OR apex retract* OR apical retract*))) AND (rapid* OR accelerat* OR short* OR speed* OR rate* OR fast* OR increase*))) AND ("Tooth Resorption"[Mesh] OR tooth short* OR teeth short* OR root short* OR apex short* OR apical short* OR tooth resor* OR teeth resor* OR root resor* OR apex resor* OR apical resor* OR tooth length* OR teeth length* OR root$ length* OR apex length* OR apical length*)

EMBASE and MEDLINE (OVID) search (1193 + 435)

1. exp Orthodontics
2. orthodontic$.mp.
3. 1 or 2
4. exp Tooth Movement Techniques/
5. ((tooth or teeth or root$ or apex or apical) adj2 mov$).mp.
6. ((tooth or teeth or root$ or apex or apical) adj2 retract$).mp.
7. 4 or 5 or 6
8. 3 and 7
9. (rapid$ or accelerat$ or short$ or speed$ or rate$ or fast$ or increase$).mp.
10. 8 and 9
11. exp Tooth Resorption/
12. ((tooth or teeth or root$ or apex or apical) adj2 short$).mp.
13. ((tooth or teeth or root$ or apex or apical) adj2 resor$).mp.
14. ((tooth or teeth or root$ or apex or apical) adj2 length$).mp.
15. 11 or 12 or 13 or 14
16. 10 and 15

The Cochrane Library - The Cochrane Controlled Trials Register (CENTRAL), The Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effectiveness, Economic Evaluation Database, Health Technology Assessment Database (230)

(((mh orthodontics OR orthodontic*) AND (mh Tooth Movement OR tooth mov* OR teeth mov* OR root mov* OR root mov* OR apex mov* OR apical mov* OR tooth retract* OR teeth retract* OR root retract* OR apex retract* OR apical retract*)) AND (rapid* or accelerat* or short* or speed* or rate* or fast* or increase*)) AND (mh Tooth Resorption OR tooth short* OR teeth short* OR root short* OR apex short* OR apical short* OR tooth resor* OR teeth resor* OR root resor* OR apex resor* OR apical resor* OR tooth length* OR teeth length* OR root length* OR apex length* OR apical length*))

Scopus (857)

("orthodontic*" AND ("rapid*" OR "accelerat*" OR "short*" OR "speed*" OR "rate*" OR "fast*" OR "increase*") W/2 (("tooth" W/1 "mov*") OR ("teeth" W/1 "mov*") OR ("root" W/1 "mov*") OR ("apex" W/1 "mov*") OR ("apical" W/1 "mov*") OR ("tooth" W/1 "retract*") OR ("teeth" W/1 "retract*") OR ("root" W/1 "retract*") OR ("apex" W/1 "retract*") OR ("apical" W/1 "retract*"))) AND (("tooth" W/1 "resor*") OR ("teeth" W/1 "resor*") OR ("root" W/1 "resor*") OR ("apex" W/1 "resor*") OR ("apical" W/1 "resor*") OR ("tooth" W/1 "short*") OR ("teeth" W/1 "short*") OR ("root" W/1 "short*") OR ("apex" W/1 "short*") OR ("apical" W/1 "short*") OR ("tooth" W/1 "length*") OR ("teeth" W/1 "length*") OR ("root" W/1 "length*") OR ("apex" W/1 "length*") OR ("apical" W/1 "length*"))

Web of Science (1087)

TS=((rapid* OR accelerat* OR short* OR speed* OR rate* OR fast* OR increase*) AND (orthodontic*) AND ((tooth AND mov*) OR (teeth AND mov*) OR (root AND mov*) OR (dental AND mov*) OR (apex AND mov*) OR (apical AND mov*) OR (tooth AND retract*) OR (teeth AND retract*) OR (dental AND retract*) OR (root AND retract*) OR (apex AND retract*) OR (apical AND retract*) OR (tooth AND displac*) OR (teeth AND displac*) OR (dental AND displac*) OR (root AND displac*) OR (apex AND displac*) OR (apical AND displac*)) AND ((tooth AND resor*) OR (tooth AND resor*) OR (dental AND resor*) OR (root AND resor*) OR (apex AND resor*) OR (apical AND resor*) OR (tooth AND short*) OR (teeth AND short*) OR (dental AND short*) OR (root AND short*) OR (apex AND short*) OR (apical AND short*) OR (tooth AND length*) OR (tooth AND length*) OR (dental AND length*) OR (root AND length*) OR (apex AND length*) OR (apical AND length*)))

Google Scholar search (first 200)

Orthodontic AND *(*rapid or accelerate or short or speed or rate or fast or increase*) (*tooth movement OR teeth movement OR root movement OR dental movement OR apex movement OR apical movement OR tooth retraction OR teeth retraction OR dental retraction OR root retraction OR apex retraction OR apical retraction OR tooth displacement OR teeth displacement OR dental displacement OR root displacement OR apex displacement OR apical displacement) AND (tooth resorption OR teeth resorption OR dental resorption OR root resorption OR apex resorption OR apical resorption OR tooth shortening OR teeth shortening OR dental shortening OR root shortening OR apex shortening OR apical shortening OR tooth shortening OR tooth length OR dental length OR root length OR apex length OR apical length)

ProQuest Central (202)

((noft(rapid*) or noft(accelerat*) or noft(short*) or noft(speed*) or noft(rate*) or noft(fast*) or noft(increase*)) AND (noft(orthodontic*)) AND ((noft(tooth) AND noft(mov*)) OR (noft(teeth) AND noft(mov*)) OR (noft(root) AND noft(mov*)) OR (noft(dental) AND noft(mov*)) OR (noft(apex) AND noft(mov*)) OR (noft(apical) AND noft(mov*)) OR (noft(tooth) AND noft(retract*)) OR (noft(teeth) AND noft(retract*)) OR (noft(dental) AND noft(retract*)) OR (noft(root) AND noft(retract*)) OR (noft(apex) AND noft(retract*)) OR (noft(apical) AND noft(retract*)) OR (noft(tooth) AND noft(displac*)) OR (noft(teeth) AND noft(displac*)) OR

(noft(dental) AND noft(displac*)) OR (noft(root) AND noft(displac*)) OR (noft(apex) AND noft(displac*)) OR (noft(apical) AND noft(displac*)))) AND ((noft(tooth) AND noft(resor*)) OR (noft(tooth) AND noft(resor*)) OR (noft(dental) AND noft(resor*)) OR (noft(root) AND noft(resor*)) OR (noft(apex) AND noft(resor*)) OR (noft(apical) AND noft(resor*)) OR (noft(tooth) AND noft(short*)) OR (noft(teeth) AND noft(short*)) OR (noft(dental) AND noft(short*)) OR (noft(root) AND noft(short*)) OR (noft(apex) AND noft(short*)) OR (noft(apical) AND noft(short*)) OR (noft(tooth) AND noft(length*)) OR (noft(tooth) AND noft(length*)) OR (noft(dental) AND noft(length*)) OR (noft(root) AND noft(length*)) OR (noft(apex) AND noft(length*)) OR (noft(apical) AND noft(length*)))

US National Institutes of Health Trials Register (ClinicalTrials.gov), WHO International Clinical Trials Registry Platform and metaRegister of Controlled Trials (30)

1. orthodontic and tooth resorption
2. orthodontic and dental resorption
3. orthodontic and root resorption
4. orthodontic and apical resorption
5. orthodontic and apex resorption
6. orthodontic and tooth shortening
7. orthodontic and dental shortening
8. orthodontic and root shortening
9. orthodontic and apical shortening
10. orthodontic and apex shortening
11. orthodontic and tooth length
12. orthodontic and dental length
13. orthodontic and root length
14. orthodontic and apical length
15. orthodontic and apex length

LILACS via Brieme (162)

mh:("Orthodontics") AND (mh:("Tooth Resorption") OR mh:("Tooth Movement Techniques"))

Chapter 2, Appendix 2. List of excluded full-text studies (with reason for exclusion)

Study	Intervention	Reason for exclusion
Abbas 2016	Corticotomy by surgical bur and piezocision	Quantitative data on root resorption not reported. Authors contacted.
Ahn 2016	Corticotomy by surgical bur	Retrospective cohort study design
Bajath 2019	Micro-osteoperforations	Prospective cohort study design
Chan 2018	Micro-osteoperforations	Prospective cohort study design
Cruz 2004	Low-level Laser Therapy	Quantitative data on root resorption not reported. Authors contacted
El-Bialy 2004	Low Intensity Pulsed Ultrasound	Prospective cohort study design
Gulduren 2020	Micro-osteoperforations	Quantitative data on root resorption not reported. Authors contacted.
Halkati 2016	Corticotomy by surgical bur	Prospective cohort study design
Isola 2019	Low-level laser therapy	Quantitative data on root resorption not reported. Authors contacted and only provided number of patients which experienced OIERR.
Kau 2011	Microvibration	Prospective cohort study design
Kim 2009	Corticotomy by surgical bur	Case series
Nimeri 2014	Photobiomodulation	Prospective cohort study design
Patterson 2016	Corticotomy by piezocision	Prospective cohort study design
Pavlin 2015	Microvibration	Quantitative data on root resorption not reported. Authors contacted. Data to be presented in upcoming manuscript.
Sharma 2015	Corticotomy by surgical bur	Conference abstract. Quantitative data on root resorption not reported. No contact information for authors was found.
Shetty 2019	Corticotomy by piezocision	Quantitative data on root resorption not reported. No contact information for authors was found.
Wang 2013	Corticotomy by surgical bur	Prospective cohort study
Yu 2013	Corticotomy by piezocision	Quantitative data on root resorption not reported. Authors contacted.

Chapter 2, Appendix 3. Justifications for Cochrane Risk of Bias Tool

Unique ID	1	**Study ID**	1	**Assessors**	AR, KC
Ref or Label	Aboalnaga 2019	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	**Comparator**	No MOPs	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1
Domain	**Signalling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	- computer generated randome numbers - opaque sealed envelopes were used
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			NI	
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			Y	Patients and clinicians were aware of which side MOPs was performed
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PN	OIERR unlikely to be affected by non-blinded patients and clinicians
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	ITT analysis perfromed
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	Outcome data avalable for all randomized participants
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			N	Used CBCT and Malmgran classification
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			PN	All outcomes assessed simultaneously by a blinded examiner
	4.3 Were outcome assessors aware of the intervention received by study participants?			N	No, assessor was blinded
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			PY	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	Data for OIERR was presented for both pre- and post- canine retraction timepoints
	5.3 ... multiple eligible analyses of the data?			PN	All outcome data for OIERR was reported
	Risk of bias judgement			**Low**	
Overall bias	**Risk of bias judgement**			**Low**	

Unique ID	2	**Study ID**	2	**Assessors**	AR, KC
Ref or Label	Alkebsi 2017	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	**Comparator**	No MOPs	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1
Domain	**Signalling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	- Computer generated random number sequence - Opaque envelopes selected by the patient
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	Split mouth design
	Risk of bias judgement			**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			Y	Patients and clinicians were aware of which side MOPs was performed
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			Y	Additonal interventions (replacement of mini-screw, additon of glass ionomer cement to raise
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			PY	Removal of occlusal interferences with the additon of glass ionomer cement may influence
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			Y	Split mouth study design
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			PY	ITT analysis was used. 3 subjects were excluded after the MOP intevention due to poor
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Some concerns**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	3 out of 35 subjects were excluded from the analysis after randomization
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	The use of periapical radiogrpahs to measure root lengths are not reliable compared to CBCT
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Same measurement method used for all patients at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All data about OIERR was reported
	5.3 ... multiple eligible analyses of the data?	N	Appropriate analysis was used
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	3	**Study ID**	3	**Assessors**	AR, KC
Ref or Label	Al Okla 2018	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	PBM	**Comparator**	No PBM	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	- Only statement about randomization is that the study was "randomized, double-blind clinical trial -
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	No information on how patients were assigned to intervention
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	No information on baseline characteristics of groups
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	- Patients were not aware if they were given a placebo device - Due to diffrences in the devices (wired vs wireless), it is likely that the clinician was aware of the assigned intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	No reports of deviations which arose due to the experimental context
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PN	Naive "per-protocol" analysis was used which did not take into account patients which dropped out
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	PY	12 patients out of 38 dropped out of the study
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	12 out of 38 participants dropped out of the study post-randomization
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	No sensitivity analysis was performed and analysis methods did not correct for bias
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	Reasons for dropping out of the study were reported and are unlikely to affect OIERR
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Y	Periapical radiographs are unreliable compared to CBCT when assessing root length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Measurements in both groups were likely done at the same time
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No published protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All data for OIERR was collected
	5.3 ... multiple eligible analyses of the data?	N	Only one type of analysis was appropriate
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	1	Study ID	1	Assessors	AR, KC
Ref or Label	Aboalnaga 2019	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	Comparator	No MOPs	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- computer generated randome numbers - opaque sealed envelopes were used
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians were aware of which side MOPs was performed
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	OIERR unlikely to be affected by non-blinded patients and clinicians
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis perfromed
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcome data avalable for all randomized participants
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Used CBCT and Malmgran classification
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	All outcomes assessed simultaneously by a blinded examiner
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	No, assessor was blinded
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Data for OIERR was presented for both pre- and post- canine retraction timepoints
	5.3 ... multiple eligible analyses of the data?	PN	All outcome data for OIERR was reported
	Risk of bias judgement	Low	
Overall bias	**Risk of bias judgement**	Low	

Unique ID	2	Study ID	2	Assessors	AR, KC
Ref or Label	Alkebsi 2017	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	Comparator	No MOPs	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Computer generated random number sequence - Opaque envelopes selected by the patient
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Split mouth design
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians were aware of which side MOPs was performed
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Y	Additonal interventions (replacement of mini-screw, additon of glass ionomer cement to raise
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	PY	Removal of occlusal interferences with the additon of glass ionomer cement may influence
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Y	Split mouth study design
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used. 3 subjects were excluded after the MOP intevention due to poor
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	Some concerns	

Unique ID	4	Study ID	4	Assessors	AR, KC
Ref or Label	Alqadasi 2019	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	Comparator	No MOPs	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	- Enveloppes were shuffled and patients were asked to pick an envelope - Opaque envelopes were used
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	No information
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians were aware of which side MOPs was performed on due to split mouth design
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	It is unlikely that knowledge of the intervention side would affect OIERR
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used. No dropouts were recorded
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data was available for all randomized patients
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	CBCT was used to measure tooth length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	OIERR measurements done using the same method and at comparable timepoints.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Assessor was blinded during the data analysis phase
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Only one outcome measurement was used (root length before and after treatment)
	5.3 ... multiple eligible analyses of the data?	N	Appropriate analysis was perfromed
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	5	Study ID	5	Assessors	AR, KC
Ref or Label	Ang Khaw 2018	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LLLT	Comparator	No LLLT	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- computer generated randomization scheme - laser device was configured by an assitant other than the main operator and the allocation was conceled until after data analysis
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Split mouth design, therefor both groups had similar characteristics
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Both patients and clinicians were blinded to the intervention though the use of various setting on the laser device
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used and all patients who were enrolled and randomized completed the trial (no
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	

	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data on OIERR was available for all patients randomized
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Micro-CT was used to determine total volume of resorption craters
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement methods were used at similar timepoints for both groups
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The outcomes assessor was blinded to the intervention group until data analysis was
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All outcome data for OIERR was reported
	5.3 ... multiple eligible analyses of the data?	N	Only one type of analysis was appropriate for this outcome
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	6	**Study ID**	6	**Assessors**	AR, KC
Ref or Label	Bahammam 2016	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Corticotomy + graft	**Comparator**	No Corticotomy	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Randomization performed using a computer software package - Patients were masked with respect to assignment but this was not described in detail
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Baseline characteristics reportsd were similar. However, baseline root length was not reported
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	- It is likely that patients were aware if they received a bone graft (intervention) - Clinicians were informed of group assignment once the corticotomy was perfromed, to determine the
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No additional interventions beyond those in the study protocol
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	Modified ITT analysis was perfromed, excluding data from patients which dropped out of the trial
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	Outcome data was not available for 6 out of the 33 patients which were randomized
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	No data was provided about which groups the patients wich dropped out belonged to
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	Dropout from trial were due to missed appointments and poor oral hygiene, which are not likely a result of the intervention
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Periapical radiographs are not reliable for measuring root length compared to CBCT
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	One operater performed the data analysis. All measurements were obtained using the same
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	Data was presented as the mean root length for all 4 teeth analyzed.
	5.3 ... multiple eligible analyses of the data?	PN	Only one type of analysis was appropriate to determine difference in root lengths between
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	7	Study ID	7	Assessors	AR, KC
Ref or Label	Bansal 2019	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPS	Comparator	No MOPs	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Papers with the words "experimental" and "control" were placed in opaque sealed envelopes and shuffled before patients were assigned. Pt assignment was recorded by an
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics similar.
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians were not blinded to the delivery of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviation from the study protocol was recorded during the study
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used. All pateints enrolled and randomized completed the trial.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data for all randomized patients was available
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	CBCT was used to measure root volume. There is some doubt about the reliability of volumetric
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement methods were used for data at similar timepoints.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All data was reported for OIERR. However, pre- and post- treatment root volume data was not
	5.3 ... multiple eligible analyses of the data?	PN	Only one type of analysis was appropriate for this outcome.
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	8	Study ID	8	Assessors	AR, KC
Ref or Label	Charavet 2016	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Piezocision	Comparator	No Piezocision	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Statistics department generated the allocation sequence. - Sealed opaque envelopes were used to conceal the allocation
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	No difference in baseline characteristics was found
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians cannot be blinded due to the nature of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the protocol were recorded
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used. Two patients did not present for post-treatment CBCT (1 from each

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Yes data was availbale for almost all patients that were randomized (1 patient from each group
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Medical CT was used to assess Malmgren classification of roots
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement protocols were used for data from similar timpoints in both groups
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	Only qualitative information about OIERR can be obtained from Malmgren classification
	5.3 ... multiple eligible analyses of the data?	N	Only one analysis was considered appropriate
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	9	**Study ID**	9	**Assessors**	AR, KC
Ref or Label	Charavet 2019	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Corticotomy by piezocision	**Comparator**	No corticotomy by piezocision	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Allocation sequence was generated by statistics department of the university - Sealed opaque enveloppes
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	No difference in baseline characteristics
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians cannot be blinded due to the nature of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used, excluding missing outcome data from 2 patients (one from each
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Yes, outcome data was available for most of the patients randomized. There were 2 patients that
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	CBCT was used for malmgren classificiation, which only gives a qualitative description of
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement protocols were used for both groups at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All outcome measurements were reported
	5.3 ... multiple eligible analyses of the data?	PN	All analyses were reported
	Risk of bias judgement	**Low**	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	A modified ITT analysis was used and only included patients with complete outcome data
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	24 out of 47 patients that were randomized were not included in the final analysis due to lack of
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	Analysis methods did not coorrect for bias and sensitivity analysis was not performed.
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N	Most missing data for outcomes was due to excluded non-compliant patients
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	CBCT was used to compare pre- and post-treatment root length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	The same measurement prootocol was used for all groups at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded during data analysis
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to pre-registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All outcomes related to OIERR were reported. However, only rate of OIERR. The raw data for
	5.3 ... multiple eligible analyses of the data?	PN	All analyses were appropriate and reported.
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	12	**Study ID**	12	**Assessors**	AR, KC
Ref or Label	Elkalza 2018	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	**Comparator**	Corticotomy by piezocision	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Patients were randomly allocated y a sequence generated by computer software and the allocation was centrally conceled
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics of groups not reported
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians could not be blinded due to the nature of the interventions
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was done. No dropouts were reported
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data for all patients was reported. No dropouts were reported.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	CBCT was used to measure tooth length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Measurments protocols were the same for both groups at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	No information about blinding of outcome assessor
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	Knowledge of the intervention may influence the measurement of the OIERR.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was registeered
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All measurements of OIERR were repoorted
	5.3 ... multiple eligible analyses of the data?	N	Appropriate analysis of was used

	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	13	**Study ID**	13	**Assessors**	AR, KC
Ref or Label	Goymen 2019	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LLLT or PBM	**Comparator**	No LLLT or PBM	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1
Domain	**Signalling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			NI	No details provided about how the patients were randomized into the 3 groups
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	Split mouth design. Some baseline characteristics were reported. Pre-treatment root
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	Patients were likely aware of the intervention they received, even if a sham laser was used. Clinicians were also aware of the intervention.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PN	No deviations from study protocol were reported.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	ITT analysis was used. No dropouts were reported.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	Data for all participants was reported.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			N	Micro-CT was used to assess root resorption craters
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	Same measurement protocol was used for all patients at similar timpoints
	4.3 Were outcome assessors aware of the intervention received by study participants?			NI	Unclear if outcome assessors were blinded
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			Y	Knowledge of the intervention may have affected the measurement of OIERR if an assessor favors one of the interventions
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			PN	
	Risk of bias judgement			**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			NI	No protocol was registered
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	All measurements of OIERR were reported
	5.3 ... multiple eligible analyses of the data?			N	All analyses were appropriate.
	Risk of bias judgement			**Some concerns**	
Overall bias	**Risk of bias judgement**			**Some concerns**	

Unique ID	14	**Study ID**	14	**Assessors**	AR, KC
Ref or Label	Ng 2017	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LLLT	**Comparator**	No LLLT	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1
Domain	**Signalling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	- A remote computerized random number generator was used - Sequentially numbered, opaque, sealed envelopes were also used
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	Baseline data was similar for both groups. However, baseline root volume was not reported.
	Risk of bias judgement			**Low**	
Bias due to deviations from	2.1.Were participants aware of their assigned intervention during the trial?			Y	Both types of lasers were not visiable to the naked eye so both the patient and the clinician were blinded to the interventioon
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			N	No deviations from the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	

intended interventions	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used to report data for all patients randomized
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcome data for all patients were reported. All patients randomized completed the trial
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Micro-CT was used to measure volume of root resorption craters
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement protocols were the same for all patients and at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessor was blinded until after the data analysis was completed
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All OIERR measurements were reported
	5.3 ... multiple eligible analyses of the data?	N	Appropriate analysis was used and reported
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	15	**Study ID**	15	**Assessors**	AR, KC
Ref or Label	Raza 2015	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LIPUS	**Comparator**	No LIPUS	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Sequence generation procedure was not reported. Premolars on one side were randomized to receive active LIPUS transducers
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	No baseline characteristics were reported
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	The clinician, the study coordinator and the patient were blinded to the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used, excluding missing outcome data from 2 patients. No comparison
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Outcome data for almost all randomized patients. 2 out of 12 patients were not included in the final
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Micro-CT was used to measure volume of root resorption craters
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement protocol was used for both groups and at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors was blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	Protocol was not registered a priori
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All outcomes related to OIERR were reported

the reported result	5.3 ... multiple eligible analyses of the data?	N	All analyses were reported and deemed appropriate
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	16	**Study ID**	16	**Assessors**	AR, KC
Ref or Label	Shoreibah 2012a	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Corticotomy by surgical bur	**Comparator**	No corticotomy by surgical bur	**Source**	Journal article(s) with results of the trial
Outcome	OOIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Not reported in this study
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	Baseline characteristics were not reported
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Not possible to blind the clinicians or the patients due to the nature of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations to the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used. All recruited patients coompleted the study
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data for all randomized patients was reported
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Periapical radiographs were used to assess pre- and post-treatment root length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement protocol was the same for all patients at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was registered a priori
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All outcomes related to OIERR were reported
	5.3 ... multiple eligible analyses of the data?	N	All anylyses were reported and were appropriate
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	17	**Study ID**	17	**Assessors**	AR, KC
Ref or Label	Shoreibah 2012b	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Corticotomy by surgical bur + grafting	**Comparator**	Corticotomy by surgical bur + no grafting	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Only stated that patients were randomly divided into groups
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	Not reported in this study
	Risk of bias judgement	**Some concerns**	
	2.1.Were participants aware of their assigned intervention during the trial?	Y	Not possible to blind patients or clinicians due to the nature of the outcome
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations form the study protocol were reported

Bias due to deviations from intended interventions	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used, all recruited patients completed the study
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcome data for all randomized patients was resported
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Peariapical radiographs were used to assess pre- and post-treatment root length (less reliable than
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement protocols were the same for both groups and were assessed at similar protocols
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was registered a priori
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All OIERR measurements were reported
	5.3 ... multiple eligible analyses of the data?	PN	All analyses were reported and were appropriate.
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	18	**Study ID**	18	**Assessors**	AR, KC
Ref or Label	Sousa 2011	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LLLT	**Comparator**	No LLLT	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Random sequence generation and allocation concealment were not discussed in detail. Only reported that intervention was applied to a canine chosen at random
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Split mouth design, baseline characteristics were likely similar but not reported
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Patients were not aware which side of the mouth was laser irradiated. Clinician was aware of which side was laser irradiated due to the nature of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations to the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used, all patients recruited completed the study
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data for all randomized patients was reported
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Periapical radiogrpahs were used for Malmgren classification
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement protocols were the same for all groups and were completed at similar timpoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessor was blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was published a priori

Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	10	**Study ID**	10	**Assessors**	AR, KC
Ref or Label	DiBiase 2016	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Vibration	**Comparator**	No vibration	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Randomization sequence was generated by computer software - Randomizatiion was done externally at a central location and independent from the clinical operators after recruitment
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Groups were all balanced for baseline characteristics
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	- Patients and clinicians could not be blinded to the use of the Acceledent deivce, but the patients were blinded to whether they had a functional or sham device - The sham device did not vibrate,
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the reported protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Coomplete case-analysis approach was used since missingness was classified as missing-at-
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Yes, data for most of the randomized patients was available. 9 out of 81 patients were lost.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Periapical radiographs are not reliable for measuring root length icompared to CBCT
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Measurement protocols were the same for both groups and taken from similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All outcome variables were reported
	5.3 ... multiple eligible analyses of the data?	PN	All analyses were reported
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	11	**Study ID**	11	**Assessors**	AR, KC
Ref or Label	El-Bialy 2020	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LIPUS	**Comparator**	No LIPUS	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Randomized allocation sequence created by an independant third party - Active side was done on a per-site basis
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Split-mouth study, so baseline charecteristics were similar
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN	- LIPUS device does not make a sound or light for either group - Patient and clinician was blinded too which side was active or inactive
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	

Unique ID	1	Study ID	1	Assessors	AR, KC
Ref or Label	Aboalnaga 2019	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	Comparator	No MOPs	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- computer generated randome numbers - opaque sealed envelopes were used
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians were aware of which side MOPs was performed
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	OIERR unlikely to be affected by non-blinded patients and clinicians
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis perfromed
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcome data avalable for all randomized participants
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Used CBCT and Malmgran classification
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	All outcomes assessed simultaneously by a blinded examiner
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	No, assessor was blinded
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Data for OIERR was presented for both pre- and post- canine retraction timepoints
	5.3 ... multiple eligible analyses of the data?	PN	All outcome data for OIERR was reported
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	2	Study ID	2	Assessors	AR, KC
Ref or Label	Alkebsi 2017	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	Comparator	No MOPs	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Computer generated random number sequence - Opaque envelopes selected by the patient
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Split mouth design
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians were aware of which side MOPs was performed
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Y	Additonal interventions (replacement of mini-screw, additon of glass ionomer cement to raise
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	PY	Removal of occlusal interferences with the additon of glass ionomer cement may influence
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Y	Split mouth study design
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used. 3 subjects were excluded after the MOP intevention due to poor
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Some concerns**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	3 out of 35 subjects were excluded from the analysis after randomization
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	The use of periapical radiogrpahs to measure root lengths are not reliable compared to CBCT
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Same measurement method used for all patients at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All data about OIERR was reported
	5.3 ... multiple eligible analyses of the data?	N	Appropriate analysis was used
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	3	**Study ID**	3	**Assessors**	AR, KC
Ref or Label	Al Okla 2018	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	PBM	**Comparator**	No PBM	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	- Only statement about randomization is that the study was "randomized, double-blind clinical trial -
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	No information on how patients were assigned to intervention
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	No information on baseline characteristics of groups
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	- Patients were not aware if they were given a placebo device - Due to diffrences in the devices (wired vs wireless), it is likely that the clinician was aware of the assigned intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI	No reports of deviations which arose due to the experimental context
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PN	Naive "per-protocol" analysis was used which did not take into account patients which dropped out
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	PY	12 patients out of 38 dropped out of the study
	Risk of bias judgement	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	12 out of 38 participants dropped out of the study post-randomization
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	No sensitivity analysis was performed and analysis methods did not correct for bias
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	Reasons for dropping out of the study were reported and are unlikely to affect OIERR
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Y	Periapical radiographs are unreliable compared to CBCT when assessing root length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Measurements in both groups were likely done at the same time
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No published protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All data for OIERR was collected
	5.3 ... multiple eligible analyses of the data?	N	Only one type of analysis was appropriate
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	4	Study ID	4	Assessors	AR, KC
Ref or Label	Alqadasi 2019	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	Comparator	No MOPs	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	PY	- Enveloppes were shuffled and patients were asked to pick an envelope - Opaque envelopes were used
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	No information
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians were aware of which side MOPs was performed on due to split mouth design
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN	It is unlikely that knowledge of the intervention side would affect OIERR
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used. No dropouts were recorded
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data was available for all randomized patients
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	CBCT was used to measure tooth length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	OIERR measurements done using the same method and at comparable timepoints.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Assessor was blinded during the data analysis phase
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Only one outcome measurement was used (root length before and after treatment)
	5.3 ... multiple eligible analyses of the data?	N	Appropriate analysis was perfromed
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	5	Study ID	5	Assessors	AR, KC
Ref or Label	Ang Khaw 2018	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LLLT	Comparator	No LLLT	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- computer generated randomization scheme - laser device was configured by an assitant other than the main operator and the allocation was conceled until after data analysis
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Split mouth design, therefor both groups had similar characteristics
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Both patients and clinicians were blinded to the intervention though the use of various setting on the laser device
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used and all patients who were enrolled and randomized completed the trial (no
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	

	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data on OIERR was available for all patients randomized
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Micro-CT was used to determine total volume of resorption craters
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement methods were used at similar timepoints for both groups
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The outcomes assessor was blinded to the intervention group until data analysis was
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All outcome data for OIERR was reported
	5.3 ... multiple eligible analyses of the data?	N	Only one type of analysis was appropriate for this outcome
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	6	**Study ID**	6	**Assessors**	AR, KC
Ref or Label	Bahammam 2016	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Corticotomy + graft	**Comparator**	No Corticotomy	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Randomization performed using a computer software package - Patients were masked with respect to assignment but this was not described in detail
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Baseline characteristics reportsd were similar. However, baseline root length was not reported
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	- It is likely that patients were aware if they received a bone graft (intervention) - Clinicians were informed of group assignment once the corticotomy was perfromed, to determine the
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No additional interventions beyond those in the study protocol
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	Modified ITT analysis was perfromed, excluding data from patients which dropped out of the trial
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	Outcome data was not available for 6 out of the 33 patients which were randomized
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PN	No data was provided about which groups the patients wich dropped out belonged to
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PN	Dropout from trial were due to missed appointments and poor oral hygiene, which are not likely a result of the intervention
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Periapical radiographs are not reliable for measuring root length compared to CBCT
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	One operater performed the data analysis. All measurements were obtained using the same
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	Data was presented as the mean root length for all 4 teeth analyzed.
	5.3 ... multiple eligible analyses of the data?	PN	Only one type of analysis was appropriate to determine difference in root lengths between
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	7	Study ID	7	Assessors	AR, KC
Ref or Label	Bansal 2019	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPS	Comparator	No MOPs	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Papers with the words "experimental" and "control" were placed in opaque sealed envelopes and shuffled before patients were assigned. Pt assignment was recorded by an
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics similar.
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians were not blinded to the delivery of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviation from the study protocol was recorded during the study
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used. All pateints enrolled and randomized completed the trial.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data for all randomized patients was available
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	CBCT was used to measure root volume. There is some doubt about the reliability of volumetric
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement methods were used for data at similar timepoints.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All data was reported for OIERR. However, pre- and post- treatment root volume data was not
	5.3 ... multiple eligible analyses of the data?	PN	Only one type of analysis was appropriate for this outcome.
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	8	Study ID	8	Assessors	AR, KC
Ref or Label	Charavet 2016	Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Piezocision	Comparator	No Piezocision	Source	Journal article(s) with results of the trial
Outcome	OIERR	Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Statistics department generated the allocation sequence. - Sealed opaque envelopes were used to conceal the allocation
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	No difference in baseline characteristics was found
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians cannot be blinded due to the nature of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the protocol were recorded
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used. Two patients did not present for post-treatment CBCT (1 from each

	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Yes data was availbale for almost all patients that were randomized (1 patient from each group
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Medical CT was used to assess Malmgren classification of roots
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement protocols were used for data from similar timpoints in both groups
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	Only qualitative information about OIERR can be obtained from Malmgren classification
	5.3 ... multiple eligible analyses of the data?	N	Only one analysis was considered appropriate
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	9	**Study ID**	9	**Assessors**	AR, KC
Ref or Label	Charavet 2019	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Corticotomy by piezocision	**Comparator**	No corticotomy by piezocision	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Allocation sequence was generated by statistics department of the university - Sealed opaque enveloppes
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	No difference in baseline characteristics
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians cannot be blinded due to the nature of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used, excluding missing outcome data from 2 patients (one from each
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Yes, outcome data was available for most of the patients randomized. There were 2 patients that
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	CBCT was used for malmgren classificiation, which only gives a qualitative description of
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement protocols were used for both groups at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All outcome measurements were reported
	5.3 ... multiple eligible analyses of the data?	PN	All analyses were reported
	Risk of bias judgement	**Low**	

Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	10	**Study ID**	10	**Assessors**	AR, KC
Ref or Label	DiBiase 2016	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Vibration	**Comparator**	No vibration	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Randomization sequence was generated by computer software - Randomizatiion was done externally at a central location and independent from the clinical operators after recruitment
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Groups were all balanced for baseline characteristics
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PY	- Patients and clinicians could not be blinded to the use of the Acceledent deivce, but the patients were blinded to whether they had a functional or sham device - The sham device did not vibrate,
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the reported protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Coomplete case-analysis approach was used since missingness was classified as missing-at-
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Yes, data for most of the randomized patients was available. 9 out of 81 patients were lost.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Periapical radiographs are not reliable for measuring root length icompared to CBCT
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Measurement protocols were the same for both groups and taken from similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All outcome variables were reported
	5.3 ... multiple eligible analyses of the data?	PN	All analyses were reported
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	11	**Study ID**	11	**Assessors**	AR, KC
Ref or Label	El-Bialy 2020	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LIPUS	**Comparator**	No LIPUS	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Randomized allocation sequence created by an independant third party - Active side was done on a per-site basis
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Split-mouth study, so baseline charecteristics were similar
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN	- LIPUS device does not make a sound or light for either group - Patient and clinician was blinded too which side was active or inactive
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	A modified ITT analysis was used and only included patients with complete outcome data
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	24 out of 47 patients that were randomized were not included in the final analysis due to lack of
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N	Analysis methods did not coorrect for bias and sensitivity analysis was not performed.
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	N	Most missing data for outcomes was due to excluded non-compliant patients
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	CBCT was used to compare pre- and post-treatment root length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	The same measurement prootocol was used for all groups at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded during data analysis
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to pre-registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All outcomes related to OIERR were reported. However, only rate of OIERR. The raw data for
	5.3 ... multiple eligible analyses of the data?	PN	All analyses were appropriate and reported.
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	12	**Study ID**	12	**Assessors**	AR, KC
Ref or Label	Elkalza 2018	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	MOPs	**Comparator**	Corticotomy by piezocision	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	- Patients were randomly allocated y a sequence generated by computer software and the allocation was centrally conceled
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics of groups not reported
	Risk of bias judgement	**Low**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians could not be blinded due to the nature of the interventions
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was done. No dropouts were reported
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data for all patients was reported. No dropouts were reported.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	CBCT was used to measure tooth length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	Measurments protocols were the same for both groups at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	No information about blinding of outcome assessor
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	Knowledge of the intervention may influence the measurement of the OIERR.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was registeered
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All measurements of OIERR were repoorted
	5.3 ... multiple eligible analyses of the data?	N	Appropriate analysis of was used

	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	13	**Study ID**	13	**Assessors**	AR, KC
Ref or Label	Goymen 2019	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LLLT or PBM	**Comparator**	No LLLT or PBM	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1
Domain	**Signalling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			NI	No details provided about how the patients were randomized into the 3 groups
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	Split mouth design. Some baseline characteristics were reported. Pre-treatment root
	Risk of bias judgement			**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			PY	Patients were likely aware of the intervention they received, even if a sham laser was used. Clincians were also aware of the intervention.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PY	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			PN	No deviations from study protocol were reported.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	ITT analysis was used. No dropouts were reported.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	Data for all participants was reported.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			N	Micro-CT was used to assess root resorption craters
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	Same measurement protocol was used for all patients at similar timpoints
	4.3 Were outcome assessors aware of the intervention received by study participants?			NI	Unclear if outcome assessors were blinded
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			Y	Knowledge of the intervention may have affected the measurement of OIERR if an assessor favors one of the interventions
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			PN	
	Risk of bias judgement			**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			NI	No protocol was registered
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	All measurements of OIERR were reported
	5.3 ... multiple eligible analyses of the data?			N	All analyses were appropriate.
	Risk of bias judgement			**Some concerns**	
Overall bias	**Risk of bias judgement**			**Some concerns**	

Unique ID	14	**Study ID**	14	**Assessors**	AR, KC
Ref or Label	Ng 2017	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LLLT	**Comparator**	No LLLT	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1
Domain	**Signalling question**			**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	- A remote computerized random number generator was used - Sequentially numbered, opaque, sealed envelopes were also used
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			PN	Baseline data was similar for both groups. However, baseline root volume was not reported.
	Risk of bias judgement			**Low**	
Bias due to deviations from	2.1.Were participants aware of their assigned intervention during the trial?			Y	Both types of lasers were not visiable to the naked eye so both the patient and the clinician were blinded to the interventioon
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			N	No deviations from the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?			NA	

intended interventions	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used to report data for all patients randomized
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcome data for all patients were reported. All patients randomized completed the trial
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Micro-CT was used to measure volume of root resorption craters
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement protocols were the same for all patients and at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessor was blinded until after the data analysis was completed
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Similar to registered protocol
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All OIERR measurements were reported
	5.3 ... multiple eligible analyses of the data?	N	Appropriate analysis was used and reported
	Risk of bias judgement	**Low**	
Overall bias	**Risk of bias judgement**	**Low**	

Unique ID	15	**Study ID**	15	**Assessors**	AR, KC
Ref or Label	Raza 2015	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LIPUS	**Comparator**	No LIPUS	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Sequence generation procedure was not reported. Premolars on one side were randomized to receive active LIPUS transducers
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	No baseline characteristics were reported
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	The clinician, the study coordinator and the patient were blinded to the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used, excluding missing outcome data from 2 patients. No comparison
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	Outcome data for almost all randomized patients. 2 out of 12 patients were not included in the final
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Micro-CT was used to measure volume of root resorption craters
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement protocol was used for both groups and at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors was blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
Bias in selection of	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	Protocol was not registered a priori
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All outcomes related to OIERR were reported

the reported result	5.3 ... multiple eligible analyses of the data?	N	All analyses were reported and deemed appropriate
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	16	**Study ID**	16	**Assessors**	AR, KC
Ref or Label	Shoreibah 2012a	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Corticotomy by surgical bur	**Comparator**	No corticotomy by surgical bur	**Source**	Journal article(s) with results of the trial
Outcome	OOIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Not reported in this study
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	Baseline characteristics were not reported
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Not possible to blind the clinicians or the patients due to the nature of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations to the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used. All recruited patients coompleted the study
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data for all randomized patients was reported
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Periapical radiographs were used to assess pre- and post-treatment root length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement protocol was the same for all patients at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was registered a priori
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All outcomes related to OIERR were reported
	5.3 ... multiple eligible analyses of the data?	N	All anylyses were reported and were appropriate
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	17	**Study ID**	17	**Assessors**	AR, KC
Ref or Label	Shoreibah 2012b	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Corticotomy by surgical bur + grafting	**Comparator**	Corticotomy by surgical bur + no grafting	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Only stated that patients were randomly divided into groups
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	Not reported in this study
	Risk of bias judgement	**Some concerns**	
	2.1.Were participants aware of their assigned intervention during the trial?	Y	Not possible to blind patients or clinicians due to the nature of the outcome
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations form the study protocol were reported

Bias due to deviations from intended interventions	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	ITT analysis was used, all recruited patients completed the study
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Outcome data for all randomized patients was resported
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PY	Peariapical radiographs were used to assess pre- and post-treatment root length (less reliable than
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement protocols were the same for both groups and were assessed at similar protocols
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**High**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was registered a priori
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	All OIERR measurements were reported
	5.3 ... multiple eligible analyses of the data?	PN	All analyses were reported and were appropriate.
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**High**	

Unique ID	18	**Study ID**	18	**Assessors**	AR, KC
Ref or Label	Sousa 2011	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	LLLT	**Comparator**	No LLLT	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Random sequence generation and allocation concealment were not discussed in detail. Only reported that intervention was applied to a canine chosen at random
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	Split mouth design, baseline characteristics were likely similar but not reported
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Patients were not aware which side of the mouth was laser irradiated. Clinician was aware of which side was laser irradiated due to the nature of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations to the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used, all patients recruited completed the study
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data for all randomized patients was reported
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	Periapical radiogrpahs were used for Malmgren classification
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Measurement protocols were the same for all groups and were completed at similar timpoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessor was blinded to the intervention
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was published a priori

Bias in selection of the reported result	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All outcomes measures were reported
	5.3 ... multiple eligible analyses of the data?	N	Appropriate analysis was used
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	19	**Study ID**	19	**Assessors**	AR, KC
Ref or Label	Tan 2011	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Vibration	**Comparator**	No vibration	**Source**	Non-commercial trial registry record (e.g. Clinical
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Reported that Acceledent was only active on one side and that this side was randomly assigned Allocation concealment was not reported
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	Not reported in this study
	Risk of bias judgement	**Some concerns**	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	Not possible to blind patients or clinicians due to the nature of the intervention
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used, all patients completed the study but complaince varied between 73-100%
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data for all randomized patients was reported
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	Micor-CT was used to measure volume of resorption craters
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	The same measurement protocols were used for all groups and at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Did not state details about how the outcomes were assessed
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	Knowledge of the outcome may have influenced the assessment of the outcome, although it was unlikely since no conflict of interests were reported
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was registered a prior
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All OIERR measures were reported
	5.3 ... multiple eligible analyses of the data?	N	All analyses were reported and appropriate.
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Unique ID	20	**Study ID**	20	**Assessors**	AR, KC
Ref or Label	Thind 2018	**Aim**	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Corticotomy by surgical bur	**Comparator**	corticotomy by piezocision	**Source**	Journal article(s) with results of the trial
Outcome	OIERR	**Results**		**Weight**	1

Domain	**Signalling question**	**Response**	**Comments**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	NI	Only reported that the trial was randomized into two groups
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	Not reported clearly in this study
	Risk of bias judgement	**Some concerns**	
	2.1.Were participants aware of their assigned intervention during the trial?	Y	Patients and clinicians cannot be blinded due to the nature of the outcome
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	

Bias due to deviations from intended interventions	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	No deviations from the study protocol were reported
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	ITT analysis was used, 3 patients dropped out of the study due to "personal issues". No
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Data was available for 40 out of the 43 patients which were ransdomized.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	PN	CBCT was used to measure tooth length
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	The same measurement protocol was used for both groups at similar timepoints
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Outcome assessment was not described in this study
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	Knowledge of the intervention could influence the outcome measurements, but it is unlikely due to lack of conflict of interest
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN	
	Risk of bias judgement	**Some concerns**	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	No protocol was published a prior
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	All outcomes for OIERR were reported
	5.3 ... multiple eligible analyses of the data?	N	All analyses were reported and deemed appropriate
	Risk of bias judgement	**Some concerns**	
Overall bias	**Risk of bias judgement**	**Some concerns**	

Chapter 2, Appendix 4. Summary of findings table according to the GRADE guidelines

Summary of findings:

Corticotomy by surgical bur + xenograft compared to Corticotomy for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting: University-based orthodontic clinic
Intervention: Corticotomy by surgical bur + xenograft
Comparison: Corticotomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Corticotomy	**Risk with Corticotomy by surgical bur + xenograft**				
OIERR obtained by linear measurements assessed with: periapical radiograph follow up: range 14 weeks to 20 weeks	The mean OIERR obtained by linear measurements was **0** mm	MD **0.01 mm fewer** (0.08 fewer to 0.06 more)	-	22 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	The evidence is very uncertain about the effect of corticotomy by surgical bur + xenograft on OIERR obtained by linear measurements.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Bahammam 2016 was deemed to have a high risk of bias according to the Cochrane Risk of Bias Tool
b. Only one study was considered
c. Outcomes assessed by periapical radiographs

Summary of findings:

Corticotomy by surgical bur + bioactive glass graft compared to Corticotomy for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting: University-based orthodontic clinic
Intervention: Corticotomy by surgical bur + bioactive glass graft
Comparison: Corticotomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Corticotomy	**Risk with Corticotomy by surgical bur + bioactive glass graft**				
OIERR obtained by linear measurements assessed with: periapical radiographs follow up: range 12 weeks to 20 weeks	-	SMD **0.2 SD more** (0.62 fewer to 1.01 more)	-	42 (2 RCTs)	⨁⨁◯◯ LOW [a,b,c]	Corticotomy by surgical bur + bioactive glass graft may result in little to no difference in OIERR obtained by linear measurements.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Bahammam 2016 and Shoreibah 2012b were deemed to have a high risk of bias according to the Cochrane Risk of Bias Tool.
b. Small sample size
c. Outcome measured by periapical radiographs

Summary of findings:

Corticotomy by surgical bur compared to Control for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting: University-based clinics and hospitals
Intervention: Corticotomy by surgical bur
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with Corticotomy by surgical bur**				
OIERR obtained by linear measurements assessed with: periapical radiographs follow up: range 14 weeks to 20 weeks	The mean OIERR obtained by linear measurements was **0** %	MD **9.2 % fewer** (3.29 fewer to 15.11 fewer)	-	20 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	The evidence is very uncertain about the effect of corticotomy by surgical bur on OIERR obtained by linear measurements.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Shoreibah 2012a was deemed to have a high risk of bias according to the Cochrane Risk of Bias Tool
b. Only on included study
c. Outcome measured by periapical radiograph

Summary of findings:

Corticotomy by surgical bur compared to corticotomy by piezocision for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting:
Intervention: Corticotomy by surgical bur
Comparison: corticotomy by piezocision

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with corticotomy by piezocision	**Risk with Corticotomy by surgical bur**				
OIERR obtained by linear measurements assessed with: CBCT follow up: mean 12 months	The mean OIERR obtained by linear measurements was **0** mm	MD **2.69 mm more** (1.77 more to 3.61 more)	-	40 (1 RCT)	⨁⨁◯◯ LOW [a,b,c]	Corticotomy by surgical bur may increase OIERR obtained by linear measurements .

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Thind 2018 was deemed to have an unclear risk of bias according to the Cochrane Risk of Bias Tool.
b. Only one study was considered
c. Small sample size

Summary of findings:

Corticotomy by piezocision compared to Control for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting: University-based orthodontic clinics and hospitals
Intervention: Corticotomy by piezocision
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with Corticotomy by piezocision**				
OIERR obtained by Malmgren classification assessed with: Medical CT, CBCT follow up: range 198 days to 540 days	-	SMD **0.21 SD more** (0.36 fewer to 0.78 more)	-	48 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	Corticotomy by piezocision likely results in little to no difference in OIERR obtained by Malmgren classification.
OIERR obtained by linear measurements assessed with: CBCT	The mean OIERR obtained by linear measurements was **0** mm	MD **1.19 mm fewer** (3.44 fewer to 1.06 more)	-	16 (1 RCT)	⨁⨁◯◯ LOW [b,c]	Corticotomy by piezocision may result in little to no difference in OIERR obtained by linear measurements.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Charavet 2016 and Charavet 2019 had different study protocols. Outcome assessment was also not in the same manner.
b. Elkalza 2018 was deemed to have an unclear risk of bias according to the Cochrane Risk of Bias Tool.
c. Only one study was considered

Summary of findings:

Micro-osteoperforations compared to Control for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting: University-based orthodontic clinics and hospitals
Intervention: Micro-osteoperforations
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with Micro-osteoperforations**				
OIERR obtained by linear measurements assessed with: periapical radiographs, CBCT follow up: mean 3 months	-	SMD **0.11 SD more** (0.29 fewer to 0.51 more)	-	96 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	Micro-osteoperforations may have little to no effect on OIERR obtained by linear measurements but the evidence is very uncertain.
OIERR obtained by volumetric measurements assessed with: CBCT follow up: mean 6 months	The mean OIERR obtained by volumetric measurements was **0** cubic millimeters	MD **1.57 cubic millimeters more** (0.6 fewer to 3.73 more)	-	120 (1 RCT)	⨁⨁⨁◯ MODERATE [d]	Micro-osteoperforations likely result in little to no difference in OIERR obtained by volumetric measurements.
OIERR obtained by Malmgren classification assessed with: CBCT follow up: mean 4 months	No differences were found between the pre- and post-retraction canine root resorption scores in the control and MOP groups.			36 (1 RCT)	⨁⨁◯◯ LOW [d,e]	Micro-osteoperforations may result in little to no difference in OIERR obtained by Malmgren classification.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Multiple studies with unclear or high risk of bias bias according to the Cochrane Risk of Bias Tool.
b. Outcome assessed using different imaging modalities
c. Alkebsi 2018 used periapical radiographs to measure OIERR
d. Only one study was considered
e. Malgrem Score was used for qualitative assessment of OIERR

Summary of findings:

Microvibration compared to Control for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting: University-based orthodontic clinics and hospitals
Intervention: Microvibration
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with Microvibration**				
OIERR obtained by linear measurements assessed with: periapical radiographs follow up: mean 201.6 days	The mean OIERR obtained by linear measurements was **0** mm	MD **0.09 mm more** (0.35 fewer to 0.53 more)	-	50 (1 RCT)	⨁⨁◯◯ LOW [a,b]	Microvibration may result in little to no difference in OIERR obtained by linear measurements.
OIERR obtained by volumetric measurements assessed with: Micro-CT follow up: mean 1 months	The mean OIERR obtained by volumetric measurements was **0** cubic milimeters	MD **0.01 cubic milimeters fewer** (0.5 fewer to 0.48 more)	-	30 (1 RCT)	⨁⨁◯◯ LOW [b,c]	Microvibration may result in little to no difference in OIERR obtained by volumetric measurements .

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. DiBiase 2016 was deemed to have an high risk of bias according to the Cochrane Risk of Bias Tool.
b. Only one study was considered
c. Tan 2011 employed a split mouth design and were deemed to have an some concerns of risk of bias according to the Cochrane Risk of Bias Tool.

Summary of findings:

LLLT compared to Control for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting: University-based orthodontic clinics
Intervention: LLLT
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with LLLT**				
OIERR obtained by volumetric measurements assessed with: Micro-CT follow up: mean 1 months	-	SMD **0.24 SD fewer** (0.77 fewer to 0.29 more)	-	100 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	LLLT may result in little to no difference in OIERR obtained by volumetric measurements.
OIERR (Malmgren score) assessed with: periapical radiographs follow up: mean 4 months	The mean OIERR (Malmgren score) was **0**	MD **0.07 fewer** (0.32 fewer to 0.18 more)	-	20 (1 RCT)	⨁◯◯◯ VERY LOW [c,d,e]	The evidence is very uncertain about the effect of lLLT on OIERR assessed by the Malmgren score.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardised mean difference; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Goymen 2019 and Tan 2011 were deemed to have some concerns of risk of bias according to the Cochrane Risk of Bias Tool.
b. Ng 2017 found that LLLT had a protective effect on OIERR, whereas the other 3 included studies found that LLLT had no effect on OIERR
c. Sousa 2011 was deemed to have some concerns of risk of bias according to the Cochrane Risk of Bias Tool
d. Only one study was considered
e. Malmgren score was used for the qualitative assessment of OIERR.

Summary of findings:

LIPUS compared to Control for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting: University-based and private practice orthodontic clinics
Intervention: LIPUS
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with LIPUS**				
Rate of OIERR obtained by linear measurements assessed with: CBCT follow up: mean 24 weeks	The mean rate of OIERR obtained by linear measurements was **0** mm/week	MD **0.01 mm/week lower** (0.03 lower to 0)	-	26 (1 RCT)	⨁⨁◯◯ LOW [a,b]	LIPUS may result in a slight reduction in rate of OIERR obtained by linear measurements.
OIERR obtained by volumetric measurements assessed with: Micro-CT follow up: mean 4 weeks	The mean OIERR obtained by volumetric measurements was **0** cubic millimeters	MD **0.53 cubic millimeters fewer** (0.74 fewer to 0.32 fewer)	-	40 (1 RCT)	⨁⨁◯◯ LOW [b,c]	LIPUS may result in a slight reduction in OIERR obtained by volumetric measurements.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. El-Bialy 2020 was deemed to have some concerns of risk of bias according to the Cochrane Risk of Bias Tool.
b. Only one study was considered.
c. Raza 2015 was deemed to have some concerns of bias according to the Cochrane Risk of Bias Tool

Summary of findings:

Photobiomodulation compared to Control for accelerating tooth movement in patients undergoing orthodontic treatment

Patient or population: accelerating tooth movement in patients undergoing orthodontic treatment
Setting:
Intervention: Photobiomodulation
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	**Risk with Photobiomodulation**				
OIERR obtained by linear measurements assessed with: periapical radiogrpahs follow up: range 4 months to 8 months	The mean OIERR obtained by linear measurements was **0** mm	MD **0.26 mm more** (0.25 fewer to 0.77 more)	-	44 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	The evidence is very uncertain about the effect of photobiomodulation on OIERR obtained by linear measurements.
OIERR obtained by volumetric measurements assessed with: Micro-CT follow up: mean 1 months	The mean OIERR obtained by volumetric measurements was **0** cubic militmeters	MD **0.15 cubic militmeters fewer** (0.2 fewer to 0.11 fewer)	-	20 (1 RCT)	⨁⨁◯◯ LOW [b,d]	Photobiomodulation may reduce OIERR obtained by volumetric measurements slightly.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Al Okla 2018 was deemed to have a high risk of bias according to the Cochrane Risk of Bias Tool
b. Only one study was considered.
c. Periapical radiographs were used to assess linear measurements of OIERR, which are less precise than measurements obtained by CBCT
d. Goymen 2019 was deemed to have a some concerns of risk of bias according to the Cochrane Risk of Bias Tool

Chapter 3, Appendix

Table 1. ICC for intra-rater reliability analysis of measurements for tooth volume at T0

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.995[a]	.986	.998	579.815	11	22	.000
Average Measures	.998[c]	.995	.999	579.815	11	22	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition. The between-measure variance is excluded from the denominator variance.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table 2. ANOVA for intra-rater reliability analysis of measurements for tooth volume at T0

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		1181420.02	11	107401.820		
Within People	Between Items	77.002	2	38.501	.208	.814
	Residual	4075.164	22	185.235		
	Total	4152.167	24	173.007		
Total		1185572.19	35	33873.491		

Grand Mean = 473.8028

Figure 1. Line graph for intra-rater reliability analysis measurements of tooth volume at T0

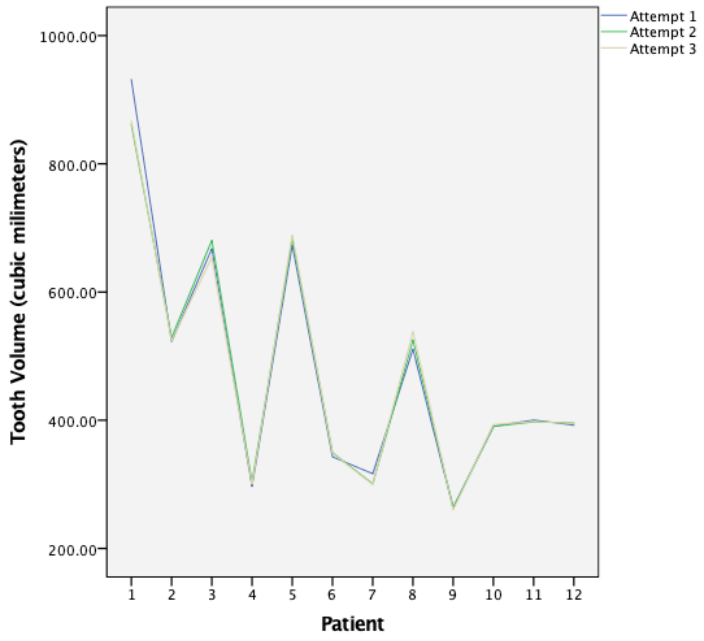


Table 3. ICC for intra-rater reliability analysis of measurements for tooth volume at T1

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.999[a]	.997	1.000	2536.680	11	22	.000
Average Measures	1.000[c]	.999	1.000	2536.680	11	22	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition. The between-measure variance is excluded from the denominator variance.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table 4. ANOVA for intra-rater reliability analysis of measurements for tooth volume at T1

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		1086869.38	11	98806.308		
Within People	Between Items	32.977	2	16.489	.423	.660
	Residual	856.923	22	38.951		
	Total	889.900	24	37.079		
Total		1087759.28	35	31078.837		

Grand Mean = 455.7639

Figure 2. Line graph for intra-rater reliability analysis measurements of tooth volume at T1

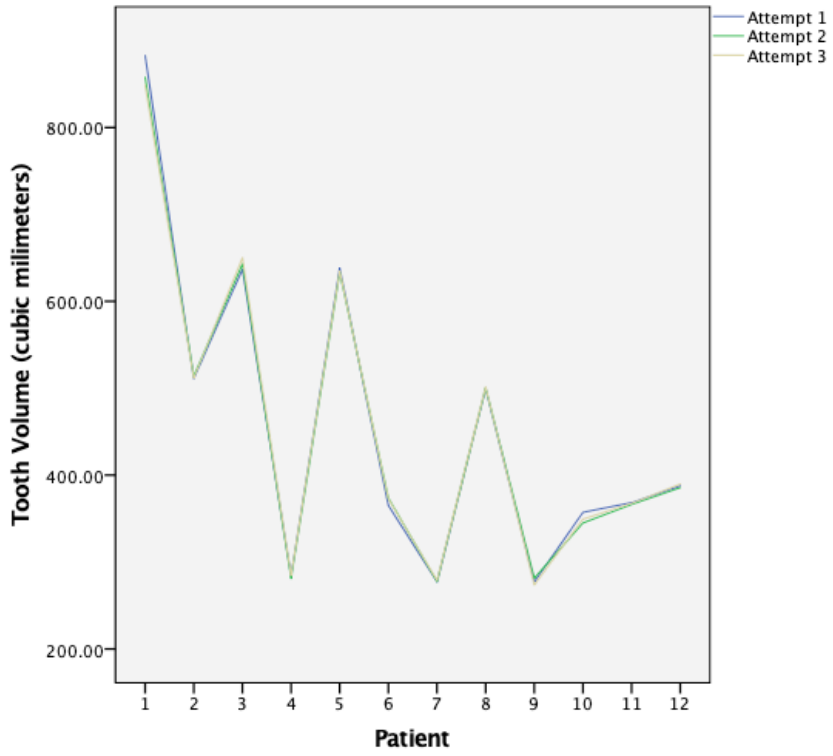


Table 5. ICC for intra-rater reliability analysis of measurements for root volume at T0

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.992[a]	.978	.997	361.805	11	22	.000
Average Measures	.997[c]	.993	.999	361.805	11	22	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition. The between-measure variance is excluded from the denominator variance.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table 6. ANOVA for intra-rater reliability analysis of measurements for root volume at T0

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		344741.293	11	31340.118		
Within People	Between Items	12.112	2	6.056	.070	.933
	Residual	1905.675	22	86.622		
	Total	1917.787	24	79.908		
Total		346659.080	35	9904.545		

Grand Mean = 227.8000

Figure 3. Line graph for intra-rater reliability analysis measurements of root volume at T0

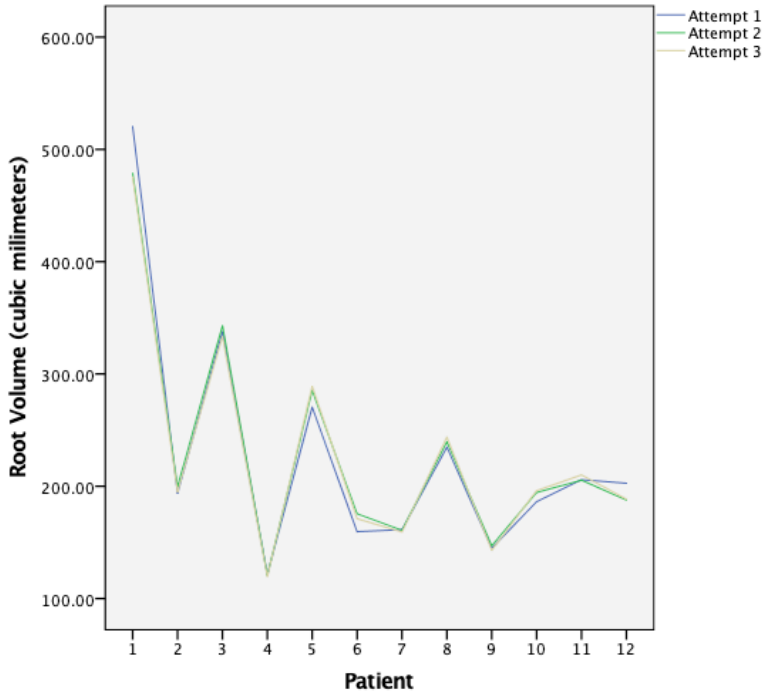


Table 7. ICC for intra-rater reliability analysis of measurements for root volume at T1

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.993[a]	.980	.998	398.111	11	22	.000
Average Measures	.997[c]	.993	.999	398.111	11	22	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition. The between-measure variance is excluded from the denominator variance.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table 8. ANOVA for intra-rater reliability analysis of measurements for root volume at T1

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		300898.519	11	27354.411		
Within People	Between Items	61.511	2	30.755	.448	.645
	Residual	1511.629	22	68.710		
	Total	1573.140	24	65.548		
Total		302471.659	35	8642.047		

Grand Mean = 212.7944

Figure 4. Line graph for intra-rater reliability analysis measurements of root volume at T1

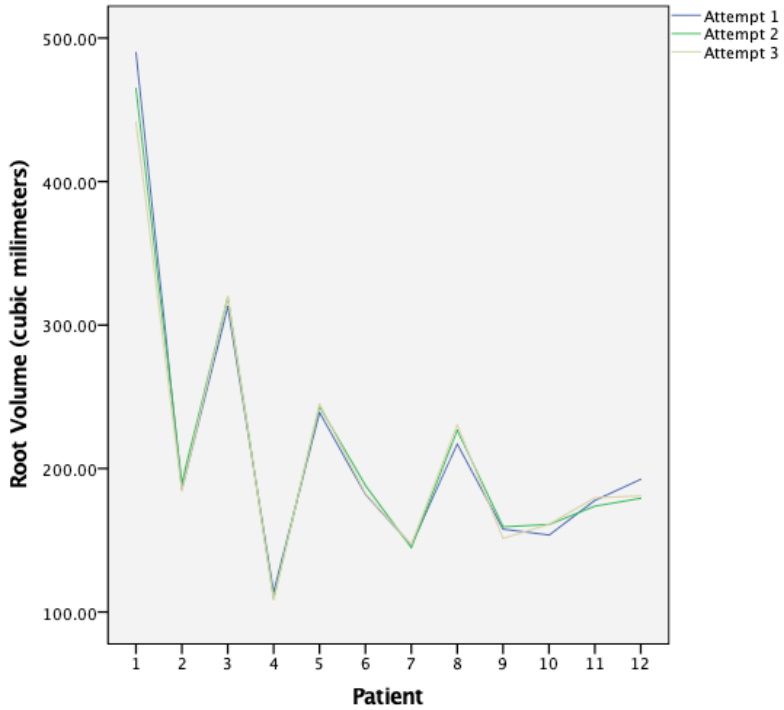


Table 9. ICC for intra-rater reliability analysis of change in root volume measurements

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.953[a]	.881	.985	61.291	11	22	.000
Average Measures	.984[c]	.957	.995	61.291	11	22	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type C intraclass correlation coefficients using a consistency definition. The between-measure variance is excluded from the denominator variance.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table 10. ANOVA for intra-rater reliability analysis of change in root volume measurements

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		2124.219	11	193.111		
Within People	Between Items	7.557	2	3.779	1.199	.320
	Residual	69.316	22	3.151		
	Total	76.873	24	3.203		
Total		2201.092	35	62.888		

Grand Mean = -6.0722

Figure 5. Line graph for intra-rater reliability analysis measurements for change in root volume

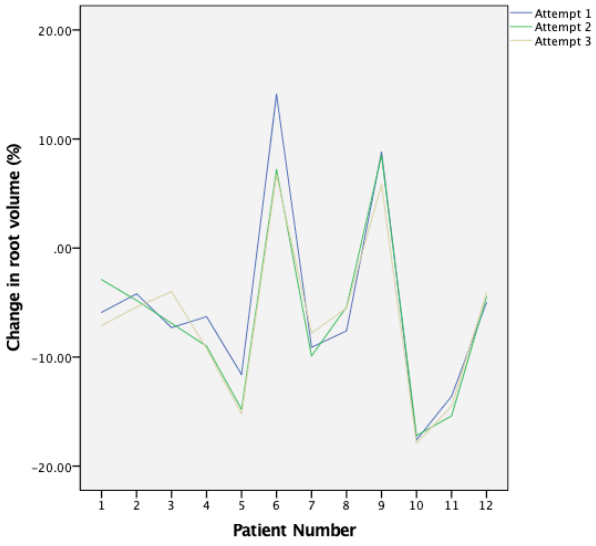


Table 11. ICC for inter-rater reliability analysis of whole tooth volume measurements at T0

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.966[a]	.911	.989	102.644	11	22	.000
Average Measures	.989[c]	.969	.996	102.644	11	22	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table 12. ANOVA for inter-rater reliability analysis of whole tooth volume measurements at T0

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		1354632.33	11	123148.394		
Within People	Between Items	7559.534	2	3779.767	3.150	.063
	Residual	26394.855	22	1199.766		
	Total	33954.389	24	1414.766		
Total		1388586.72	35	39673.906		

Grand Mean = 478.3819

Figure 6. Line graph for inter-rater reliability analysis of whole tooth volume measurements at T0

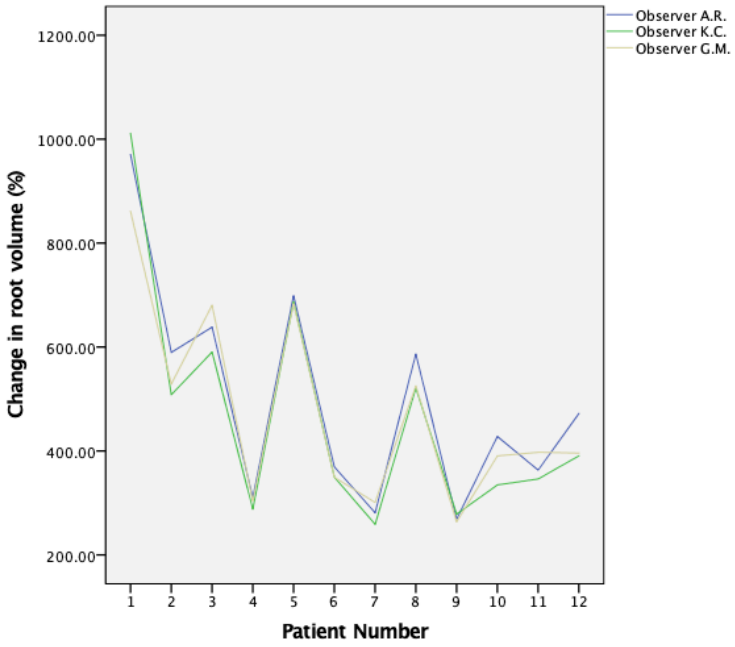


Table 13. ICC for inter-rater reliability analysis of whole tooth volume measurements at T1

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.962[a]	.735	.991	233.985	11	22	.000
Average Measures	.987[c]	.893	.997	233.985	11	22	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table 14. ANOVA for inter-rater reliability analysis of whole tooth volume measurements at T1

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		1247186.45	11	113380.586		
Within People	Between Items	25257.579	2	12628.789	26.062	.000
	Residual	10660.374	22	484.562		
	Total	35917.953	24	1496.581		
Total		1283104.40	35	36660.126		

Grand Mean = 467.9922

Figure 7. Line graph for inter-rater reliability analysis of whole tooth volume measurements at T1

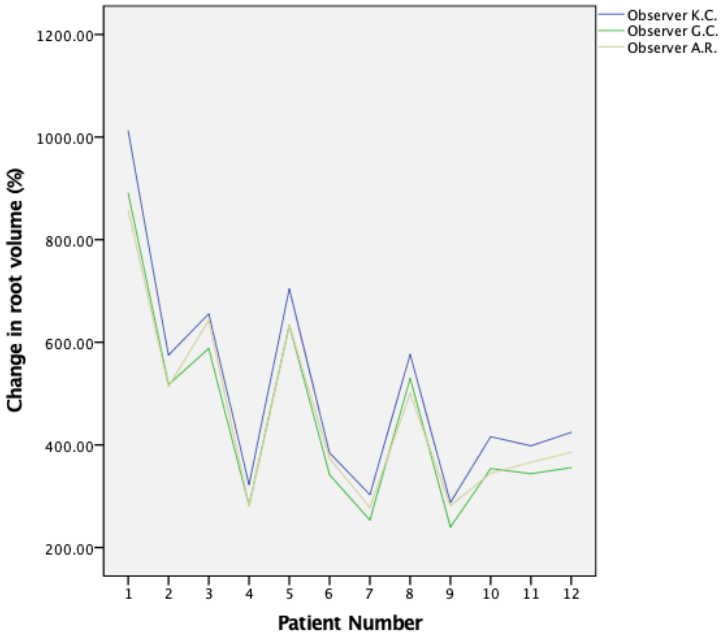


Table 15. ICC for inter-rater reliability analysis of root volume measurements at T0

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.931[a]	.822	.978	49.898	11	22	.000
Average Measures	.976[c]	.933	.993	49.898	11	22	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table 16. ANOVA for inter-rater reliability analysis of root volume measurements at T0

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		456862.440	11	41532.949		
Within People	Between Items	5922.591	2	2961.295	3.558	.046
	Residual	18311.747	22	832.352		
	Total	24234.338	24	1009.764		
Total		481096.778	35	13745.622		

Grand Mean = 231.3186

Figure 8. Line graph for inter-rater reliability analysis of root volume measurements at T0

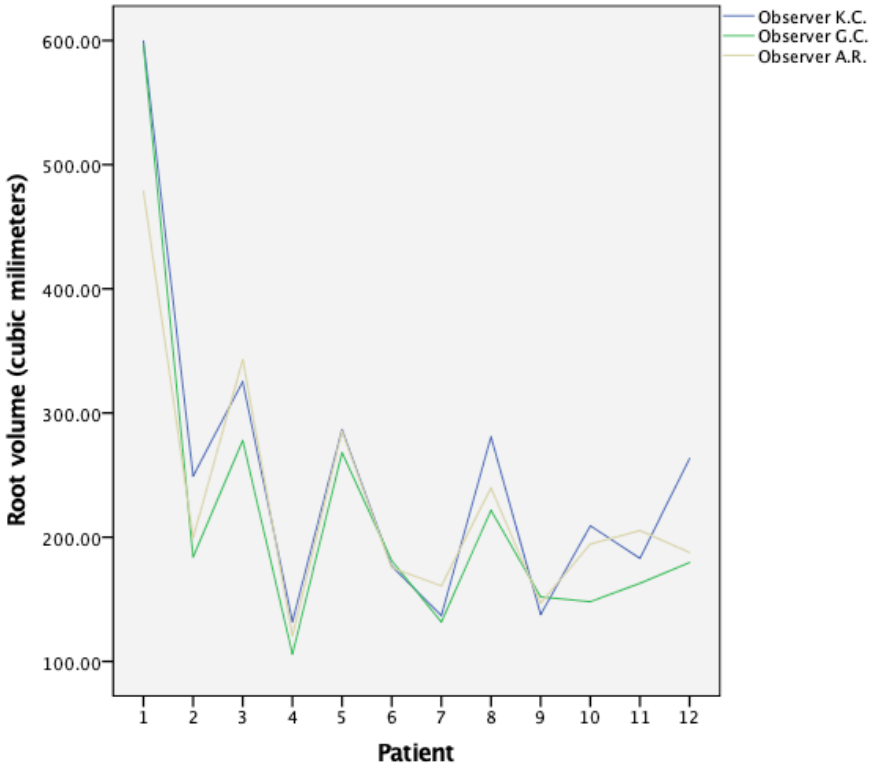


Table 17. ICC for inter-rater reliability analysis of root volume measurements at T1

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.933[a]	.817	.979	55.953	11	22	.000
Average Measures	.977[c]	.931	.993	55.953	11	22	.000

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

Table 18. ANOVA for inter-rater reliability analysis of root volume measurements at T1

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		451685.373	11	41062.307		
Within People	Between Items	7004.201	2	3502.100	4.772	.019
	Residual	16145.139	22	733.870		
	Total	23149.340	24	964.556		
Total		474834.713	35	13566.706		

Grand Mean = 222.3022

Figure 9. Line graph for inter-rater reliability analysis of root volume measurements at T1

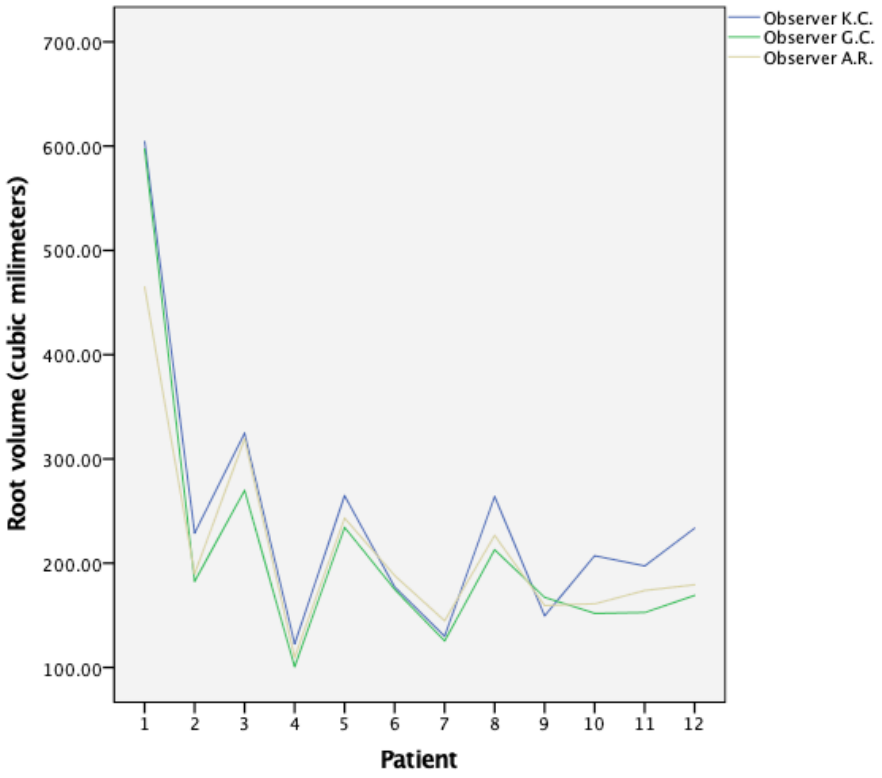


Table 19. ICC for inter-rater reliability analysis of change in root volume measurements

Intraclass Correlation Coefficient

	Intraclass Correlation[b]	95% Confidence Interval		F Test with True Value 0			
		Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.386[a]	.052	.727	3.052	11	22	.012
Average Measures	.653[c]	.141	.889	3.052	11	22	.012

Two-way mixed effects model where people effects are random and measures effects are fixed.

a. The estimator is the same, whether the interaction effect is present or not.

b. Type A intraclass correlation coefficients using an absolute agreement definition.

c. This estimate is computed assuming the interaction effect is absent, because it is not estimable otherwise.

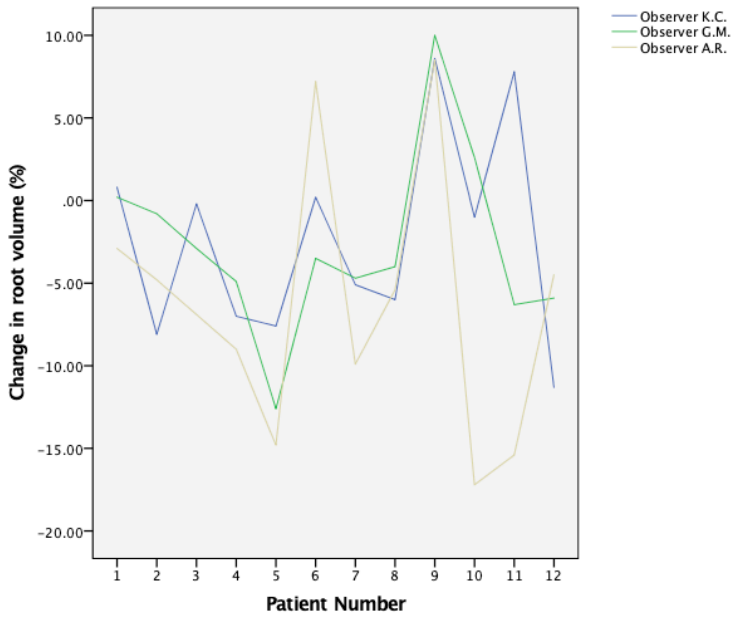
Table 20. ANOVA for intra-rater reliability analysis of change in root volume measurements

ANOVA

		Sum of Squares	df	Mean Square	F	Sig
Between People		891.973	11	81.088		
Within People	Between Items	109.415	2	54.707	2.059	.151
	Residual	584.432	22	26.565		
	Total	693.847	24	28.910		
Total		1585.820	35	45.309		

Grand Mean = -3.8000

Figure 10. Line graph for intra-rater reliability analysis measurements for change in root volume

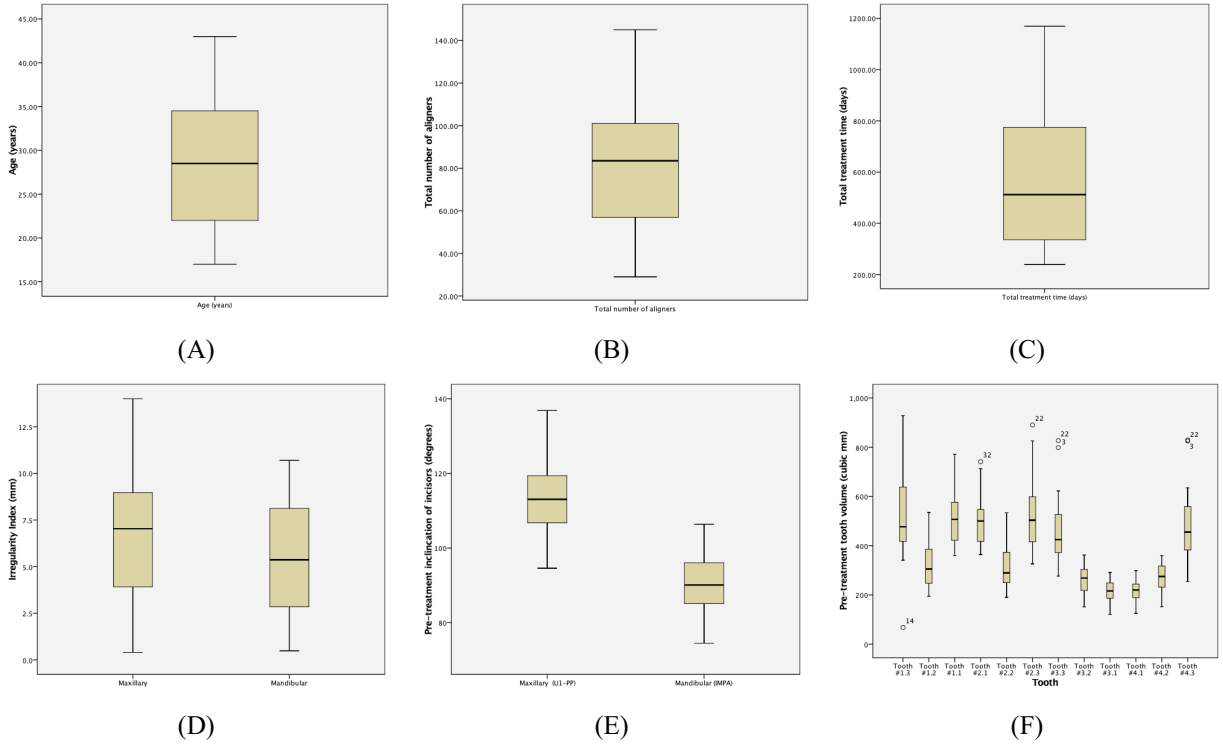


Chapter 4, Appendix

Table 1: Model assumptions for one-way MANOVA for baseline characteristics

Assumption	Method of Assessment	Conclusion	Explanation
Independence of observations	N/A	**Assumed**	Data for each variable was obtained from a different patient and the data obtained from one patient does not influence the data obtained from other patients
Multivariate normality	Boxplot for each response variable and matrix scatterplot plot for each pair of response variables (See Appendix, Figure 2)	**Not assumed**	The boxplots revealed multiple variables which were not normally distributed. Therefore, it follows that multivariate normality cannot be assumed. However, MANOVA is robust to violations of multivariate normality if groups are of nearly equal size (n=16 in all groups in this study)
Multivariate outliers	p-value of the Mahalanobis distance	**None**	Although there appeared to be univariate outliers by visual inspection, there were none as assessed by the p-value of the Mahalanobis distance being greater than 0.001 for all response variables considered jointly
Linear relationship between each pair of dependent variables	Visual inspection of the scatterplot matrix (Appendix, Figure 3)	**Assumed**	All cells in the scatterplot matrix display a linear or elliptical pattern
Homogeneity of covariance-variance matrices	Box's M-test	**N/A**	There are fewer than two non-singular cell covariance matrices
Hypothesis for the overall MANOVA test (OG = OrthoPulse, CG = Control Group)	$H_0: \begin{Bmatrix} \mu_{OGtoothvol13} \\ \mu_{OGtoothvol12} \\ \mu_{OGtoothvol11} \\ \dots \\ \mu_{OGtotaltxtime} \end{Bmatrix} = \begin{Bmatrix} \mu_{CGtoothvol13} \\ \mu_{CGtoothvol12} \\ \mu_{CGtoothvol11} \\ \dots \\ \mu_{CGtotaltxtime} \end{Bmatrix}$ $H_a: \begin{Bmatrix} \mu_{OGtoothvol13} \\ \mu_{OGtoothvol12} \\ \mu_{OGtoothvol11} \\ \dots \\ \mu_{OGtotaltxtime} \end{Bmatrix} \neq \begin{Bmatrix} \mu_{CGtoothvol13} \\ \mu_{CGtoothvol12} \\ \mu_{CGtoothvol11} \\ \dots \\ \mu_{CGtotaltxtime} \end{Bmatrix}$		

Figure 2: Boxplots of the baseline characteristics of the intervention groups: (A) age, (B) total number of aligners, (C) total treatment time, (D) irregularity index, (E) pre-treatment inclination of incisors and (F) Tooth volume



(A) (B) (C)

(D) (E) (F)

Figure 3: Scatterplot matrix of the baseline characteristics of the intervention groups

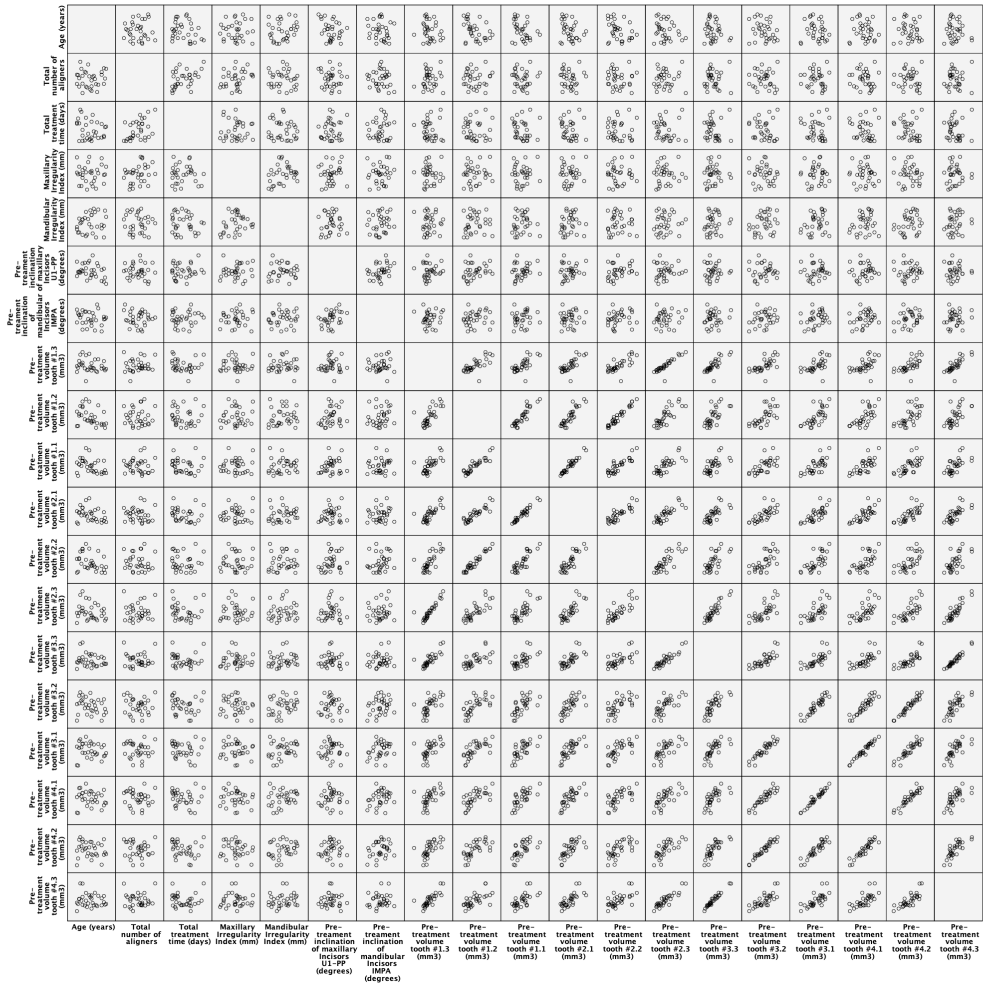


Table 2: Results for MANOVA for baseline characteristics

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Intercept	Pillai's Trace	.998	374.091[b]	19.000	12.000	.000	.998
	Wilks' Lambda	.002	374.091[b]	19.000	12.000	.000	.998
	Hotelling's Trace	592.310	374.091[b]	19.000	12.000	.000	.998
	Roy's Largest Root	592.310	374.091[b]	19.000	12.000	.000	.998
Intervention	Pillai's Trace	.859	3.836[b]	19.000	12.000	.011	.859
	Wilks' Lambda	.141	3.836[b]	19.000	12.000	.011	.859
	Hotelling's Trace	6.074	3.836[b]	19.000	12.000	.011	.859
	Roy's Largest Root	6.074	3.836[b]	19.000	12.000	.011	.859

a. Design: Intercept + Intervention

b. Exact statistic

Table 3: Baseline characteristics of participants in the two groups (continuous variables)

	Intervention	Mean	Std. Deviation	Sig
Age (years)	Control	27.38	8.28	
	OrthoPulse	29.94	7.67	0.371
	Total	28.66	7.96	
Total number of aligners	Control	81.50	29.08	
	OrthoPulse	81.13	32.12	0.973
	Total	81.31	30.14	
Total treatment time (days)	Control	767.25	243.81	
	OrthoPulse	377.31	125.86	<0.0005*
	Total	572.28	275.08	
Maxillary Irregularity Index (mm)	Control	7.04	3.68	
	OrthoPulse	6.70	3.84	0.802
	Total	6.87	3.70	
Mandibular Irregularity Index (mm)	Control	5.59	3.38	
	OrthoPulse	5.49	3.07	0.932
	Total	5.54	3.17	
Pre-treatment inclination of maxillary incisors U1-PP (degrees)	Control	114.55	9.34	
	OrthoPulse	112.42	10.77	0.554
	Total	113.48	9.98	
Pre-treatment inclination of mandibular incisors IMPA (degrees)	Control	91.75	8.23	
	OrthoPulse	88.18	7.57	0.211
	Total	89.96	7.99	
Pre-treatment volume tooth #1.3 (mm^3)	Control	491.24	194.19	
	OrthoPulse	566.78	168.67	0.249
	Total	529.01	182.99	
Pre-treatment volume tooth #1.2 (mm^3)	Control	318.59	104.05	
	OrthoPulse	337.35	94.19	0.597
	Total	327.97	98.09	
Pre-treatment volume tooth #1.1 (mm^3)	Control	499.31	106.63	
	OrthoPulse	517.22	96.06	0.621
	Total	508.26	100.25	
Pre-treatment volume tooth #2.1 (mm^3)	Control	493.89	100.57	
	OrthoPulse	505.71	93.61	0.733
	Total	499.80	95.76	

Pre-treatment volume tooth #2.2 (mm^3)	Control	310.61	100.27	
	OrthoPulse	325.92	97.82	0.665
	Total	318.27	97.75	
Pre-treatment volume tooth #2.3 (mm^3)	Control	504.59	138.21	
	OrthoPulse	549.30	144.60	0.378
	Total	526.94	140.98	
Pre-treatment volume tooth #3.3 (mm^3)	Control	448.56	127.06	
	OrthoPulse	471.97	134.36	0.616
	Total	460.26	129.18	
Pre-treatment volume tooth #3.2 (mm^3)	Control	257.61	64.42	
	OrthoPulse	265.90	50.28	0.688
	Total	261.75	57.00	
Pre-treatment volume tooth #3.1 (mm^3)	Control	210.05	51.96	
	OrthoPulse	216.52	33.93	0.679
	Total	213.28	43.29	
Pre-treatment volume tooth #4.1 (mm^3)	Control	211.78	50.33	
	OrthoPulse	216.19	36.49	0.778
	Total	213.99	43.30	
Pre-treatment volume tooth #4.2 (mm^3)	Control	257.38	59.38	
	OrthoPulse	280.42	48.66	0.239
	Total	268.90	54.67	
Pre-treatment volume tooth #4.3 (mm^3)	Control	472.14	133.20	
	OrthoPulse	487.40	134.48	0.749
	Total	479.77	131.89	

Table 4: Baseline characteristics of participants in the two groups (nominal variables)

	OrthoPulse + Clear aligners (N = 16)	Clear aligners (N = 16)
Gender (N, %)		
Male	11 (69%)	12 (75%)
Female	5 (31%)	4 (25%)
Type of Malocclusion (N, %)		
Class I	7 (44%)	7 (44%)
Class II	7 (44%)	7 (44%)
Class III	2 (12%)	2 (12%)

Table 5: Model assumptions for MANOVA (presence of root resorption)

	Method of Assessment	Conclusion	Explanation
Independence of observations	N/A	**Assumed**	Data for each variable was obtained from a different patient and the data obtained from one patient does not influence the data obtained from other patients
Multivariate normality	Boxplot for each response variable and matrix scatterplot plot for each pair of response variables (See Appendix, Figure 4 and 5)	**Not assumed**	The boxplots revealed multiple variables which were not normally distributed. Therefore, it follows that multivariate normality cannot be assumed. However, MANOVA is robust to violations of multivariate normality if groups are of nearly equal size (n=16 in all groups in this study)
Multivariate outliers	p-value of the Mahalanobis distance	**None**	Although there appeared to be univariate outliers by visual inspection, there were no as assessed by the p-value of the Mahalanobis distance being greater than 0.001 for all response variables considered jointly
Linear relationship between each pair of dependent variables	Visual inspection of the scatterplot matrix (Appendix, Figure 2)	**Assumed**	
Homogeneity of covariance-variance matrices	Box's M-test	**N/A**	No between-subjects factors
Hypothesis for the overall MANOVA test	$H_0: \begin{Bmatrix} \mu_{\%\Delta tooth13} \\ \mu_{\%\Delta tooth12} \\ \mu_{\%\Delta tooth11} \\ \dots \\ \mu_{\%\Delta tooth43} \end{Bmatrix} = \begin{Bmatrix} 0 \\ 0 \\ 0 \\ \dots \\ 0 \end{Bmatrix}$	$H_a: \begin{Bmatrix} \mu_{\%\Delta tooth13} \\ \mu_{\%\Delta tooth12} \\ \mu_{\%\Delta tooth11} \\ \dots \\ \mu_{\%\Delta tooth43} \end{Bmatrix} \neq \begin{Bmatrix} 0 \\ 0 \\ 0 \\ \dots \\ 0 \end{Bmatrix}$	

Figure #4: Boxplots of the percentage change in root volume for different teeth in both intervention groups for all teeth

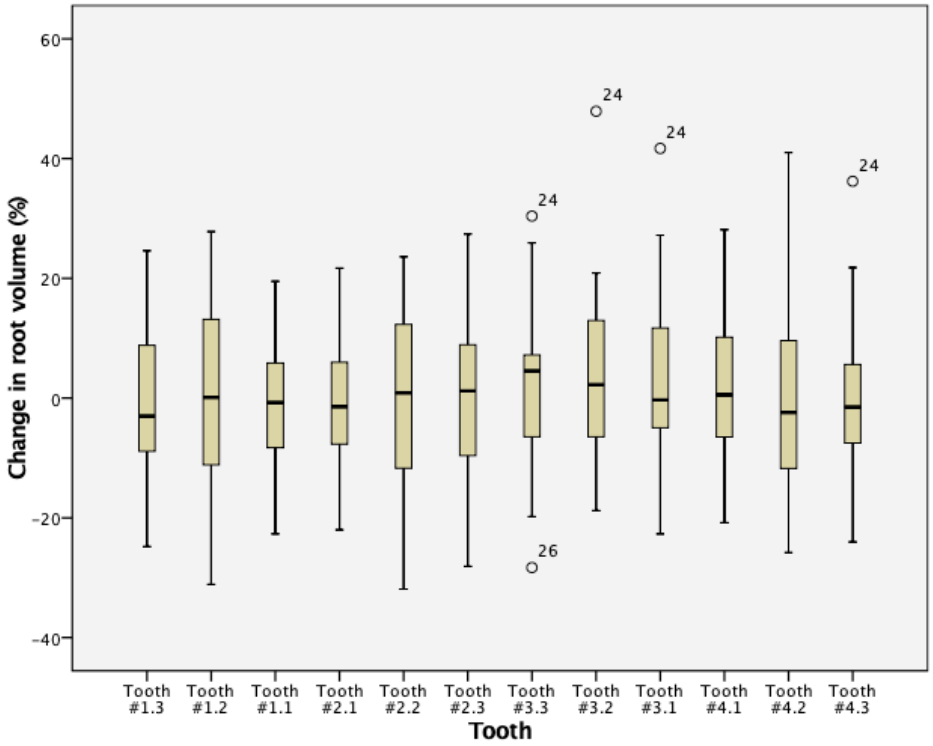


Figure 5: Scatterplot matrix of percentage change in root volume for all teeth

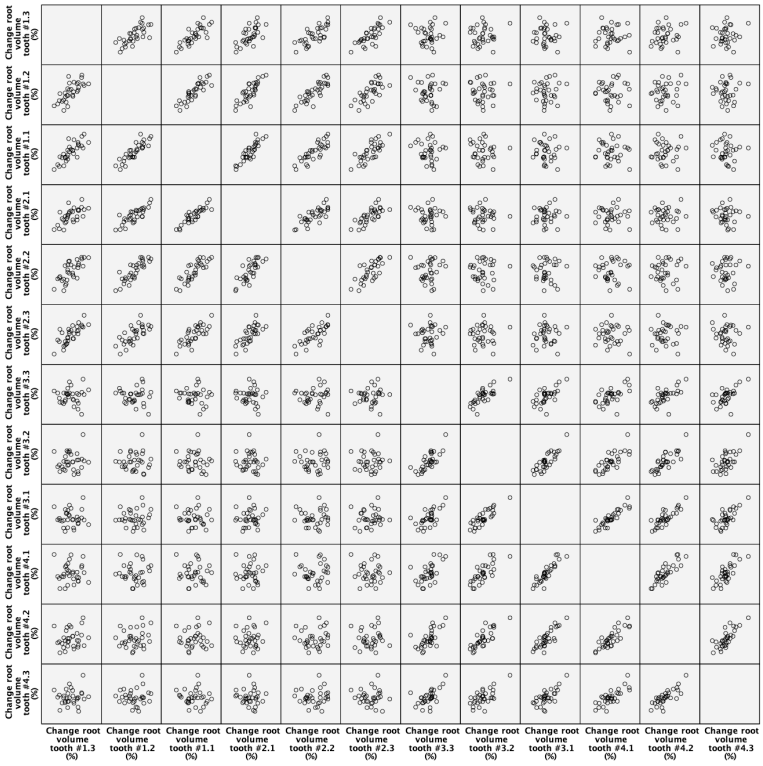


Table 6: Results for MANOVA with change in root volume data

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Intercept	Pillai's Trace	.255	.571[b]	12.000	20.000	.840	.255
	Wilks' Lambda	.745	.571[b]	12.000	20.000	.840	.255
	Hotelling's Trace	.342	.571[b]	12.000	20.000	.840	.255
	Roy's Largest Root	.342	.571[b]	12.000	20.000	.840	.255

a. Design: Intercept

b. Exact statistic

Table 7: Model assumptions for ANCOVA (change in root volume)

	Method of Assessment	Conclusion	Explanation
Independence of observations	N/A	**Assumed**	Data for each variable was obtained from a different patient and the data obtained from one patient does not influence the data obtained from other patients
Normality	Boxplot for each dependent and independent variable (See Appendix, Figure 6 and 7)	**Not assumed**	The boxplots revealed multiple variables which were not normally distributed. Therefore, it follows that multivariate normality cannot be assumed. However, ANCOVA is robust to violations of multivariate normality if the sample sizes of both groups are similar in size (n=16) and similarly skewed.
Multivariate outliers	p-value of the Mahalanobis distance	**None**	Although there appeared to be univariate outliers by visual inspection, there were no as assessed by the p-value of the Mahalanobis distance being greater than 0.001 for all response variables considered jointly
Linear relationship between each pair of dependent and independent variables	Visual inspection of the scatterplot matrices (Appendix, Figure 5,8,9,10)	**Assumed**	
Homogeneity of variances	Levene's test (Appendix, Table	**Assumed**	p-value for all teeth > 0.05
Multicollinearity		**Present**	Statistically significant, strong positive correlation between number of

			aligners and total treatment time, and upper and lower incisor inclination (Appendix, Table 7 and Figure 11,12)
Sphericity	Mauchly Test of Sphericity (Appendix, Table 8)	**Assumed**	$\chi 2(65) = 314.603$, $p < 0.0005$, which indicates that these data violate the sphericity assumption. Greenhouse-Geisser ε correction was used.
Hypotheses for the overall ANCOVA test			See Appendix, Table 11

Figure 6: Boxplots for percentage change in root volume for all teeth and interventions

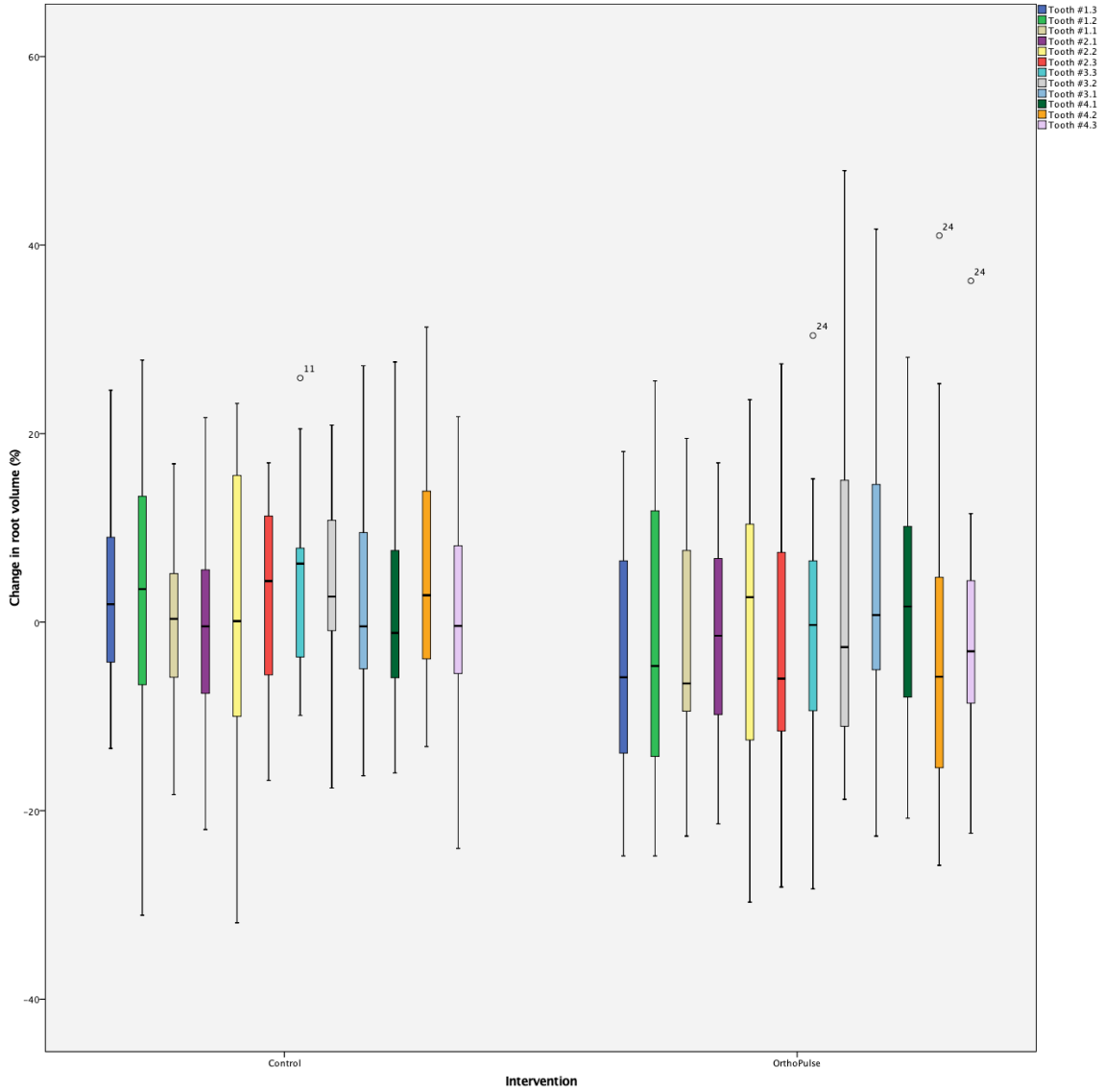
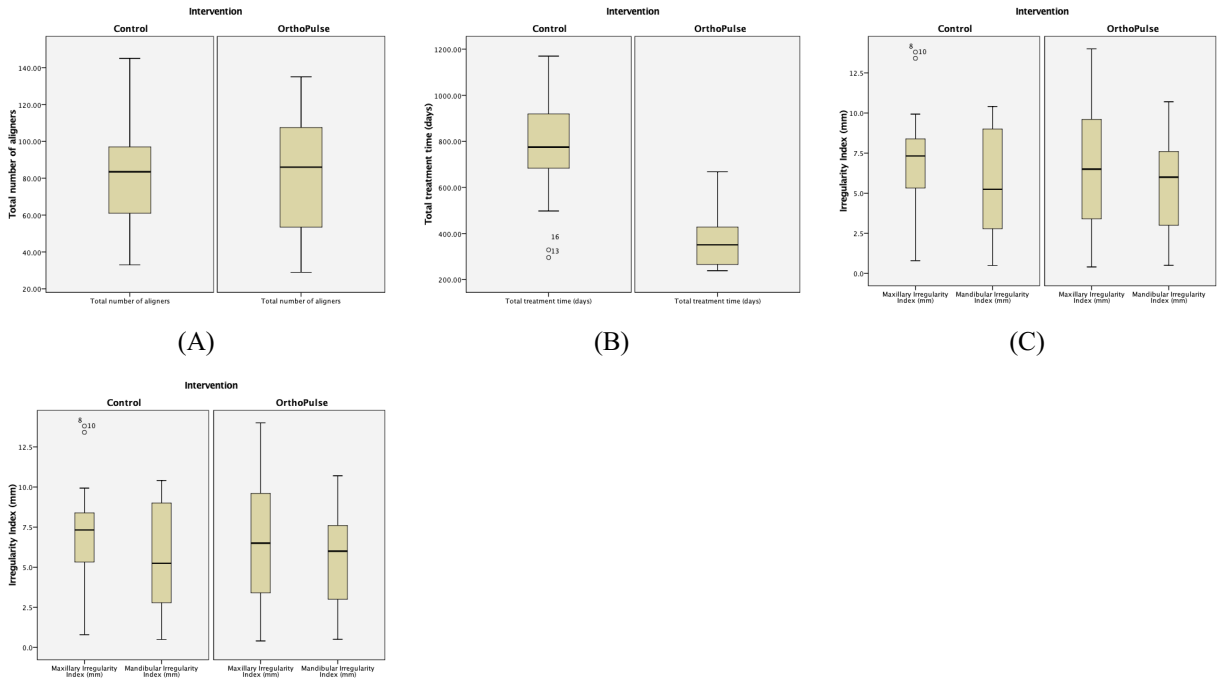


Figure 7: Boxplots of the baseline characteristics of the intervention groups: (A) total number of aligners, (B) total treatment time, (C) irregularity index, (D) change of inclination of incisors



(A) (B) (C)

(D)

Figure 8: Scatterplot matrix for change in root volume data for all teeth and interventions

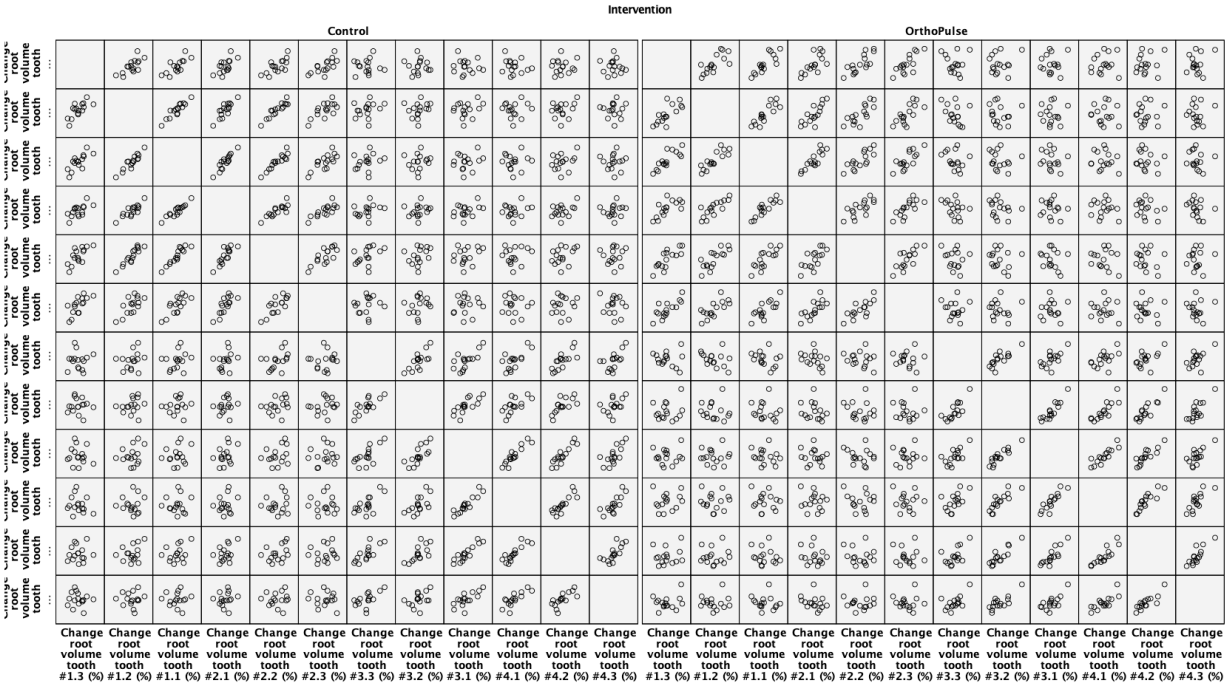


Figure 9: Scatterplot matrix for treatment time, total number of aligners, incisor inclination and irregularity index for all teeth and interventions

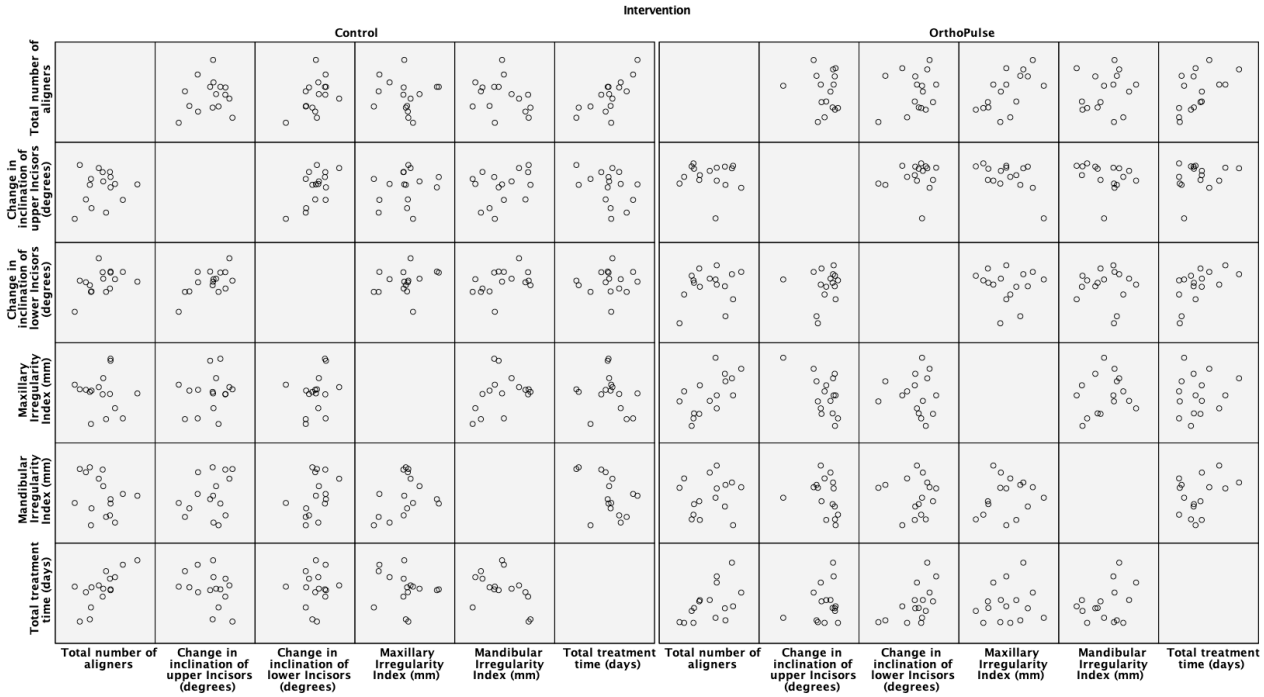


Figure 10: Scatterplot matrix for treatment time, total number of aligners, incisor inclination and irregularity index for all teeth and interventions combined

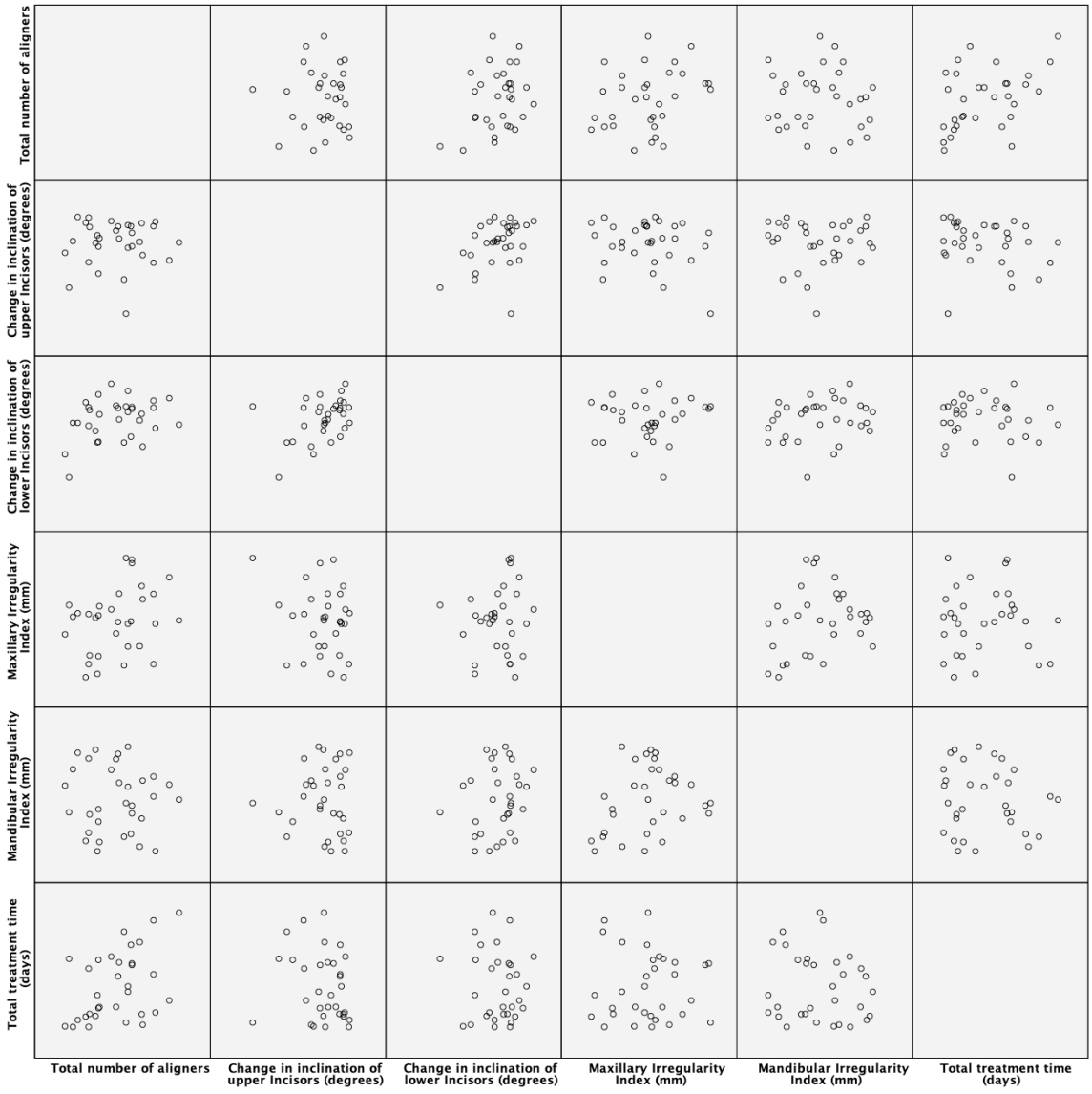


Table 8: Levene's test of Equality of Variances between the intervention groups at each tooth for the percentage change in root length

Levene's Test of Equality of Error Variances[a]

	F	df1	df2	Sig.
Change root volume tooth #1.3 (%)	1.164	1	30	.289
Change root volume tooth #1.2 (%)	.321	1	30	.575
Change root volume tooth #1.1 (%)	3.040	1	30	.092
Change root volume tooth #2.1 (%)	.087	1	30	.770
Change root volume tooth #2.2 (%)	.000	1	30	.993
Change root volume tooth #2.3 (%)	1.980	1	30	.170
Change root volume tooth #3.3 (%)	1.930	1	30	.175
Change root volume tooth #3.2 (%)	3.581	1	30	.068
Change root volume tooth #3.1 (%)	.846	1	30	.365
Change root volume tooth #4.1 (%)	.686	1	30	.414
Change root volume tooth #4.2 (%)	1.061	1	30	.311
Change root volume tooth #4.3 (%)	.034	1	30	.855

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a. Design: Intercept + num_intervention
Within Subjects Design: root_volume

Table 9: Pearson correlation for treatment time, total number of aligners, incisor inclination and irregularity index for all teeth and interventions

Correlations

		Intervention	Total treatment time (days)	Total number of aligners	Change in inclination of upper Incisors (degrees)	Change in inclination of lower Incisors (degrees)	Maxillary Irregularity Index (mm)	Mandibular Irregularity Index (mm)
Intervention	Pearson Correlation	1	-.720**	-.006	.124	.304	-.046	-.016
	Sig. (2-tailed)		.000	.973	.499	.091	.802	.932
	N	32	32	32	32	32	32	32
Total treatment time (days)	Pearson Correlation	-.720**	1	.434*	-.188	-.082	-.018	-.126
	Sig. (2-tailed)	.000		.013	.302	.655	.921	.492
	N	32	32	32	32	32	32	32
Total number of aligners	Pearson Correlation	-.006	.434*	1	.011	.310	.289	-.077
	Sig. (2-tailed)	.973	.013		.953	.084	.109	.676
	N	32	32	32	32	32	32	32
Change in inclination of upper Incisors (degrees)	Pearson Correlation	.124	-.188	.011	1	.395*	-.218	.013
	Sig. (2-tailed)	.499	.302	.953		.025	.231	.945
	N	32	32	32	32	32	32	32
Change in inclination of lower Incisors (degrees)	Pearson Correlation	.304	-.082	.310	.395*	1	.082	.192
	Sig. (2-tailed)	.091	.655	.084	.025		.655	.293
	N	32	32	32	32	32	32	32
Maxillary Irregularity Index (mm)	Pearson Correlation	-.046	-.018	.289	-.218	.082	1	.260
	Sig. (2-tailed)	.802	.921	.109	.231	.655		.151
	N	32	32	32	32	32	32	32
Mandibular Irregularity Index (mm)	Pearson Correlation	-.016	-.126	-.077	.013	.192	.260	1
	Sig. (2-tailed)	.932	.492	.676	.945	.293	.151	
	N	32	32	32	32	32	32	32

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Figure 11: Scatterplot comparing intervention, total treatment time and total number of aligners

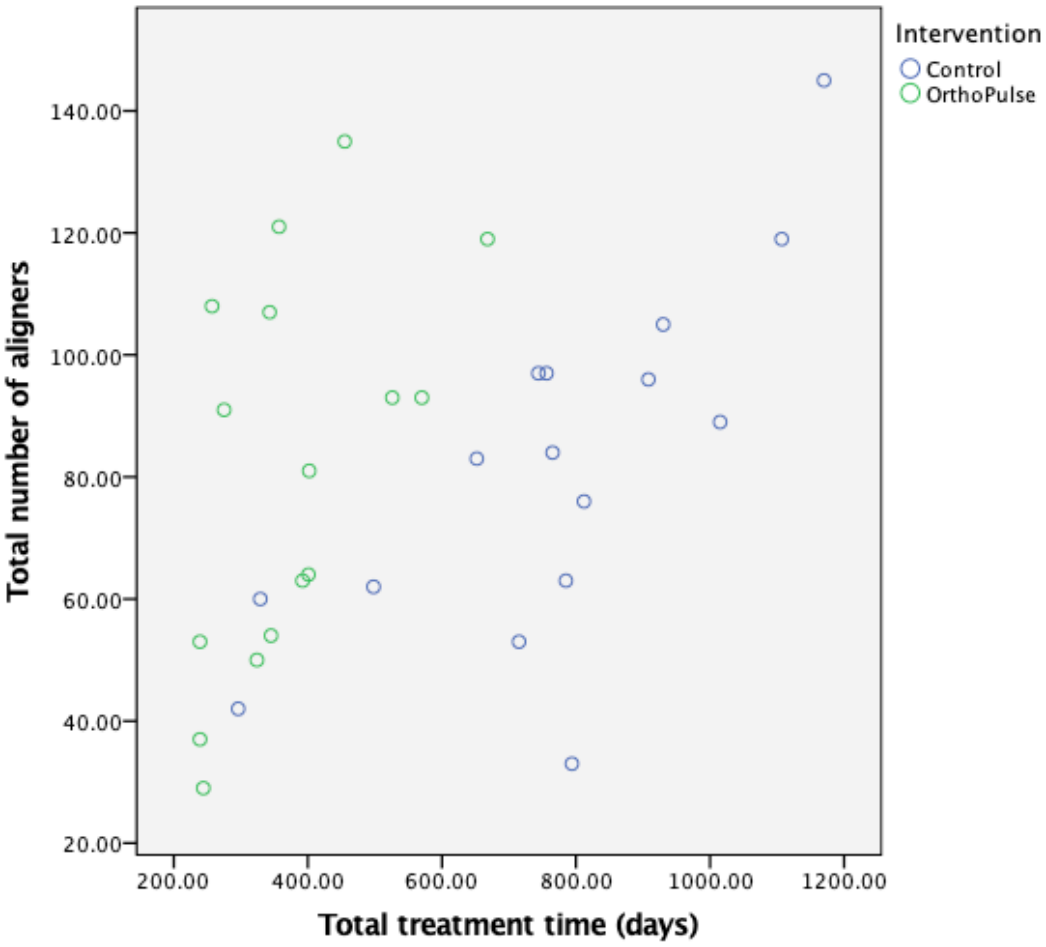


Figure 12: Scatterplot comparing intervention and change in inclination of maxillary and mandibular incisors

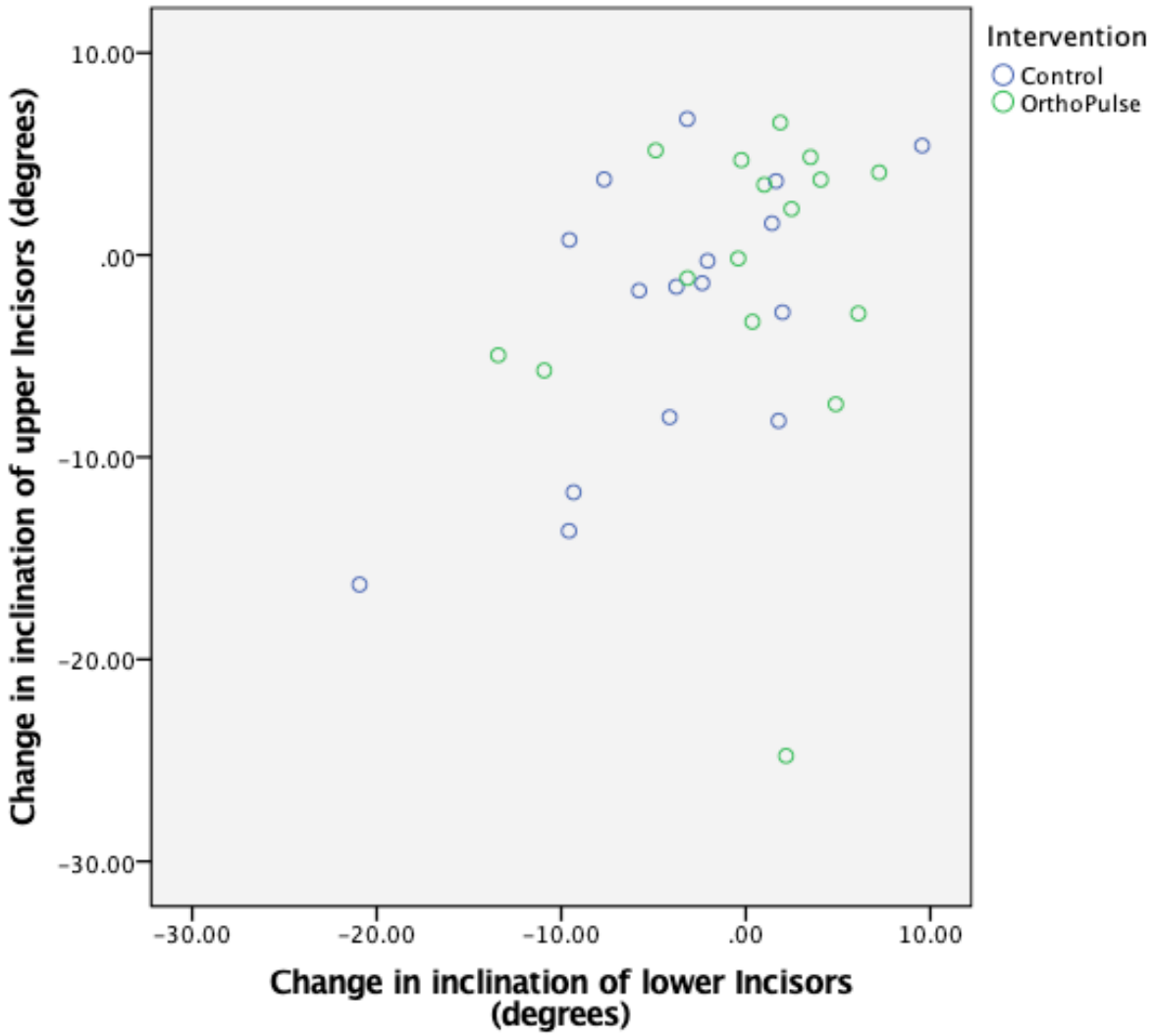


Table 10: Mauchly Test of Sphericity for percentage change in root length

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b]		
					Greenhouse-Geisser	Huynh-Feldt	Lower-bound
root_volume	.000	314.603	65	.000	.196	.218	.091

Tests the null hypothesis that the error covariance matrix of the orthonormalized transformed dependent variables is proportional to an identity matrix.

a. Design: Intercept + num_intervention
Within Subjects Design: root_volume

b. May be used to adjust the degrees of freedom for the averaged tests of significance. Corrected tests are displayed in the Tests of Within-Subjects Effects table.

Variable root_volume: percentage change in root volume, variable num_intervention: intervention

Table 11: Hypotheses for ANCOVA involving change in root volume data

Hypotheses
H_o : Differences in mean percentage change in root volume between OrthoPulse and control patients are the same for all teeth H_a : Differences in mean percentage change in root length between OrthoPulse and control patients are the same for all teeth
H_o : Mean percentage change in root volume is the same for OrthoPulse and control patients H_a : Mean percentage change in root volume is not the same for OrthoPulse and control patients
H_o : Mean percentage change in root volume is the same for all teeth H_a : Mean percentage change in root length is not the same for all four teeth
Note: Although other hypotheses exist which include covariates, they are not presented here since they were not included in the final statistical model.

Table 12: Tests of Within-Subject Effects for change in root volume data

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
root_volume	Sphericity Assumed	902.543	11	82.049	.683	.755
	Greenhouse-Geisser	902.543	2.153	419.135	.683	.519
	Huynh-Feldt	902.543	2.403	375.637	.683	.534
	Lower-bound	902.543	1.000	902.543	.683	.415
root_volume * num_intervention	Sphericity Assumed	737.367	11	67.033	.558	.862
	Greenhouse-Geisser	737.367	2.153	342.428	.558	.588
	Huynh-Feldt	737.367	2.403	306.891	.558	.606
	Lower-bound	737.367	1.000	737.367	.558	.461
Error (root_volume)	Sphericity Assumed	39644.092	330	120.134		
	Greenhouse-Geisser	39644.092	64.600	613.682		
	Huynh-Feldt	39644.092	72.081	549.994		
	Lower-bound	39644.092	30.000	1321.470		

Variable root_volume: percentage change in root volume, variable num_intervention: intervention

Table 13: Tests of Between-Subject Effects for change in root volume data

Tests of Between-Subjects Effects

Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	99.328	1	99.328	.113	.739
num_intervention	933.442	1	933.442	1.065	.310
Error	26304.317	30	876.811		

Variable num_intervention: intervention

Table 14: Determination of root volume present at 2mm coronal from the tooth apex

	% of root volume					
Patient	Mx Central	Mx Lateral	Mx Canine	Md Central	Md lateral	Md canine
1	3.37	7.06	1.62	9.23	3.62	1.71
2	2.25	3.27	0.84	4.56	3.74	1.63
3	3.75	3.86	2.28	4.98	6.55	3.41
4	3.08	5.56	2.06	1.94	3.82	2.17
5	4.78	7.03	3.68	2.40	4.09	2.11
6	4.27	8.58	3.76	4.59	3.77	3.02
7	3.59	2.76	1.47	5.03	3.99	1.29
8	2.57	2.91	1.61	4.18	1.44	1.23
9	5.05	7.72	2.53	5.58	4.08	3.23
10	5.21	6.86	2.78	4.77	4.88	1.75
Mean	3.79	5.56	2.26	4.73	4.00	2.15
Minimum	2.25	2.76	0.84	1.94	1.44	1.23
Maximum	5.21	8.58	3.76	9.23	6.55	3.41