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EFFECTIVENESS, EFFICIENCY AND MOLECULAR MECHANISM OF SURGICAL AND NON-SURGICAL METHODS USED IN ACCELERATED ORTHODONTIC TOOTH MOVEMENT. PART I: SYSTEMATIC REVIEW AND META-ANALYSIS OF SURGICAL METHODS.

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EFFECTIVENESS, EFFICIENCY AND MOLECULAR MECHANISM OF SURGICAL AND NON-SURGICAL METHODS USED IN ACCELERATED ORTHODONTIC TOOTH MOVEMENT.
PART I: SYSTEMATIC REVIEW AND META-ANALYSIS OF SURGICAL METHODS.

Summary

Background. Several surgical methods have been developed to accelerate orthodontic tooth movement, in past few years various randomized controlled trials have been published and this controversial topic was in need of an actualization.

Objective. To assess the effectiveness and describe the molecular mechanism involved in surgical methods used in accelerated orthodontics.

Search methods. Electronic database searches (MEDLINE, EMBASE, The Cochrane Library, and LILACS) were performed until June 2018 using controlled terms identified in the articles included in the theoretical framework. Additional controlled and uncontrolled vocabulary was identified using the search tools provided by the databases according to the PICO question.

Selection criteria. Articles were screened for randomized controlled trials using adjunctive surgical methods to accelerate orthodontic tooth movement, i.e. corticotomy, accelerated osteogenic orthodontics, periodontal distraction, corticision, piezopuncture, piezosurgery, piezocision and micro-osteoperforations; with the following primary outcome measures: velocity of tooth movement; distance of accumulated tooth movement; total treatment time; and levels of inflammatory and bone remodeling markers in saliva or gingival crevicular fluid.

Data collection and analysis. Two independent authors evaluated the included articles using a standardized form to extract data, including quality indicators. Risk of bias was assessed using the Cochrane risk of bias tool.

Results. The searches resulted in 2.043 articles. After application of inclusion criteria, 17 randomized controlled trials were included in this systematic review. Of these, 8 evaluated the effect of corticotomies, 4 of piezocision, 4 of micro-osteoperforations, and 1 of periodontal ligament distraction.

Conclusions. Weak evidence suggests that corticotomy and piezocision are effective in accelerating orthodontic tooth movement in the first months of treatment. Strong evidence suggests that piezocision is unable to reduce the treatment time required to correct mandibular crowding and to perform en-masse retraction. High evidence suggests that micro-osteoperforations is able to accelerate maxillary canine retraction. Weak evidence suggests a positive correlation between stimulation of RAP accelerated tooth movement, however randomized clinical trials are still needed. Corticotomies and minimally invasive surgical procedures are safe to the periodontium.

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Key words: Accelerated tooth movement, Bone Remodeling, Systematic review, Meta-analysis.

Introduction

Conventional orthodontic treatment on average requires less than 2 years to complete(1). This treatment duration is considered extensive, especially by adult patients who increasingly seek for shorter and more efficient treatments(2). Since alveolar bone remodeling is the basis of orthodontic tooth movement(3), several surgical and non-surgical methods have been developed to accelerate this process and thus increase the speed of tooth movement(4,5).

Surgically facilitated orthodontic therapy is a procedure that uses conventional orthodontic forces through a healing wound to accelerate orthodontic tooth movement(6). Frost(7) described wound healing as a complex process characterized by a transient increase in tissue remodeling. He termed this process *regional acceleratory phenomenon* (RAP) and it has been described as the biological basis of surgically accelerated tooth movement(2). Cortical activation is defined as the injury that generates the biochemical changes that in turn induce and potentiate the RAP. It begins with a sterile, cytokine-mediated inflammatory process that increase bone remodeling and triggers transient regional osteopenia, which in turn accelerates orthodontic tooth movement(2,8,9).

Wilcko and Wilcko developed one of the surgically facilitated orthodontic tooth movement techniques, known as *periodontally accelerated osteogenic orthodontics* (PAOO), which consists in the combination of selective alveolar corticotomy after full-thickness flap elevation with bone grafts and conventional orthodontic forces. PAOO has the ability to accelerate orthodontic tooth movement and gives the possibility for contouring the bone phenotype(8–11). However, this procedure is considered invasive and therefore less accepted by the patients(12). For this reason, a number of different techniques have been developed, including as piezo-surgery(13), corticision(14), piezocision(12), piezopuncture(15), and micro-osteoperforations(16). These approaches aim for a minimally invasive surgical intervention that generates the necessary injury in the cortical bone to activate a response at the alveolar bone and periodontal ligament, which in turn accelerates orthodontic tooth movement.

In recent years, several systematic reviews(17–30) on accelerated orthodontic tooth movement have been published. Two of these reviews evaluated the biological mechanism involved in surgery facilitated orthodontic tooth movement and concluded that there is an increase in regional bone remodeling based on

histological data(21,23). However, the authors only included animal studies, excluding recent studies in humans that would provide information more valuable for current clinical practice. The aim of Part I of this review was to systematically search the literature to evaluate the effectiveness and describe the molecular mechanisms involved in surgically facilitated orthodontic tooth movement in humans. In addition, we aimed to answer the following questions: 1) Does surgical methods performed in conjunction with orthodontic treatment significantly increase the speed of tooth movement and shorten the treatment time?; 2) Which molecular mechanisms are involved in surgical methods used in accelerated orthodontics?; and 3) What is the effect of surgical methods used in accelerated orthodontics on periodontal parameters and periodontal biotype?

Material and methods

This systematic review was based on a specific protocol developed following the guidelines outlined in the Cochrane Handbook of Systematic Reviews of Interventions and the PRISMA statement, and registered in the National Institute of Health Research Database (www.crd.york.ac.uk; 42017064638).

Eligibility criteria

Eligibility criteria were determined according to the PICO question and are shown in Table 1.
Exclusion criteria are shown in Table 1.

Search methods for identification of studies

Electronic database searches (MEDLINE, Supplementary Table 1; EMBASE, Supplementary Table 2; the Cochrane Library, Supplementary Table 3; and LILACS, Supplementary Table 4) were performed using controlled and uncontrolled terms identified from articles included in the theoretical framework. Additional controlled and uncontrolled vocabulary was identified using the databases search tools based on the PICO question. The reference lists of all included articles were also searched for relevant studies. The search was restricted to studies published in English and Spanish. No restriction was applied on the date of publication and no filter was used to retrieve specific types of publications. The databases were searched to June 2018.

Data collection and analysis

Two independent authors (M.A.A. and C.M.F.) evaluated the titles and abstracts of the studies that were found through the search strategy and performed a full-text assessment of the potentially eligible studies. Any disagreement regarding the eligibility was resolved by discussion or consultation with a third reviewer (R.M.).

A standardized form was used to extract data from the included studies for the quality assessment. The information extracted included: reference list, study objective, study design, study population, sampling method, interventions, description of the control group, follow-up time, presence of biases, measured results and comments.

Quality assessment and risk of bias

Three authors (M.A.A., C.M.F. and J.F.A.) independently assessed the data quality. The differences were solved by discussion or consultation with a fourth reviewer (R.M.).

The risk of bias was assessed following the Cochrane Collaboration's Tool for Assessing Risk of Bias as described in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions.* The following domains were classified as low, high, or unclear risk of bias on each individual study:

1. Selection bias
    - 1.a. Random sequence generation
    - 1.b. Allocation concealment
2. Performance bias
    - 2.a. Blinding of participants and personnel
    - 2.b. Blinding of outcome assessment
3. Attrition bias
    - 3.a. Incomplete outcome data
4. Reporting bias
    - 4.a. Selective reporting
5. Other bias
    - 5.a. Other sources of bias.

Summary measures and approach to synthesis

1. Assessment of heterogeneity

We analyzed the heterogeneity of the included studies to evaluate the possibility of performing a quantitative synthesis or meta-analysis. We assessed the clinical heterogeneity by examining the characteristics of the study and treatment protocol, and the similarities of the participants, setting, interventions, materials, data collection method, and measures used to assess the outcomes of treatment. The statistical heterogeneity was assessed using the I2 statistic.

2. Data synthesis

We pooled the data of the articles that had similar study populations, interventions, and outcomes. The intervention effect was expressed as weighted mean differences (WMD). For continuous outcomes, we used 95% CI. Finally, we used random-effect models for meta-analyses.

3. Summary of results

We created a table to highlight the main characteristics (Table 2) and the results (Table 3) of the included studies.

Results

Description of studies

The electronic database search resulted in 2039 references. Four additional articles were identified through other sources. After removal of duplicates, a total of 889 articles were screened by title and abstract. Full-text evaluation of 31 potentially relevant studies was performed. After further assessment, 14 studies were excluded. Finally, 17 randomized controlled trials (RCTs) were included in this review (16,31–46) (Figure 1).

Of the 17 RCTs included, 8 had not been included in previous systematic reviews(37,38,41–46).

Risk of bias within the studies

There is no homogeneity among the studies regarding the risk of bias. Five out of the 17 included studies presented with low risk of bias in most of the evaluation criteria. The all of the studies showed a high potential risk in terms of performance bias, most likely due to impossibility of blinding. Overall, the quality of the studies is acceptable. (Supplemental Table 5 and Table 4)

Qualitative synthesis

In order to conduct the qualitative analysis, all included studies were divided into 4 groups according to the intervention used to accelerate the orthodontic tooth movement. The analysis was made based on the outcomes proposed in the eligibility criteria. Table 3 provides a detailed view of the outcomes of the included studies.

1. Corticotomy. This intervention was performed in 8 studies(31–38) by doing a mucoperiosteal flap elevation in the area of interest, followed by vertical cuts and/or

perforations on the alveolar bone to accomplish bone activation(31–33,36). Additionally, some studies placed bone grafts in the operated area(33,35,37,38). A meta-analysis was not performed because some of the data was missing or could not be compared.

- *Accumulative tooth movement.* One split-mouth RCT with unclear risk of bias(32) investigated the effect of corticotomy on the accumulative tooth movement in maxillary canine retraction. The authors found that the accumulative canine retraction was significantly higher in the experimental side vs. the control side at 1, 2, 3 and 4 months after surgery (*P*=0,01).

- *Rate of tooth movement.* Four split-mouth RCTs investigated the effect of corticotomy on the rate of maxillary canine retraction. Of these, three were at unclear risk of bias(31,32,36) and one at high risk of bias(33). Abbas et al.(31) found that the rate of canine crown tip were greater (*P*<0,05) in the corticotomy side compared to the control side at 2, 4, 6, 8, 10 and 12 weeks after surgery. Another study(36) also found a higher rate of tooth movement in the experimental side from week 1 to 12 (*P*<0,05).

Aboul-Ela et al.(32) reported a higher rate of anteroposterior movement of the canines (*P*<0,01) in the experimental side compared to the non-operated side at all measurement times (Month 1, 2, 3, and 4) after the intervention. Similarly, Jahanbakshi et al.(33) found that the velocity of tooth movement was significantly higher in the experimental side compared to the control side from month 1 to month 4, with a pooled rate of canine retraction of 1,8 ± 0,17 mm/month vs. 1,1 ± 7,39 mm/month (*P*<0,001).

- *Treatment duration.* Four parallel-group RCTs, three with high risk of bias(34,35,38) and one with unclear risk of bias(37), investigated the effect of corticotomy on the treatment time needed for en masse retraction of anterior teeth after premolar extraction, on the treatment time needed for mandibular decrowding, and the total treatment time from bracketing to debonding. Bhattacharya et al.(34) found that the en masse retraction time after premolar extraction was significantly higher in the control group as compared to the corticotomy group (*P*<0,001). Shoreibah et al.(35) reported a reduced treatment duration in the experimental group compared to the controls when correcting mandibular crowding from the beginning of treatment until debonding (17,5 weeks vs. 49,0 weeks); and Abbas and Moutamed(38) reported an accelerated mandibular decrowding in the experimental group compared to the controls (74,5 ± 7,7 days vs. 141,7 ± 21,3 days). However, these studies did not show *P*-values. Aristizabal et al.(37) evaluated the total treatment time of a comprehensive orthodontic treatment and found no statistical difference between the

experimental group and the controls (8,20 ± 4,49 months vs. 13,40 ± 6,26 months; *P*=0,17).

- *Molecular mechanism.* Only one parallel-group RCT, which was at unclear risk of bias(37), attempted to describe the biological mechanisms involved in surgically facilitated orthodontics. The authors analyzed the urinary deoxypyridinoline (DPD), but due to the great inter- and intra-group variance of this bone resorption biomarker, no conclusion could be drawn. However, an increased bone turnover was noted 2 days after surgery in most patients of the experimental group; DPD increased between T1 and T2 and decreased in T3 almost to baseline level. In most of the control subjects, the DPD remained stable across all measurements.

- *Periodontal parameters.* Five studies, two split-mouth RCTs with unclear risk of bias(31,32), and three parallel-group RCTs with high(35,38) and unclear risk of bias(37), investigated this outcome. Except for the gingival index scores, which were found to be significantly higher (*P*<0.05) at the end of the treatment on the operated side compared to the non-operated side(32), no differences were found in any of the evaluated periodontal parameters among these studies.

2. Piezocision. This intervention was performed in 5 studies(31,39–42) by doing gingival microincisions in the area of interest, followed by vertical cuts on the alveolar bone through the gingiva to accomplish bone activation. A meta-analysis was not performed because some of the data was missing or could not be compared.

- *Accumulative tooth movement.* One split-mouth RCT, which was at unclear risk of bias, investigated the effect of piezocision on the accumulative tooth movement of canine retraction compared to conventional orthodontic tooth movement. Aksakalli et al.(39) found that the accumulative canine retraction was higher in the experimental side compared to the control side after 4 weeks, although it is uncertain whether this difference is statistically significant.

- *Rate of tooth movement.* A split-mouth RCT at unclear risk of bias(31) and a parallel-group RCT at low risk of bias(41) investigated the effect of piezocision on the rate of maxillary canine retraction and the rate of en masse retraction, respectively. Abbas et al.(31) found that the rates of canine crown tip were greater (*P*<0,05) in the piezocision side compared to the control side at 2, 4, 6, 8, 10, and 12 weeks after surgery. Tunçer, et al.(41) reported that the retraction rate was slightly higher in the experimental group at all time points, except for day 90, when the rates evened. However, the difference between the groups was not statistically significant (*P*>0,05).

- *Treatment duration.* One split-mouth RCT at unclear risk of bias(39) and three parallel-group RCTs at high(40) and low risk of bias(41,42) investigated the effect of piezocision on the total treatment time, treatment time needed for canine retraction, and time needed for en masse retraction of anterior teeth and for anteroinferior alignment.

Charavet et al.(40) reported a significantly lower treatment duration from the beginning of treatment until debonding in the experimental group compared to the control group (310 days vs. 540 days; *P*<0,0001). Similarly, Aksakalli et al.(39) showed that the treatment duration for space closure after premolar extraction and canine retraction was lower in the experimental group than in the control group (3,54 ± 0,81 months vs. 5,59 ± 0,94 months), although no *P*-value was reported.

Tunçer et al.(41) reported that treatment duration for en masse retraction of anterior teeth was similar in both the experimental and control group (9,33 ± 4,10 months vs. 9,27 ± 2,55 months; *P*=0,958). Likewise, Uribe, et al.(42) found that the treatment duration for correcting mandibular crowding was similar in both the experimental and control group (102,1 ± 34,7 days vs. 112,0 ± 46,2; *P*=0,52).

- *Molecular mechanism.* One parallel-group RCT at low risk of bias(41) aimed to describe the biological response involved in piezocision-assisted orthodontics in miniscrew supported en-masse retraction cases. In this study, the authors evaluated the concentration of receptor activator of nuclear factor kappa-B ligand (RANKL) in gingival crevicular fluid (GCF) samples at the beginning of retraction (before piezocision) (T1), on day 28 (T2) and at the end of retraction (T3). This bone biomarker showed an unlike pattern between groups, the experimental group showed a decrease at T2-T1 followed by an increase at T3-T2 and the control group showed a steady increase at both time intervals. However, the difference between groups was not statistically significant (*P*>0,05).

- *Periodontal parameters.* Two split-mouth RCTs at unclear risk of bias(31,39) and one parallel-group RCT at high risk of bias(40) investigated these parameters. None of these studies found differences between the groups in any of the evaluated periodontal parameters.

3. Micro-osteoperforation. This intervention was performed in 2 parallel-group RCTs at unclear(16) and low risk of bias(43), and 2 split-mouth RCTs at low risk of bias(44,45). Micro-osteoperforations were made in the area of interest through the gingiva to accomplish bone activation, without any flap or incision. Of these four studies, three could be compared and a meta-analysis was performed.

- *Accumulative tooth movement.* Alikhani et al.(16), Kundi(43), Khan et al.(44) and Alkebsi et al.(45) evaluated the effect of micro-osteoperforations on accumulative tooth movement of maxillary canine retraction. Micro-osteoperforations were performed distal to the experimental canine in the experimental group, but not in the control group. Both maxillary canines were retracted, and movement was measured after 28 days. Alikhani et al.(16), Kundi(43), and Khan et al.(44) reported that the accumulative tooth movement was significantly larger in the experimental group compared to the controls (*P*<0,05). In contrast, Alkebsi et al.(45) found no statistically significant difference in the accumulative tooth movement between the micro-osteoperforation and the control side at month 1(*P*=0,77), month 2 (*P*=0,50) and month 3 (*P*=0,76).

- *Molecular mechanism.* Alikhani et al.(16) attempted to investigate the biological mechanisms involved in surgically facilitated orthodontics with micro-osteperforations. The authors evaluated the inflammatory response by measuring the levels of 8 proinflammatory cytokines (IL-1α, IL-1β, IL-6, IL8, TNFα, CCL2, CCL3, CCL5) in the GCF samples obtained from the distobuccal sites of the canines at different time points (Before retraction, 24 hours, 1 day, 7 days and 28 days). Protein analysis showed a statistically significant increase in the level of the 8 cytokines after 24 hours in both the experimental and control groups, when compared with their levels before retraction (*P*<0,05). At 24 hours and at 7 days, the levels of IL-1α, IL-1β, IL8, TNFα, CCL3, CCL5 were significantly higher in the experimental group than in the control group (*P*<0,05). At day 28, the levels of IL-1α and IL-1β were still significantly higher in the experimental group than in the control group (*P*<0,05). Although the other proinflammatory cytokines (IL8, TNFα, CCL2, CCL3, CCL5) were elevated in the experimental group compared to the control group, these differences were not shown to be statistically significant (*P*>0,05).

- *Periodontal parameters.* One split-mouth RCT at low risk of bias(45) investigated this outcome by evaluating the periodontal index and plaque index, and found no differences in any of the evaluated parameters between the groups at baseline and after 3 months (*P*=1.000).

4. Periodontal ligament distraction. This intervention was performed in one split-mouth RCT at high risk of bias(46). The authors evaluated the effect of periodontal ligament distraction on the rate and accumulative tooth movement of maxillary canine retraction after premolar extraction compared to conventional orthodontic tooth movement. The rates of canine retraction were greater (*P*=0,002) in the experimental side compared to the control side at 1st and 2nd month after surgery; however no statistically significant difference was found at 3rd month. The

accumulative tooth movement was significantly larger in the experimental side compared to the control side at 3-month follow-up (*P*=0,002).

Quantitative synthesis of included studies

Three studies could be compared and a meta-analysis was performed for quantitative synthesis of micro-osteoperforations for one month follow-up period(43–45).

1. Micro-osteoperforations. The effect of micro-osteoperforation on accumulative tooth movement (mm) of canine retraction was assessed in three studies eligible for meta-analysis. All these studies evaluated canine retraction in a first premolar extraction space. The meta-analysis was suggestive of a higher accumulative tooth movement with micro-osteoperforations compared to controls for the first month of retraction (WMD=0.70; 95% CI: 0.10, 1.30; I-squared= 97,2% *P*=0,000). The overall quality of evidence supporting this intervention was high (Figure 2).

Discussion

Orthodontists have focused on accelerating orthodontic tooth movement to reduce the treatment time and risks associated with its duration. Since bone remodeling is the biological basis of dental movement, different surgical and non-surgical methods have been developed for these purposes.

To date, several systematic reviews on accelerated orthodontic tooth movement have been published, but to the best of our knowledge this is the first to include human studies on methods for accelerating orthodontic tooth movement and the molecular mechanisms involved in these processes. In this review, we systematically searched the literature for the best evidence on seven types of surgical interventions.

In this systematic review we included 17 RCTs, which evaluated four types of interventions and five outcomes.

Does conventional orthodontic treatment combined with surgical interventions significantly increase the speed of tooth movement and shorten the treatment duration compared to conventional orthodontics alone?

Seventeen studies evaluated surgical approaches to accelerate orthodontic tooth movement. Four studies, most of them with unclear risk of bias(31–33,36), evaluated the speed of tooth movement after corticotomy and showed that this method can accelerate maxillary canine retraction approximately twice as fast as conventional orthodontic movement during the first two months of treatment. Although the

differences in canine retraction remained stable between groups in the following month of treatment, the difference started to decrease by the end of the third month. Finally, control groups and experimental groups ended up with similar speed of tooth movement. This reduction pattern of the difference between groups, could be associated with the decrease of the effect of RAP. According to Frost, the RAP typically lasts about four months in bone (7).

Regarding piezocision and accelerated maxillary canine retraction, similar results were obtained by one study with unclear risk of bias(39). However, when the effectiveness of corticotomy in accelerating canine distalization was compared to that of piezocision, a study with unclear risk of bias reported that corticotomy exhibited grater rates of canine movement(31).

The difference in the effectiveness between corticotomy and piezocision can be attributed to the divergence in the extension of the surgical intervention. Cortical activation is the injury that generates the biochemical changes that in turn induce and potentiate the normal healing process known as RAP(2). Since piezocision does not require flap elevation–which increases the inflammatory response of the underlying bone–(47)and the extension of corticotomies are greater when performed with burs than with piezoelectric scalpels(48), it is reasonable to assume that a more conservative intervention results in a milder RAP.

Micro-osteoperforations (MOPs) were evaluated in four studies(16,43–45). One of them with unclear(16) and two with low(43,44) risk of bias, reported that MOPs on average, increase the rate of canine retraction by 2–3 fold when compared to the controls. However, the measurements were made only until day 28 in all three studies, which hinders the possibility of comparing their long-term effectiveness with other surgical techniques. In contrast, a study that used 3D digital model measurements and that made a three month follow up, found no significant difference in tooth movement between the MOPs and control sides from baseline to months 1-3(45).

One study with high risk of bias evaluated interseptal bone reduction(46) and showed that it can enhance the rate of canine retraction if interseptal bone is sufficiently reduced at the first and second month. But again, the difference in the amount of canine movement between the groups decreased with time, resulting in no statistically differences by the end of the third month.

Five studies(34,38,39,41,42) aimed to determine the time needed to perform different tooth movements using corticotomy and piezocision. One study with high(34) risk of bias, evaluated the effect of corticotomy on en-masse retraction of upper anterior teeth after premolar extraction and found a statistically significant reduction in the treatment time required to close extraction spaces; on the other

hand, one study with low risk of bias(41) evaluated the effect of piezocision on en-masse retraction time as well, and found that this technique was ineffective in accelerating this type of movement. Another study with unclear risk of bias(39) found that piezocision reduced the time of maxillary canine distalization, although no *P* value was given(39). The remaining two studies evaluated the time needed to align the lower mandibular teeth using corticotomy and piezocision. The first study(38). which was at high risk of bias, showed that corticotomy reduced the time of mandibular decrowding. However, no *P* value was given. The second study(42), which was at low risk of bias, showed no statistically significant difference between piezocision and conventional orthodontics in the time required to correct mandibular crowding.

Two studies with high(35) and unclear(37) risk of bias evaluated the total treatment duration using corticotomy. The first study(35) suggests that corticotomy significantly reduces the time from the beginning of treatment until de-bonding, but no *P* value was given. In contrast, the second study(37) reported no statistically significant difference in the total treatment time, although the authors found a reduction in the treatment time in the experimental group, but the difference was not statistically significant (*P*=0,17). With regard to the effect of piezocision in the treatment duration, one study with unclear risk of bias(40) reported that the overall treatment time was significantly lower in the test group than in the control group (P<0,00001), the control group exhibited a 43% increase in the mean treatment time compared with the experimental group.

Since there were substantial methodological differences between all these studies, it is difficult to interpret their results. This heterogeneity did not make it possible to perform a meta-analysis for each intervention. Although we could observe that corticotomy accelerate different orthodontic tooth movements, including maxillary canine retraction, en masse retraction of upper anterior teeth, and alignment of anterior lower teeth. However, the studies that evaluated these outcomes were at unclear risk of bias(31–33,36,38), and since the acceleratory effect of this surgical intervention decreased with time and all of the studies evaluated these movements for a short period of time, their effectiveness in the long-term acceleration of tooth movement is still questionable.
On the other hand, according to one unclear risk of bias study(37), the corticotomy was unable to significantly reduce the total treatment time of a comprehensive orthodontic treatment; but according to one high risk of bias studies(35), the corticotomy was effective in reducing the total time of treatment. These results reflect the conflicting findings of the corticotomy in the total treatment time, which hampers the possibility of drawing solid conclusions.

Regarding the effect of piezocision and MOPs on accelerating the tooth movement, the findings were contradictory, however the studies about piezocision that were executed with high quality standards and were at low risk of bias(41,42) showed ineffectiveness of this intervention in accelerating en-masse retraction(41), and no significant difference in the time required to correct mandibular crowding(42). Nevertheless, it is important to bear in mind that these results may be due to the limited extent of the injury performed during the piezocision. It would be very important to compare the effectiveness of the piezocision with different extensions of the surgical injury. With respect to MOPs it is difficult to drawing solid conclusions, because three studies with low risk of bias(43–45) showed contradictory results, however the meta-analysis was suggestive of a higher accumulative tooth movement with micro-osteoperforations compared to controls for the first month of canine retraction.

Which molecular mechanisms are involved in surgically facilitated orthodontic tooth movement?

Three studies evaluated the molecular mechanisms involved in accelerated orthodontic tooth movement. The first study(16), which was at unclear risk of bias, analyzed 8 inflammatory cytokines and chemokines from GCF samples of patients with MOPs. At 24 hours the levels of the 8 inflammatory markers (IL-1α, IL-1β, IL-6, IL8, TNFα, CCL2, CCL3, CCL5) were significantly higher in the experimental group than in the control group (P<0,05). At day 28, the levels of IL-1α and IL-1β were still significantly higher in the experimental group than in the control group (P<0,05). Although the levels of the rest of cytokines and chemokines were higher at day 28 in the experimental group compared to the control group, the differences were not statistically significant. These findings are consistent with the inflammatory phase of the regional acceleratory phenomenon, which explains the accelerated movement after surgery. The second study(37), which was at unclear risk of bias and evaluated the effect of corticotomy, aimed to correlate urinary DPD levels with the rate of bone resorption. Since the results showed a great variance between individuals and between groups, no conclusions could be drawn, however the DPD value in the experimental group increased 2 days after surgery and then decrease 6 months after surgery, while in the control group the DPD values remained stable. This findings could be also consistent with the accelerated bone remodeling phase of the regional acceleratory phenomenon RAP.

The findings in these two RCT studies could be consistent with the positive correlation between stimulation of RAP and an increased orthodontic tooth movement. The RAP was first described by Frost in the 80's(7), and then the term

was coined by the Wilcko brothers to explain the molecular mechanism that occurs in surgically facilitated orthodontic tooth movement(2). The injury caused by corticotomy is the necessary stimulus to activate RAP, which is characterized by an initial inflammatory phase that triggers osteoclastogenesis via RANK/RANKL, which in turn increases bone remodeling and thus tooth movement. This phenomenon is transient and decreases with time, which is consistent with the decreasing difference over time in the cytokine and chemokine levels between the groups(16).

On the other hand, one study at low risk of bias(41). evaluated the effect of piezocision on the biological response of accelerated tooth movement, by means of receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL concentration showed an unlike pattern, but the difference between groups was not significant. These results may be compatible with the conservative extent of the surgical injury during the piezocision procedure, which did not made the sufficient bone stimuli for the RANKL to increase.

To date, this is the only evidence available of the molecular mechanism involved in surgically facilitated orthodontic tooth movement in humans. To determine the duration of RAP after surgical methods, it is imperative to investigate what happens after the levels of inflammatory markers increase, which bone resorption and bone formation markers are expressed, as well as the time they remain elevated.

What is the effect of surgically facilitated orthodontic tooth movement on periodontal parameters and periodontal biotype?

Eight studies evaluated the effect of accelerated orthodontic tooth movement on periodontal parameters. Five studies, most of them at unclear risk of bias(31,32,35,37,38), evaluated the effect of corticotomy on periodontal parameters. Of these, two(31,32) evaluated plaque index, gingival index, probing depth, attachment level, and gingival recession index when corticotomies were performed with submarginal flap elevation. The remaining three studies evaluated probing depth(35,37,38) and gingival recession(37) when corticotomies were performed with intracrevicular full-thickness flap elevation. All these studies showed no statistically significant difference in plaque index, attachment loss, gingival recession index, and probing depth between the operated and non-operated groups. However, one study(32) showed that gingival index scores, which assess the qualitative changes in the gingiva (no inflammation to severe inflammation), were significantly higher on the experimental side compared to the control side at the end of the study; this

difference between groups may be due to the difficulty of performing adequate oral hygiene in the operated area.

Four studies evaluated the effect on periodontal parameters of minimally invasive surgical procedures in the acceleration of tooth movement, such as piezocision(31,39,40) and MOPs(45). These studies showed no significant differences in any of the periodontal parameters.

The existing evidence suggests that corticotomies and minimally invasive surgical procedures do not cause detrimental effects on the periodontium. This can be attributed to the fact that all studies included patients who had adequate oral hygiene before treatment (16,31-46), and some of them implemented measures that aimed to preserve the periodontium, such as a strict oral hygiene of the patient. Also, the fact that the marginal bone was not incised during surgery could be associated with this finding. Furthermore, the flap design (intrasulcular flap, submarginal flap or non-flap techniques), did not influence the preservation of the periodontium.

Conclusions

- Weak but statistically significant evidence suggests that corticotomy is effective in accelerating orthodontic tooth movement in the first two months of treatment.
- Weak but statistically significant evidence suggests that piezocision is able to accelerate orthodontic tooth movement in the first month of treatment. However, strong evidence suggest that this surgical method does not reduce the treatment time required to correct mandibular crowding and to perform en-masse retraction.
- High and statistically significant evidence suggest that micro-osteoperforations is able to accelerate maxillary canine retraction for the first 28 days of treatment.
- Weak but statistically significant evidence suggest that periodontal ligament distraction is able to accelerate maxillary canine retraction.
- Weak evidence suggests a positive correlation between stimulation of RAP and an increased orthodontic tooth movement in humans, however randomized clinical trials evaluating inflammatory and bone remodeling markers at different time points of treatment are still needed.
- Corticotomies and minimally invasive surgical procedures do not cause detrimental effects on the periodontium.

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Conflict of interest statement
The authors declare not to have any conflict of interest.

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Figure legends

Figure 1. Flow chart of study selection.
Figure 2. Meta-analysis for micro-osteoperforations. Random-effects meta-analysis of rate of canine retraction with micro-osteoperforations vs. controls for an assessment period of 28 days.

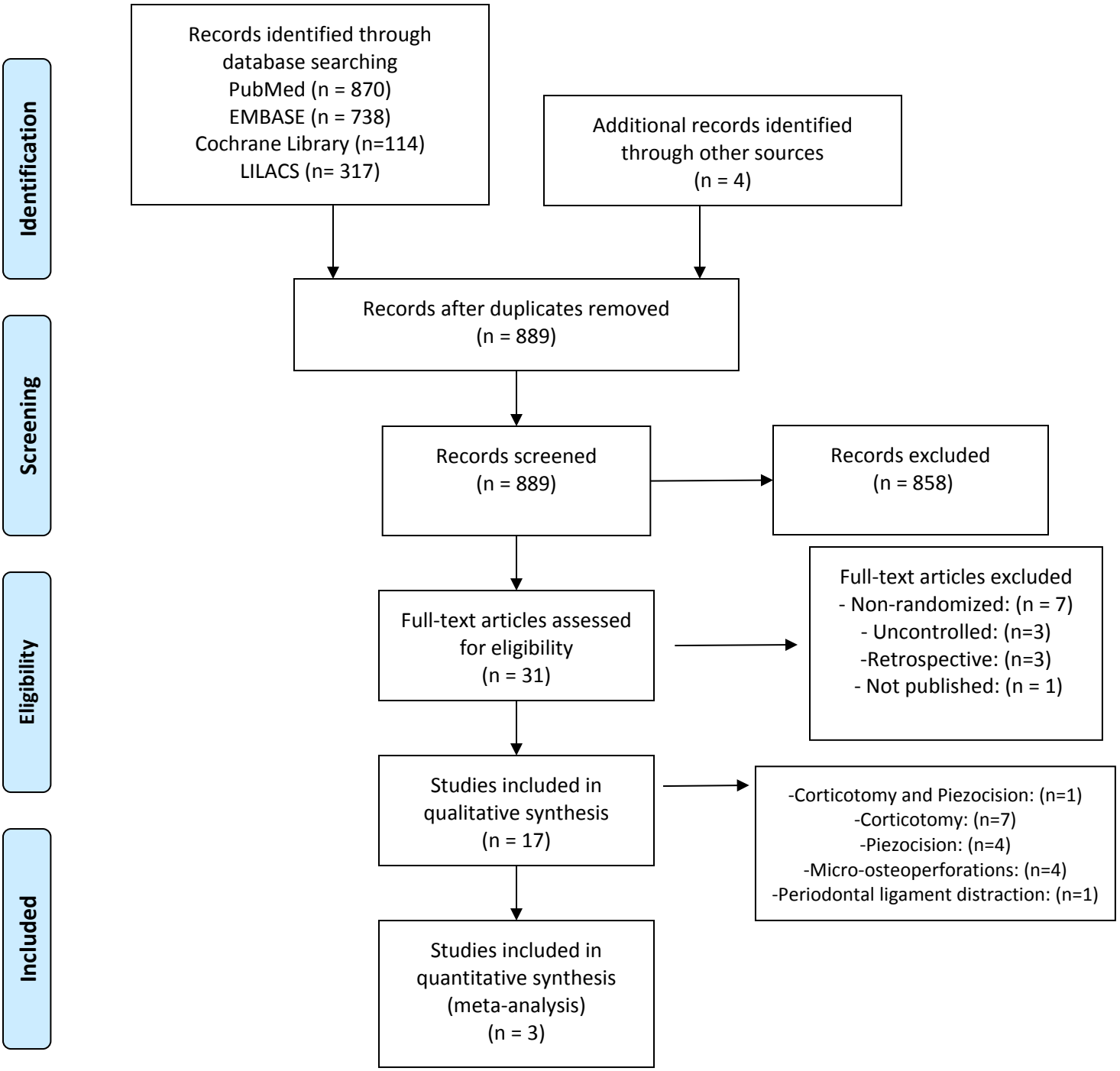
Table legends

Table 1. Eligibility criteria according to the PICOS question

Table 2. Characteristics of Included studies
OTM: Orthodontic Tooth Movement.
NR: Not Reported in the study protocol.

Table 3. Results of included studies
NE: Not Evaluated.

Table 4. Risk of bias summary for included studies
+: Low risk of bias
?: Unclear risk of bias
-: High risk of bias
By an agreement of the authors, the quality of the studies was classified according to the risk of bias rating in each of the 7 domains. Studies with one or more minus signs and only one plus sign are considered at high risk of bias. Studies with one or more question mark and two or three plus signs are considered at unclear risk of bias. Studies with plus signs only, except at the third domain were considered at low risk of bias.



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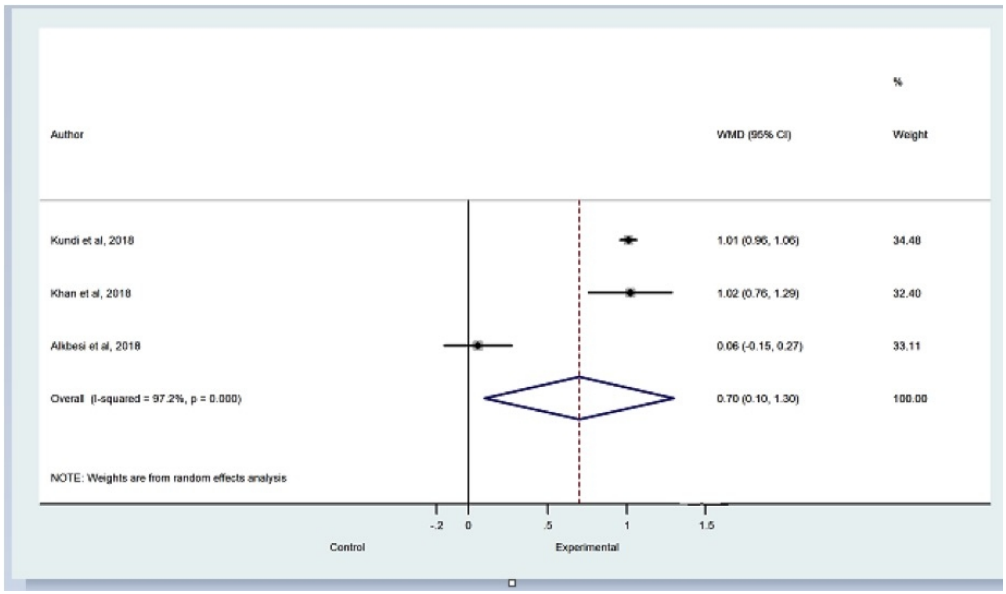

Figure 2. Meta-analysis for micro-osteoperforations. Random-effects meta-analysis of rate of canine retraction with micro-osteoperforations vs. controls for an assessment period of 28 days.

323x189mm (72 x 72 DPI)

Table 1. Eligibility criteria according to the PICOS question	
1. Participants characterisitcs	Patients of any gender and any age.
2. Interventions	Surgical interventions performed in conjunction with bonded and fixed orthodontic treatment to accelerate tooth movement, i.e. corticotomy, accelerated osteogenic orthodontics; periodontal distraction; corticision; piezopuncture; piezosurgery; piezocision; micro-osteoperforations.
3. Comparisions	Conventional orthodontic treatment.
4. Outcome measures	Main outcome measures: velocity of tooth movement, distance of accumulated tooth movement, total treatment time, and levels of inflammatory and bone remodeling markers in saliva or gingival crevicular fluid. Secondary outcome measures: periodontal parameters, namely probing depth, insertion level, bleeding sites, and periodontal biotype.
5. Study desing	Randomized controlled trials.
6. Exclusion criteria	Studies including participants with systemic diseases, craniofacial malformations, dental pathologies, or who underwent orthognathic surgery or were receiving pharmacological therapy that affects bone metabolism.

Table 2. Characteristics of Included studies

Author, year	Study design	Sample description (size, sex, age) Exp/Controls	Treatment comparision	Intervention	Post-treatment	Force application after intervention	Type of movement and biomechanics	Orthodontic adjustments	Follow-up time	Oral hygiene	Site, setting
Abbas et al. 2016	RCT - Randomized split mouth study	**Total:** 20 patients, 15-25years. **Corticotomy:** 10 patients. Experimental: 10 canines. Control: 10 canines. **Piezocision:** 10 patients. Experimental: 10 canines. Control: 10 canines	Corticotomy + OTM vs OTM Piesocision + OTM vs OTM	Corticotomy. **Zone:** maxillary canine region (buccal). **Mucosa:** Submarginal flap elevation from the mesial surface of the maxillary lateral incisor to the mesial surface of the maxillary second premolar. **Bone:** vertical cuts were made in the mesial and distal aspect of the experimental canine with a piezotome starting 2-3mm below the alveolar crest. Microperforations were made facially along the canine rooth. In the mesial wall of the extracted premolar alveolus the bundle bone was removed. The depths of the holes were confirmed by the drop felt when the cancellous bone was reached. **Graft:** No. **Piezocision. Zona:** maxillary canine region (buccal). **Mucosa:** no flap elevation, interproximal vertical microincisions were made through the gingiva. **Bone:** vertical cuts were made in the mesial and distal aspect of the experimental canine with a piezotome. In the mesial wall of the extracted premolar alveolus the bundle bone was removed. **Graft:** No	NR	Immediately	The initial phase of leveling and alignment was first completed. On the day before the surgery one maxillary premolar was randomly selected and extracted and the other premolar was extracted on the day of surgery. **Type of movement**: maxillary canine. retraction. **Biomechanics:** retraction was made on a SS 0,016X0,022 archwire, using NiTi closed-coil spring (150g) from the first maxillary molar hook to the canine. **Anchorage:** Dental. **Prescription:**Roth . **Slot:**0.022	Every 2 weeks	12 weeks (3 months)	The patients most have adequate oral hygiene before strating the trial. It is not reported if additional measures of oral hygiene were implemented	Egypt, Ain Shams University

Aboul- Ela et al. 2011	RCT - Randomized split mouth study	13 adult patients, 8 female - 5 male, mean age 19 years. **Experimental:** 13 canines. **Control**: 13 canines	Corticotomy + OTM vs OTM	**Zone:** maxillary canine region (buccal). **Mucosa:** Submarginal flap elevation from the mesial surface of the maxillary lateral incisor to the mesial surface of the maxillary second premolar. **Bone:** Using a number 2 round bur and an adequate irrigation, vestibular cortical perforations were made extending from lateral incisor to the first premolar area. The depth of the holes approximated the width of the buccal cortical bone. **Graft:** No	NR	Immediately	The initial phase of leveling and alignment was first completed. One maxillary premolar was randomly selected and extracted on the day before surgery and the other premolar was extracted on the day of surgery. **Type of movement:** maxillary canine retraction. **Biomechanics:** retraction was made on a SS 0,016X0,022 archwire, using NiTi closed-coil spring (150g) from a TAD to the canine hooks. **Anchorage:** TAD between maxillary first molar and second premolar. **Prescription:**NR. **Slot:** NR	NR	4 months	The patients most have adequate oral hygiene before strating the trial and were expected to comply with the instructions regarding strict attention to oral hygiene measures and keeping the follow-up visits..	Egypt, Cairo University.

Jahanbakhshi et al. 2016	RCT - Randomized split mouth study	15 adult female patients. **Experimental:** 15 canines. **Control**: 15 canines	Corticotomy + OTM vs OTM	**Zone:** Buccal side from distal surface of the canine to mesial surface of the second premolar. **Mucous:** Flap elevation. **Bone:** Using a number 2 round bur, vertical grooves were made in the distal surface of the canine and a similar groove in the mesial surface of the second premolar. In addition 10 perforations on the first premolar bone were created. In the same session, the first premolar was extracted on both sides. The vertical groove with depth of 0.5–1 mm. Two mm of marginal crestal bone held intact. **Graft:** No	NR	2 weeks	After initial segmental leveling and alignment, one maxillary cuadrant was randomly assigned to have corticotomy. The maxillary first premolars were extracted on the day of surger in both sides. **Type of movement:** maxillary canine retraction. **Biomechanics:** retraction was made with a simple open vertical loop using SS0.016 × 0.016 archwire with a 200g force. **Anchorage:** To enhance posterior segment anchorage in all patients, strap up was extended to the second molar. The anchorage segment was additionally stabilized by use of a miniscrew on the buccal segment between the first and second molar, tying second premolar to the screw. **Prescription:**Roth. **slot:** 0.018	Every 2 weeks	4 months	The patients most have adequate oral hygiene before strating the trial. It is not reported if additional measures of oral hygiene were implemented	Iran, Isfahan Azad University.

Al-Naoum et al. 2014	RCT - Randomized split mouth study	**TOTAL:** 30 patients (15 males-15 females) Age: 20.04±3,63 years. **Experimental:** 30 canines. **Control:** 30 canines.	Corticotomy + OTM vs OTM	**Zone:** Buccal and palatal area of maxillary canine. **Mucous:** Flap elevation. **Bone:** Horizontal incision was made above de canine apex, vertical incisions were also made 1 to 2mm apical to the alveolar crest, in the vestibular and lingual area of maxillary canine. Small corticotomy perforations were drilled in the buccal and palatal cortical bone (about 20 perforations on each side). **Graft:** No	Tramadol® 50-mg tablets (the patients were allowed to take them only when they belived the pain was severe)	Immediately	Leveling and alignment were performed. After insertion of a SS 0,019x0,025, the maxillary first premolars were extracted, four weeks before surgery. **Type of movement:** maxillary canine retraction. **Biomechanics:** Retraction was made using sentalloy NiTi closed coil spring (120g) from first maxillary molar hook to the canine hook, on a SS 0.019 x 0.025 arch wire**.** **Anchorage:** Dental anchorage. Transpalatal arch was used for anchorage reinforcement in both groups. **Prescription:** MBT**. Slot:** 0,022	NR(coil activation once)	12 weeks (3 months)	The patients most have adequate oral hygiene before strating the trial. It is not reported if additional measures of oral hygiene were implemented	Syria, The University of Al-Baath.

Bhattacharya et al. 2014	RCT	**Total:** 20 patients, 15-25 years. **Control:** 10 patients, 15-25 years. (9 females and 1 male). **Experimental:** 10 patients, 16-25 years (9 females and 1 male).	Corticotomy + OTM vs OTM	**Zone:** Buccal and palatal maxillary alveolar region from mesial surface of maxillary first premolar of one side to the other side. **Mucous:** Flap elevation. **Bone:** With round bur under proper saline irrigation, vertical grooves were placed in the interradicular spaces from a point 2-3mm above the alveolar crest. Horizontal corticotomy cuts were made joining these vertical cuts, from labial and lingual sides of the maxillary alveolar region. 1st premolars were extracted, at the same time of surgery. **Graft:** Demineralised Freeze Dried Bone Allograft.	NR	2 weeks	Leveling and alignment were performed until SS 0,016x0,022 archwire fits passively in the bracket slots. **Type of movement:** En masse retraction of maxillary anterior teeth. **Biomechanics:** Retraction was made on SS0,016X0,022 archwire using a NiTi closed coil spring, which delivered a constant force of 250g between de first molar and the canine. **Anchorage:** Dental anchorage, Transpalatal arch was used for anchorage reinforcement in both groups. **Prescription:**MBT. **Slot:** 0.022	(coil activation once)	Until closing the extraction space	The patients most have adequate oral hygiene before strating the trial. It is not reported if additional measures of oral hygiene were implemented.	India, Department of Orthodontics, Institute of Dental Sciences.
Shoreibah et al. 2012	RCT	**TOTAL:** 20 patients (17 females and 3 males) with an age range of 18.4 to 25.6 years. **Control:**10 patients. **Experimental:** 10 patients	Corticotomy + OTM vs OTM	**Zone:** Buccal region between the lower canines. **Mucous:** Flap elevation. **Bone:** With a round bur under proper saline irrigation, vertical grooves were made in the interradicular spaces starting 1-2mm below the alv eolar crest. **Graft:** Allograft was only put in cases where dehisence and fenestrations were observed when lifting flap.	Antibiotics, anti-inflammatories and analgesics for 7 days. Patients were instructed to rinse twice daily for two minutes for a period of two weeks using 0,12% clorhexidine gluconate.	Immediately	**Type of movement:** alignment **Biomechanics:** archwire sequence NiTi 0.012, 0.014, 0.016 and 0.018 until reaching SS 0,019x0,025. **Prescription:** Roth. **Slot:** 0.022	every 2 weeks	Until removing brackets.	The patients most have adequate oral hygiene before strating the trial. Initial periodontal therapy consisted of full mouth scalling. Four to six weeks following the initial phase of treatment a re-evaluation was performes to assess periodontal contidion.	Egypt,Al Azhar University

Aristizabal et al. 2016	RCT	**TOTAL:** 10 Patients, ages ranging from 18 to 40 years. **Control:** 5 patients (5 males, mean age: 29.6±9.8 year). **Experimental:** 5 patients (5 males, mean age: 28.5±6.3 years)	Corticotomy + OTM vs OTM	**Zone**: Buccal region of both archs. **Mucous**: Flap elevation. **Bone:** vertical grooves were made in the interradicular spaces. **Graft:** Bone Allograft (Puros™, Zimmer Dental)	NR	2 days after surgery	**Type of movement:** alignment. **Biomechanics**: using Damon Q self ligating brackets. archwire sequence: Patients in both groups were first treated using Unity 0.014 inch wire. **Prescription:** DamonQ. **Slot:** 0.022	Experimental group biweekly reviews, control group monthly reviews	Until the end of treatment	Three months before, the patients were included in a strict periodontal protocol, based on plaque control and dental prophylaxis. All patients were under periodontal control during active orthodontics treatment and were Periodontally evaluated by the same individual at two different times: before surgery and orthodontic movement (T1) and after orthodontic treatment (T2).	Colombia, Universidad del Valle.
Abbas et al. 2012	RCT	**Total:** Eight female patients, with a mean age of 22.3± 2.26. **Control**: 4 patients. **Experimental**: 4 patients	Corticotomy + OTM vs OTM	**Zone**: Buccal and lingual region between the lower canines. **Mucous**: Flap elevation. **Bone**: Vertical grooves were made with piezotome in the interradicular spaces stopping just short of the alveolar crest (about 3mm), scalloped horizontal cuts were made above de apex and cortical perforation was made at selective areas to increase blood supply to the graft material. **Graft:** Bioglass granules.	Declofenac Potassium 50 mg tablet every 8 hours. Augmentin 625 tablet (500 mg amoxicillin and 125 mg clavulanate potassium every 8 hours for 5 days after surgery.	2 weeks after surgery	**Type of movement:** Alignment. **Biomechanics:** standar brackets there is no especification about the arch sequence. **Prescription:** NR. **Slot:** NR	every 2 weeks	Until the end of treatment	The patients most have adequate oral hygiene before strating the trial. Oral hygiene instructions were implemented: During orthodontic treatment, the patient was recalled every 3 months to assess the oral hygiene and assure good periodontal health.	Egypt, Ain Shams University

Aksakalli et al. 2016	RCT - Randomized split mouth study	**Total:** 10 patients, six female and four male. Mean age was 16.3 ±2.4 years. **Control:** 10 canines. **Experimental:** 10 canines.	Piezocision+ OTM vs OTM	**Zone:** Mesial and distal region of the maxillary canine. **Mucous:** No flap elevation, vertical incisions through the gingiva on the mesiobuccal and distobuccal sides of the maxillary canines. **Bone:** vertical cuts were made in mesial and distal aspect of the canine with a piezotome 5mm apical to the interdental papilla. **Graft:** No	NR	Immediately	Before canine distalization and after the alignment and leveling phases, piezocision was performed on the experimental side. **Type of movement:** maxillary canine retraction. **Biomechanics:** retraction made using elastomeric chains (150g) on SS 0.016 x 0.022 archwire. **Anchorage**: Dental. **Prescription**: Roth. **Slot:** 0.022	every 2 weeks	Until ideal Class I canine relationships were stablished.	The patients most have adequate oral hygiene before strating the trial. e. All patients were firmly instructed to maintain regular oral hygiene.	Turkey, Bezmialem Vakif University.
Charavet et al. 2016	RCT	**Total:** 24 patients. **Control:** 12 patients (mean age 27 years). **Experimental:** 12 patients (mean age 34 years).	Piezocision + OTM vs OTM	**Zone**: Bimaxilar. **Mucous:**No flap elevation, vertical incisions through the gingiva. **Bone:** vertical cuts were made with a piezoelectric device below each interdental papilla. **Graft:** No	The patients were advised to take analgesics (paracetamol) only if necessary and to record their daily intake for 1 wk. Careful toothbrushing and the use of a mouthwash (chlorhexidine 0.2%, Perio-Aid; Dentaid Benelux) were rec- ommended for 7 d.	Immediately	**Type of movement:**Alignment. **Biomechanic:** The sequence of archwires was as follows: 0.018-in., 0.014 × 0.025–in., and 0.018 × 0.025–in. copper nickel-titanium archwires were used for alignment, while 0.019 × 0.025–in. stainless-steel archwires were used for fine-tuning. **Prescription:** Damon. **Slot:** 0.022	every 2 weeks archwires were changed only when full bracket engagement was achieved.	Until the end of treatment	Patients most have adequate dento-oral health. Full periodontal evaluations were performed.	Belgium, University Hospital of Liège.
Uribe et al. 2017	RCT	**Total:** 29 patients. **Control:** 13 patients, 6 male and 7 female (mean age 29.4 years). **Experimental:** 16 patients, 6 male and 10 female (mean age 30 years).	Piezocision + OTM vs OTM	**Zone**: mandibular anterior teeth. **Mucous:** No flap elevation, three vertical incisions through the gingiva, interproximally between the mandibular canines and lateral incisors, and central incisors. **Bone**: Vertical cuts were made with a piezoelectric device 4mm below the interdental papilla. **Graft:** No	Postoperatively, subjects were advised to rinse with chlorhexidine mouthwash twice a day for one week and take acetaminophen as needed.	Immediately	**Type of movement:** AlignmenT. **Biomechanic:** The archwire sequence for both groups was a 0.014 inch copper–nickel–titanium archwire for the first two visits followed by a 0.014 × 0.025 inch copper– nickel–titanium archwire until alignment completion. **Prescription:** Carrier self-ligating systems. **Slot**: 0.022	every 4–5 weeks	When the alignment of the lower anterior teeth was obtained	The patients most have adequate oral hygiene before strating the trial. It is not reported if additional measures of oral hygiene were implemented	USA,University of Connecticut.

Tunçer et al. 2017	RCT	**Total:** 30 patients. **control:** 15 patients, 2 male and 13 female (mean age 17,7 years). **Experimental:** 15 patients 2 male and 13 female (mean age 17 years).	Piezocision + OTM vs OTM	**Zone:** Anterior six teeth (including the distal aspects of the canines). **Mucous:** No flap elevation, vertical incisions through the gingiva of the anterior six teeth. **Bone:** vertical cuts were made in the interradicular areas of anterior six teeth (including the distal aspects of the canines) with a piezotome. **Graft:** No	Patients were advised to apply ice-bags for the first day, and avoid hot and sour food for the first 5–7 days. All patients were strictly advised to maintain good oral hygiene and avoid prolonged use of nonsteroidal anti-inflammatory drugs.	Immediately	Premolar extractions were performed at least 4 months prior to the beginning of retraction. **Type of movement:** En masse retraction of maxillary anterior teeth. **Biomechanics:** Retraction was made using NiTi closed coil spring from 7 mm long power hooks placed distal to the lateral incisors to miniscrews, adjusted to exert 250g on a 0,016x 0.022 steel arch wire. **Anchorage:** TAD-on the buccal segment between the second premolars and first molars, bilaterally. **Prescription:** MBT. **Slot:** 0.022	NR	Until the end of retraction	The patients most have adequate oral hygiene before strating the trial. All patients were strictly advised to maintain good oral hygiene.	Turkey, Başkent University
Alikhani et al. 2013	RCT	**TOTAL:** 20 patients, 5 males and 5 females (between 19-30 years). **Control:** 10 patients. **Experimental:** 10 patients	Micro-osteoperforations + OTM vs OTM.	**Zone:**Maxillary Canine region. **Mucous:** No Flap elevation. **Bone:** 3 MOPs were made distal to the maxillary canines using PROPEL. (1,5mm wide - 2-3mm depth). **Graft:** No	No pain or antibiotic medication was prescribed.	immediately	Premolar extractions were performed at least 6 months prior to the beginning of retraction. Both the experimental and control groups were leveled and aligned before retraction. **Type of movement:** Maxillary canine retraction. **Biomechanics:**Retraction was made using a niti closed coil spring (100g) from a TAD to a canine power arm. **Anchorage:** TAD. **Prescription:** MBT. **Slot:**0.022	Weekly	4 weeks	The patients most have adequate oral hygiene before strating the trial. It is not reported if additional measures of oral hygiene were implemented	USA,New York University

kundi 2018	RCT	**TOTAL:** 28 patients, 12 males and 16 females. **Control:** 14 patients, 4 males-11 females (mean age 26,4 years). **Experimental:** 14 patients, 7 males-7 females (mean age 28,4 years)	Micro-osteoperforations + OTM vs OTM.	**Zone:**Maxillary Canine region. **Mucous:** No Flap elevation. **Bone:** 3 MOPs were made distal to the maxillary canines using PROPEL (1,5mm wide). **Graft:** No	NR	Immediately	**Type of movement:** Maxillary canine retraction. **Biomechanics:**Retraction made using niti closed coil spring (100g). **Anchorage:** NR. **Prescription:** NR. **Slot:**NR	4 Weeks	4 Weeks	The patients most have adequate oral hygiene before strating the trial. It is not reported if additional measures of oral hygiene were implemented	Saudi Arabia, Aljouf University
Khan et al, 2018	RCT - Randomized split mouth study	**TOTAL:** 30 patients (18-28 years). **Control:** 15 canines. **Experimental:** 15 canines	Micro-osteoperforations + OTM vs OTM.	**Zone:**Maxillary Canine region. **Mucous:** No Flap elevation. **Bone:** 3 MOPs were performed distal to canine, using Physiodispenser (3mm depth). **Graft:** No	Pain killer and chlorhexidene mouthwash was prescribed and patient was recalled after 1 week.	Immediately	After leveling and alignment patient was referred for extraction of premolars. Miniscrews were placed bilaterally between upper second premolar and molar, to enhance anchorage. **Type of movement:** Maxillary canine retraction. **Biomechanics:** Retraction made by stretching power chain to approximately twice its resting length and refreshed after every 2 weeks. **Anchorage:** TAD were placed bilaterally between upper second premolar and molar - Anchorage was further reinforced by co-ligation of 2nd premolar, 1st and 2nd molar. **Prescription:** NR. **Slot:** NR	every 2 weeks	4 Weeks	The patients most have adequate oral hygiene before strating the trial. It is not reported if additional measures of oral hygiene were implemented	Pakistan, Islamic International Dental Hospital

Alkbesi et al. 2018	RCT - Randomized split mouth study	**TOTAL:** 32 patients, 24 females - 8 male (19.26 ±2.48 years). **Control:** 32 canines. **Experimental:** 32 canines	Micro-osteoperforations + OTM vs OTM.	**Zone:**Maxillary Canine region. **Mucous:** No Flap elevation. **Bone:** MOPs were performed using miniscrews (Aarhus Mini-Implant System, American Orthodontics) of 1.5 mm diameter and 6 mm length at 3 points distal to the canine. **Graft:** No	After the intervention, the patients were instructed to take analgesics, such as acetaminophen, only if necessary. Anti-inflammatory NSAIDs were avoided	Immediately	An operator performedextractions of the maxillary first premolars within the same week as miniscrew insertion. After that, leveling and alignment were accomplished until reaching the 0.019 3 0.025-in stain- less steel archwire. Maxillary canine retraction was started 6 months after the extractions. **Type of movement:** Maxillary canine retraction. **Biomechanics:** the extraction space was started to be closed using nickel-titanium closed-coil springs connecting the miniscrews to the power arm extending from the vertical slot of the maxillary canine bracket. **Anchorage:** Miniscrew between the maxillary first molars and second premolars to be used as direct and indirect anchorage. **Prescription:** MBT. **Slot:** 0,022	every 4 weeks	3 months	The patients most have adequate oral hygiene before strating the trial. Maintaining good oral hygiene and using chlorhexidine 0.2%, twice a day for 5 days, were recommended.	Jordan, Jordanian University of Science and Technology

Leethanakula et al. 2014	RCT - Randomized split mouth study	**TOTAL:** 18 female patients. (mean age, 21.9 years) 36 maxillary canines. **Control:**18 maxillary canines. **Experimental:** 18 maxillary canines.	Periodontal distraction + OTM vs OTM.	**Zone:** Maxillary first premolar. **Mucous:** No flap elevation. **Bone:** Extraction of the first premolar was performed on one side as a control, while extraction combined with interseptal bone reduction was performed on the experimental side using round and cylindrical carbide burs. **Graft:** No	NR	Immediately	**Type of movement:** Maxillary canine retraction. **Biomechanics**: no frictional retraction was made using elastomeric chains (150g) from a TAD to a canine power arm. In addition, a lingual button (3M Unitek) was placed on the palatal surface of each canine and first molar. Retraction force was applied on the palatal side by attaching an elastomeric chain. **Anchorage:** TAD. **Prescription:**Roth. **Slot**:NR	every 4 weeks	3 months	The patients most havegood oral hygiene, with probing depth values not exceeding 3 mm before the trial. It is not reported if additional measures of oral hygiene were implemented	Thailand, Prince of Songkla University

Table 3. Results of included studies

Author, year	Subject group	Type of study	Definition of outcomes - Orthodontic tooth movement	Summary outcome data - Orthodontic tooth movement	Definition of outcomes - Mocelular Mechanism	Summary outcome data - Mocelular Mechanism	Definition of outcomes - Periodontal Parameters	Summary outcome data - Periodontal Parameters
Abbas et al. 2016.	Corticotomy /Piezocision (Maxillary canine retraction)	RCT - Randomized split mouth study	1. Rate of tooth movement (mm/week)	**Corticotomy. 1. Rate of canine retraction** **Week 2:** Exp: 0,5±0,07mm Contr: 0,24±0.05mm **Week 4:** Exp: 0,6±0,07mm Contr: 0,34±0.08mm **Week 6:** Exp: 0,7±0,12mm Contr: 0,42±0.08mm **Week 8:** Exp: 0,78±0,1mm Contr: 0,46±0.11mm **Week 10:** Exp: 0,94±0,05mm Contr: 0,52±0.04mm **Week 12:** Exp: 1,22±0,08mm Contr: 0,58±0.04mm P<0,05 **Piezocision. 1. Rate of canine retraction** **Week 2:** Exp: 0,40±0,07mm. Contr: 0,25±0.07mm. **Week 4:** Exp: 0,50±0,07mm Contr: 0,30±0.08mm **Week 6:** Exp: 0,60±0,12mm Contr: 0,40±0.06mm **Week 8:** Exp: 0,70±0,12mm Contr: 0,45±0.09mm **Week 10:** Exp: 0,84±0,05mm Contr: 0,55±0.04mm **Week 12:** Exp: 0,99±0,10mm Contr: 0,60±0.04mm *P*<0,05	NE	NE	1. Plaque index. 2. Gingival index. 3. Probing depth, attachment level, and gingival recession were.	No differences in any of the periodontal readings (P>0.05) in either the corticotomy or the piezocision groups, as measured before the start of canine retraction and 3 months after canine retraction

Aboul- Ela et al. 2011	Corticotomy (Maxillary canine retraction)	RCT - Randomized split mouth study	1.Accumulative tooth movement (mm). 2.Rate of tooth movement (mm/month)	**1.Accumulative tooth movement** **Month 1:** Exp: 1,89mm Contr: 0,75mm **Month 2:** Exp: 3,72mm Contr: 1,61mm **Month 3:** Exp: 4,79mm Contr: 2,54mm **Month 4:**Exp: 5,68mm Contr: 3,38mm *P*=0,01 **2.Rate of tooth movement.** **Month 1:** Exp: 1,89mm/month Contr: 0,75mm/month **Month 2**: Exp: 1,83mm/month Contr: 0,86mm/month **Month 3:** Exp: 1,07mm/month Contr: 0,93mm/month **Month 4:** Exp: 0,89mm/month Contr: 0,85mm/month P<0,01	NE	NE	1. Plaque index. 2. Gingival index. 3. Probing depth, attachment level, and gingival recession were recorded.	There was no statistically significantdifference (P>0.05) in plaque index scores, attachment loss, gingival recession, and probing depth values. Gingival index scores were significantly higher (P<0.05) on the operated side.
Jahanbakhshi et al. 2016	Corticotomy (Maxillary canine retraction)	RCT - Randomized split mouth study	1. Rate of tooth movement (mm/month)	**1. Rate of tooth movement.** **Month1**. Exp:2,2±0,32mm/month. Contr: 1 ±0,13mm/month. *P*<0,0001. **Month2:**Exp:2±0,15mm/month Contr: 1,1±0,23 mm/month. *P*<0,001 **Month3:**Exp:1,8 ±0,22mm/month Contr: 1,2±0,25mm/month. *P*<0,001 **Month4:**Exp:1,4 ±0,19mm/month Contr: 1,1 ±0,12mm/month. *P*<0,001 **Total**:Exp:1,8 ±0,17mm/month. Contr: 1,1 ±7,39mm/month *P*<0,001	NE	NE	NE	NE

Al-Naoum et al. 2014	Corticotomy (Maxillary canine retraction)	RCT - Randomized split mouth study	1. Rate of tooth movement (mm/week)	**1. Rate of tooth movement** **Week 1**. Exp: 0,739 ±0,365mm/week. Contr: 0,201 ±0,149 mm/week. p<0,001. **Week 2:** Exp: 0,455±0,402mm/week. Contr: 0,105 ±0,115mm/week p<0,001 **Week 4:** Exp: 0,308 ±0,248mm/week. Contr: 0,095 ±0,161mm/week p<0,001 **Week 8:** Exp: 0,282 ±0,113mm/week. Contr: 0,124 ±0,061mm/week p<0,001 **Week 12:** Exp: 0,243±0,073mm/week Contr: 0,08 ±0,06mm/week p<0,001	NE	NE	NE	NE
Bhattacharya et al. 2014	Corticotomy (en-masse retraction)	RCT	1. Treatment duration (retraction time in days)	Treatment duration (retraction time). Exp: 130,5 ±7,37 days Contr: 234,1 ±8,91 days. P<0,001	NE	NE	NE	NE
Shoreibah et al, 2012	Corticotomy (anterior alignment)	RCT	1. Treatment duration (weeks)	Treatment duration (begining - debonding) Exp: 17,5 weeks Contr: 49 weeks.	NE	NE	1. Probing depth	**Pre-operative** Exp: 1,28±0,047mm Contr: 1,82 ±0,48mm p=0,059 **Post-operative** Exp: 1,12±0,42mm Contr: 1,76±0,46mm p=0,175 **6 months** Exp: 1,86±0,15mm Contr: 1,70±0,32mm p=0,329
Aristizabal et al. 2016	Corticotomy (Treatment time)	RCT	1. Treatment duration (months)	Treatment duration (begining - debonding) Exp: 8,2 ±4,49 months Contr: 13,4 ±6,26 months. P=0,17	1. Urine Deoxypyridinoline levels	Urine Deoxypyridinoline levels showed great variance between individuals and between groups, so no conclusion could be made. **T1: Before Treatment** Exp: 3,86 ±1,1 Contr: 7,46 ±6,1 p=0,233 **T2:2 days after surgery** Exp: 6,38±3,03 Contr: 7,88 ±5,66. p=0,614 **T3:6 months after surgery** Exp: 3,9±0,98 Contr: 4,48 ±0,48. p=0,289	1. Probing depth 2. Gingival recession	The type of treatment showed no differences in periodontal initial (T1) and final (T2) conditions. **1. Probing depth** was 1,854 ±0,748 mm at T1 and 1,531 ±0,736 mm at T2 in experimental Group. Probing depth was 1,766 ±0,808mm at T1 and 1.370 ±0,851 mm at T2 in control group. **2. Gingival Recession** was 0.475±0.518mm at T1 and 0.471±0.599 mm at T2 in experimental Group. Gingival Recession was 0.551±0.563mm at T1 and

								1.19±0.491 mm at T2 in control group.
Abbas et al. 2012	Corticotomy (mandibular decrowding)	RCT	1. Treatment duration (Days)	Treatment duration (anterior alignment) Exp: 74,5 ±7,7 days Contr: 141,7 ±21,3 days	NE	NE	1. Probing depth	Post-treatment evaluation of patients revealed no probing depths greater than 3 mm, good preservation of the interdental papillae
Aksakalli et al. 2016	Piezocision (Maxillary canine retraction)	RCT - Randomized split mouth study	1. Accumulative tooth movement (mm) 2. Treatment duration (time of canine retraction in months)	**1. Canine retraction at 1 month.** Exp: 1,53 ±0,67 mm Contr: 0,78 ±0,24mm **Canine retraction at 2 months.** Exp: 2,9 ±0,86 mm Contr: 1,73 ±0,72mm **2. Treatment duration.** Exp: 3,54 ±0,81 months Contr: 5,59 ±0,94 months	NE	NE	1. Gingival index	There was no significant difference in the pre- and postdistalization gingival indices between the two groups. **Predistalization:** Exp: 1,3±0,48 Contr: 1,4±0,51 **Postdistalization:** Exp: 1,2±0,62 Contr: 1,5±0,60
Charavet et al. 2016	Piezocision (Treatment time)	RCT	1. Treatment duration (Days)	Treatment duration (total treatment time). Exp: 310 days aporx. Contr: 540 days aprox. P<0,0001	NE	NE	1. Periodontal parameters (Recession, pocket depth, plaque index, and papilla bleeding index.	All periodontal parameters were com- parable between the 2 groups prior to and after treatment. For 3 patients (2 from the control group and 1 from the test group), increases in recession were observed in the pre- to posttreatment interval. However, the overall reces- sion scores did not increase in either group. Scars were observed in 50% of the patients in the test group and were composed of point (33%) and line (17%) scars.
Uribe et al. 2017	Piezocision (mandibular decrowding)	RCT	1. Treatment duration (Days)	**1. Treatment duration** (mandibular decrowding). Exp:102,1 ± 34,7 days. Contr: 112 ±46,2 days p=0,52	NE	NE	NE	NE

Tunçer et al. 2017	Piezocion (en-masse retraction)	RCT	1. Rate of tooth movement (mm/month) 2. Treatment duration (Months)	**1. RTM** (en-masse retraction rate) **15 days.** Exp: 0,023mm/day Contr: 0,017mm/day **30 days:** Exp: 0,02mm/day Contr: 0,017mm/day **60 days:** Exp: 0,02mm/day Contr: 0,013mm/day **90 days:** Exp: 0,015mm/day Contr: 0,015mm/day **120 days**: Exp: 0,017mm/day Contr: 0,012mm/day P > 0.05 2. The average retraction time was: Exp: 9.33 ± 4.10 months Contr: 9.27 ± 2.55 months for G2. P= 0.958	1. GCF content of receptor activator of nuclear factor κβ ligand (RANKL)	The changes in RANKL concentrations revealed that an unlike pattern was evident between groups but difference was not significant again. G.exp. showed a decrease followed by an increase at T2-T1 and T3-T2, respectively. G.contr., on the other hand, showed a steady increase at both time intervals.	NE	NE
Alikhani et al. 2013	Micro-osteoperforation (Maxillary canine retraction)	RCT	1. Accumulative tooth movement (mm)	**Canine retraction at 28 days.** Exp: 1,4mm apox Contr: 0,6mm aprox. P<0,05 On average, MOPs increased the rate of canine retraction by 2.3-fold when compared with the control group and contralateral side of the experi- mental group, which was statistically significant (P <0.05).	1. Level of cytoKines in GCF	The differences between the 2 groups in cytokine and chemokine levels were statistically significant (P <0.05). At day 28, only the activity of IL-1 in the control group was still significantly higher than its level before retraction (2.8-fold; P<0.5), whereas the rest of the inflammatory markers decreased to pre-retraction levels.	NE	NE
kundi 2018	Micro-osteoperforation (Maxillary canine retraction)	RCT	1. Accumulative tooth movement (mm)	**Canine retraction at 28 days.** Exp: 1,52mm ±0,12 Contr: 0,51mm ±0,07 P<0,0001	NE	NE	NE	NE
Khan et al. 2018	Micro-osteoperforation (Maxillary canine retraction)	RCT - Randomized split mouth study	1. Accumulative tooth movement (mm)	**Canine retraction at 4 weeks.** Exp: 2,042mm ±0,699 Contr: 1,02mm ±0,228 P<0,005	NE	NE	NE	NE

Alkbesi et al, 2018	Micro-osteoperforation (Maxillary canine retraction)	RCT - Randomized split mouth study	1. Accumulative tooth movement (mm)	**3D Model measurement.** **Canine retraction at:** **1 month.** Exp: 0,65mm ±0,26 Contr: 0,67mm ±0,34 P>0,77 **2 month.** Exp: 1,36mm ±0,49 Contr: 1,78mm ±0,50 P>0,50 **3 month.** Exp: 1,93mm ±0,74 Contr: 1,88mm ±0,67 P>076	NE	NE	1. Gingival Index. 2. Plaque index	The results showed no statistically significant differences between the MOP and control sides with the gingival and plaque indexes at baseline and after 3 months (gingival index) **1. Gingival index - T0** Exp: 1,44±0,56 Contr: 1,38±0,55 p=0,65 **T3:** Exp: 1,50±0,51 Contr: 1,63±0,49 p=0,31 **2. Plaque index - T0** Exp: 1,28±0,52 Contr: 1,25±0,51 p=0,81 **T3:** Exp: 1,27±0,45 Contr: 1,27±0,45 p=1,000
				Intraoral measurement. **Canine retraction at:** **1 month.** Exp: 1,23mm ±0,45 Contr: 1,17mm ±0,42 P>0,05 **2 month.** Exp: 2,27mm ±0,72 Contr: 2,24mm ±0,63 P>0,05 **3 month.** Exp: 3,18mm ±1,03 Contr: 3,26mm ±0,81 P>0,05	NE	NE		
Leethanakula et al, 2014	Periodontal Ligament Distraction (Maxillary canine retraction)	RCT - Randomized split mouth study	1. Rate of tooth movement (mm/week) 2. Accumulative tooth movement (mm)	**1. Rate of tooth movement.** **1 month.** Exp: 1,6mm ±1,08 Contr: 0,9mm ±0,3 P=0,002 **2 month.** Exp: 2,3mm ±1,1 Contr: 1,2mm ±0,5 P=0,002 **3 month.** Exp: 1,6mm ±0,8 Contr: 1,3mm ±0,7 P>0,05 **1. Accumulative tooth movement.** Canine retraction at 3 months. Exp: 5,4 ±1,5mm Contr: 3,4 ±0,9mm. P=0,002	NE	NE	NE	NE

Table 4. Risk of bias summary for included studies

	Abbas, 2016	Aboul- Ela, 2011	Jahanbakhshi, 2017	Bhattacharya, 2014	Shoreibah, 2012	Al-Naoum, 2014	Aristizabal, 2016	Abbas, 2012	Aksakalli, 2015	Charavet, 2016	Tunçer, 2017	Uribe, 2017	Alikhanil, 2013	Kundi, 2018	Khan, 2018	Alkebsi, 2018 2018	Leethanakula et al, 2014
Random sequence generation (Selection bias)	+	+	?	?	?	+	?	?	?	?	+	+	?	+	+	+	?
Allocation concealment (Selection bias)	+	+	?	?	?	+	?	?	?	?	+	+	?	+	+	+	?
Blinding of participants and personnel (Performance bias)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blinding of outcome assessment (Detection bias)	?	?	-	?	?	-	?	?	+	?	+	+	+	+	+	+	?
Incomplete outcome data (Attrition bias)	?	+	?	?	?	+	+	?	?	+	+	+	+	+	+	+	?
Selective reporting (Reporting bias)	-	-	+	+	-	+	+	-	+	-	+	+	-	+	+	+	+
Other bias	?	?	?	?	?	+	?	?	?	?	+	+	?	+	+	+	?

Supplemental Table 1. Search strategy PubMed

Search date (dd/mm/yyyy)	Database	Search strategy	Records identified through database searching (No filter)	Records identified through database searching (RCT filter)	Duplicates	Records after duplicates removed	Records screened (Title and abstract)	Duplicates (Title and abstract)	Records screened
6/01/2017 - 09/06/18	PubMed	(("Malocclusion"[Mesh]) AND "Alveoloplasty"[Mesh]) AND "Time"[Mesh]	4	0	0	4	0	0	0
6/01/2017 - 09/06/18	PubMed	("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy	156	15	1	155	11	0	11
8/01/2017 - 09/06/18	PubMed	((orthodontics AND corticotomy)) NOT (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy)	75	4	0	75	4	0	4
8/01/2017 - 09/06/18	PubMed	(("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) AND corticotomies	40	3	24	16	1	1	0
8/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND Periodontal health	12	1	12	0	1	1	0
8/01/2017 - 09/06/18	PubMed	((((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy)) OR (corticotomy AND orthodontics)) AND"Periodontal Attachment Loss"[Mesh]	2	1	2	0	2	2	0
8/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Gingival Recession"[Mesh]	3	1	3	0	2	2	0
8/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Periodontal Index"[Mesh]	2	1	2	0	2	2	0
8/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Periodontal Pocket"[Mesh]	2	1	2	0	1	1	0
8/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND probing depth	8	5	8	0	4	4	0
9/01/2017 - 09/06/18	PubMed	(("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) AND "Electrosurgery"[Mesh]	7	0	1	6	0	0	0
9/01/2017 - 09/06/18	PubMed	(("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) AND "Piezosurgery"[Mesh]	40	6	17	23	4	3	1
9/01/2017 - 09/06/18	PubMed	(("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) AND piezocision	22	3	19	3	3	3	0

9/01/2017 - 09/06/18	PubMed	(((((((piezoelectric AND orthodontics)) OR (piezosurgery AND orthodontics)) OR (piezocision AND orthodontics))) NOT ((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) AND "Piezosurgery"[Mesh])) NOT ((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) AND piezocision)) NOT ((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) AND piezoelectric)	59	4	13	46	3	2	1
11/01/2017 - 09/06/18	PubMed	corticotomy-facilitated orthodontics	26	4	26	0	4	4	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Bone Remodeling"[Mesh]	29	1	29	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Molecular Biology"[Mesh]	0	0	0	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND Molecular Biology	2	0	2	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Osteoblasts"[Mesh]	2	0	2	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Osteoclasts"[Mesh]	9	0	9	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Gingival Crevicular Fluid"[Mesh]	0	0	0	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Inflammation Mediators"[Mesh]	1	1	1	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND Biological mechanism	0	0	0	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "RANK Ligand"[Mesh]	4	0	4	0	0	0	0

11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Osteoprotegerin"[Mesh]	1	1	1	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND Receptor Activator of Nuclear Factor-kappa B	1	1	1	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND "Cytokines"[Mesh]	5	0	5	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((corticotomy AND orthodontics)) OR (("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh] AND corticotomy) AND regional acceleratory phenomenon	8	6	8	0	0	0	0
11/01/2017 - 09/06/18	PubMed	((((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) OR orthodontics)) AND dentoalveolar distraction	59	6	8	51	1	0	1
11/01/2017 - 09/06/18	PubMed	((((((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) OR orthodontics)) AND ligament distraction)) NOT (((((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) OR orthodontics)) AND dentoalveolar distraction)	36	4	4	32	0	0	0
13/01/2017 - 09/06/18	PubMed	((((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) OR orthodontics)) AND corticision	14	0	5	9	1	0	1
13/01/2017 - 09/06/18	PubMed	((((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) OR orthodontics)) AND alveolo centesis	0	0	0	0	0	0	0
13/01/2017 - 09/06/18	PubMed	((((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) OR orthodontics)) AND micro osteoperforations	7	2	0	7	2	0	2
13/01/2017 - 09/06/18	PubMed	((((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) OR orthodontics)) AND interseptal bone reduction	6	1	5	1	1	0	1
13/01/2017 - 10/06/18	PubMed	((("Malocclusion"[Mesh]) OR "Tooth Movement Techniques"[Mesh]) OR orthodontics) AND accelerated tooth movement	139	9	56	83	9	8	1
4/06/2017 - 10/06/18	PubMed	((accelerating tooth movement AND corticotomy)) OR (accelerated tooth movement AND corticotomy)	62	7	59	3	7	7	0
4/06/2017 - 10/06/18	PubMed	((accelerating tooth movement AND piezocision)) OR (accelerated tooth movement AND piezocision)	17	1	16	1	3	3	0
4/06/2017 - 10/06/18	PubMed	((accelerated tooth movement AND corticision)) OR (accelerating tooth movement AND corticision)	7	2	7	0	0	0	0
4/06/2017 - 10/06/18	PubMed	((accelerated tooth movement AND piezopuncture)) OR (accelerating tooth movement AND piezopuncture)	2	0	1	1	0	0	0

4/06/2017 - 10/06/18	PubMed	accelerating tooth movement AND micro-osteoperforation	1	1	1	0	0	0	0
4/06/2017 - 10/06/18	PubMed	accelerating tooth movement AND periodontal ligament distraction	0	0	0	0	0	0	0
			870	92	354	516	66	43	23

Supplemental Table 2. Search strategy EMBASE

Search date (dd/mm/yyyy)	Database	Search strategy	Records identified through database searching (No filter)	Duplicates	Records after duplicates removed	Records screened (Title and abstract)	Duplicates (Title and abstract)	Records screened
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp AND 'alveoloplasty'/exp	2	0	2	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp AND corticotomy	110	0	110	9	0	9
11/01/2017 - 10/06/18	EMBASE	orthodontics AND corticotomy	191	98	93	10	8	2
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontics AND corticotomy AND periodontal health	18	18	0	1	1	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontics AND corticotomy AND periodontal AND attachment AND loss	2	2	0	2	2	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontics AND corticotomy AND 'gingival recession'	8	8	0	2	2	0
11/01/2017 - 10/06/18	EMBASE	'malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontics AND corticotomy AND 'periodontal index'/exp	1	1	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontics AND corticotomy AND 'periodontal pocket'/exp	1	1	0	1	1	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontics AND corticotomy AND probing AND depth	8	8	0	2	2	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp AND 'electrosurgery'/exp	5	0	5	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp AND 'piezosurgery'/exp	23	10	13	4	3	1

11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp AND piezocision	16	14	2	3	3	0
11/01/2017 - 10/06/18	EMBASE	orthodontic AND piezocision	29	20	9	3	3	0
11/01/2017 - 10/06/18	EMBASE	orthodontic AND piezosurgery	52	24	28	3	3	0
11/01/2017 - 10/06/18	EMBASE	orthodontic AND piezoelectric	34	22	12	1	1	0
11/01/2017 - 10/06/18	EMBASE	corticotomy facilitated' AND orthodontics	24	24	0	3	3	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'bone remodeling'/exp	12	11	1	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'molecular biology'/exp	0	0	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND molecular AND biology	1	1	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'osteoblast'/exp	4	4	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'osteoclast'/exp	10	10	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'gingival crevicular fluid'	0	0	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'inflamation mediators'	0	0	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'biological mechanism'	0	0	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'osteoclast differentiation factor'/exp	5	5	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'osteoprotegerin'/exp	1	1	0	0	0	0

11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'receptor activator of nuclear factor kappa b'	1	1	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'cytokine'/exp	7	7	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND corticotomy AND 'regional acceleratory phenomenon'	8	8	0	0	0	0
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR orthodontic AND 'dentoalveolar distraction'	19	2	17	1	0	1
11/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR 'orthodontic'/exp OR orthodontic AND 'ligament distraction'	14	2	12	0	0	0
13/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR 'orthodontic'/exp OR orthodontic AND corticision	12	4	8	0	0	0
13/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR 'orthodontic'/exp OR orthodontic AND 'alveolocentesis'	0	0	0	0	0	0
13/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR 'orthodontic'/exp OR orthodontic AND 'osteoperforations'	4	0	4	2	0	2
13/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR 'orthodontic'/exp OR orthodontic AND interseptal AND bone AND reduction	5	1	4	1	0	1
13/01/2017 - 10/06/18	EMBASE	malocclusion'/exp OR 'orthodontic tooth movement'/exp OR 'orthodontic'/exp OR orthodontic AND accelerated AND tooth AND movement	111	46	65	5	5	0
5/06/2017 - 10/16/18	EMBASE	accelerating' AND ('tooth'/exp OR tooth) AND ('movement'/exp OR movement) AND corticotomy	21	21	0	3	3	0
5/06/2017 - 10/16/18	EMBASE	accelerating AND ('tooth'/exp OR tooth) AND ('movement'/exp OR movement) AND piezocision	7	7	0	2	2	0
5/06/2017 - 10/16/18	EMBASE	accelerating AND ('tooth'/exp OR tooth) AND ('movement'/exp OR movement) AND corticision	3	3	0	0	0	0

5/06/2017 - 10/16/18	EMBASE	accelerating AND ('tooth'/exp OR tooth) AND ('movement'/exp OR movement) AND piezopuncture	1	1	0	0	0	0
5/06/2017 - 10/16/18	EMBASE	accelerating AND ('tooth'/exp OR tooth) AND ('movement'/exp OR movement) AND 'micro osteoperforation'	1	1	0	0	0	0
5/06/2017 - 10/16/18	EMBASE	accelerating AND ('tooth'/exp OR tooth) AND ('movement'/exp OR movement) AND periodontal AND ('ligament'/exp OR ligament) AND ('distraction'/exp OR distraction)	0	0	0	0	0	0
			738	386	385	58	42	16

Supplemental Table 3. Search strategy Cochrane

Search date (dd/mm/yyyy)	Database	Search strategy	Records identified through database searching (No filter)	Records identified through database searching (RCT filter)	Duplicates	Records after duplicates removed	Records screened (Title and abstract)	Duplicates (Title and abstract)	Records screened
13/01/2017 - 10/06/18	cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics) AND accelerated tooth movement	29	29	0	29	13	0	13
13/01/2017 - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND "Alveoloplasty"	2	2	0	2	0	0	0
13/01/2017 - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND "Electrosurgery"	0	0	0	0	0	0	0
13/01/2017 - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND "Piezosurgery"	7	7	4	3	2	2	0
13/01/2017 - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND corticotomy	24	24	10	14	8	4	4
13/01/2017 - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND dentoalveolar distraction	2	2	0	2	0	0	0
13/01/2017 - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND piezocision	9	9	8	1	2	2	0

13/01/2017 - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND corticision	3	3	1	2	0	0	0
15/01/2017 - - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND alveolocentesis	0	0	0	0	0	0	0
15/01/2017 - - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND micro osteoperforations	4	4	1	3	0	0	0
15/01/2017 - - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND osteoperforations	4	4	4	0	0	0	0
15/01/2017 - - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND corticotomy-facilitated orthodontics	5	5	5	0	2	2	0
15/01/2017 - - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND interseptal bone reduction	1	1	1	0	1	1	0
15/01/2017 - - 10/06/18	Cochrane	("Malocclusion" OR "Tooth Movement Techniques" OR orthodontics OR accelerated tooth movement) AND piezoelectric	6	6	6	0	1	1	0
5/06/2017 - 10/06/18	Cochrane	Accelerating tooth movement AND corticotomy	10	10	10	0	6	6	0
5/06/2017 - 10/06/18	Cochrane	Accelerating tooth movement AND piezocision	5	5	5	0	4	4	0
5/06/2017 - 10/06/18	Cochrane	Accelerating tooth movement AND corticision	1	1	1	0	0	0	0
5/06/2017 - 10/06/18	Cochrane	Accelerating tooth movement AND piezopuncture	0	0	0	0	0	0	0
5/06/2017 - 10/06/18	Cochrane	accelerating tooth movement AND micro-osteoperforation	2	2	2	0	1	1	0
5/06/2017 - 10/06/18	Cochrane	accelerating tooth movement AND periodontal ligament distraction	0	0	0	0	0	0	0
			114	114	58	56	40	23	17

Supplemental Table 4. Search strategy Lilacs

Search date (dd/mm/yyyy)	Database	Search strategy	Records identified through database searching (No filter)	Duplicates	Records after duplicates removed	Records screened (Title and abstract)	Duplicates (Title and abstract)	Records screened
13/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics) AND accelerated orthodontics	77	0	77	10	0	10
13/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND alveoloplasty	0	0	0	0	0	0
13/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND Electrosurgery	0	0	0	0	0	0
13/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND Piezosurgery	17	10	7	2	1	1
13/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND corticotomy	85	40	45	13	9	4
13/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND dentoalveolar distraction	0	0	0	0	0	0
13/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND periodontal ligament distraction	6	0	6	0	0	0
13/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND piezocision	12	12	0	2	2	0
13/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND corticision	2	0	2	0	0	0
13/01/2016 - 10/06/18	LILACS	corticision	15	4	11	1	0	1
15/01/2016 - 10/06/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND alveolocentesis	0	0	0	0	0	0
15/01/2016 - 11/16/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND micro osteoperforations	1	1	0	0	0	0
15/01/2016 - 11/16/18	LILACS	corticotomy-facilitated orthodontics	31	20	11	6	5	1
15/01/2016 - 11/16/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND interseptal bone reduction	2	2	0	0	0	0
15/01/2016 - 11/16/18	LILACS	interseptal bone reduction	6	4	2	1	0	1

15/01/2016 - 11/16/18	LILACS	(Malocclusion OR Tooth Movement Techniques OR orthodontics OR accelerated orthodontics) AND Piezoelectric	20	9	11	3	3	0
6/06/2017 - 11/16/18	LILACS	accelerating tooth movement AND corticotomy	30	28	2	4	4	0
6/06/2017 - 11/16/18	LILACS	accelerating tooth movement AND piezocision	8	1	7	2	2	0
6/06/2017 - 11/16/18	LILACS	accelerating tooth movement AND corticision	3	3	0	0	0	0
6/06/2017 - 11/16/18	LILACS	accelerating tooth movement AND piezopuncture	1	1	0	0	0	0
6/06/2017 - 11/16/18	LILACS	accelerating tooth movement AND micro-osteoperforation	1	1	0	0	0	0
6/06/2017 - 11/16/18	LILACS	accelerating tooth movement AND periodontal ligament distraction	0	0	0	0	0	0
			317	136	181	44	26	18

Supplemental Table 5. Risk of bias of each article

	Domain	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
Abbas et al. 2016.	Support for judgement	"The patients were equally and randomly divided into 2 groups: a corticotomy group in which corticotomy was randomly assigned to 1 side of the maxillary arch (experimental side), and a piezocision group in which piezocision was randomly assigned to 1 side of the maxillary arch (experimental side). The randomization was performed with coin tosses to prevent selection bias"	"The interventions was randomly assigned to 1 side of the maxillary arch. The randomization was performed with coin tosses to prevent selection bias"	Blinding of participants and personnel during the interventions were not described.	Blinding of outcome assessment were not described.	Attrition and exclusions were not reported	Tooth movement: Outcome of the operated and nonoperated sides at all measurement times were reported. Periodontal health: Outcome of the operated and nonoperated sides at all measurement times were not reported	
	Review authors' judgement	Brief description of an adequate generation of a randomised sequence.	The coin toss method does not allow the operator or the participant to anticipate allocations prior to assignment.	It was impossible to blind participants in this study because of surgery intervention.	The study does not describe whether there was blinding of outcome assessment	The study does not describe Attrition and exclusions	The secondary result of periodontal health, although it is mentioned in the results as evaluated without significant differences, no table of results regarding this variable is found in the article.	
	Evaluation	Low	Low	High	Unclear	Unclear	High	Unclear
	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
Aboul- Ela et al. 2011	Support for judgement	"On the day before the corticotomy surgery, 1 maxillary premolar was extracted on a random basis (coin toss). When the patient was scheduled for the surgery, the other premolar was extracted, and CFO was performed"	"Corticotomy facilitated orthodontics was randomly assigned to one side of the maxillary arch - on a random basis (coin toss)"	Blinding of participants and personnel during the interventions were not described.	Blinding of outcome assessment were not described.	"We started with 15 patients, but 2 patients were excluded from the study—1 because of multiple missed appointments and the other because of poor oral hygiene"	Tooth movement and periodontal health: Outcome of the operated and nonoperated sides at all measurement times were reported incompletely, without standard deviations or p values.	
	Review authors' judgement	Brief description of an adequate generation of a randomised sequence.	The coin toss method does not allow the operator or the participant to anticipate allocations prior to assignment.	It was impossible to blind participants in this study because of surgery intervention.	The study does not describe whether there was blinding of outcome assessment	The exclusion of two patients is described in the discussion, 1 for poor hygiene and the other for missing appointments, the data of these patients are not included.	Inadequate outcome reporting.	
	Evaluation	Low	Low	High	Unclear	Low	High	Unclear

		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Jahanbakhshi et al. 2017	Domain	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	"This study was performed by using split mouth design method. **In a randomized manner**, one side of the maxillary arch on which corticotomy was applied was considered as the experimental group, and the other side without surgical intervention was considered as the control group. "	Concealment of allocations prior to assignment was not described.	Blinding of participants and personnel during the interventions were not described.	The measures to define the speed of dental movement were taken directly in the patient.	Attrition and exclusions were not reported	Outcome of the operated and nonoperated sides at all measurement times were reported	
	Review authors' judgement	The study does not describe the method used to generate the randomised sequence	The study does not describe the method used to conceal the allocation sequence	It was impossible to blind participants in this study because of surgery intervention.	Detection bias due to knowledge of the allocated interventions by outcome assessors. It is impossible to perform a blinding of the evaluator because the measurements were performed clinically, where the scars of the gum are easily seen where the intervention was performed.	The study does not describe Attrition and exclusions	Adequate outcome reporting.	
	Evaluation	Unclear	Unclear	High	High	Unclear	Low	Unclear
Bhattacharya et al. 2014	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	"Patients were randomized into control and corticotomy groups. Each group consisted of 10 subjects"	Concealment of allocations prior to assignment was not described.	Blinding of participants and personnel during the interventions were not described.	Blinding of outcome assessment were not described.	Attrition and exclusions were not reported	Outcome of the operated and nonoperated groups at all measurement times were reported	
	Review authors' judgement	The study does not describe the method used to generate the randomised sequence	The study does not describe the method used to conceal the allocation sequence	It was impossible to blind participants in this study because of surgery intervention.	The study does not describe whether there was blinding of outcome assessment	The study does not describe Attrition and exclusions	Adequate outcome reporting.	
	Evaluation	Unclear	Unclear	High	Unclear	Unclear	Low	Unclear
Shoreibah et al. 2012	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS

	Support for judgement	"Patientswere randomly divided and treated with either a modified technique of corticotomy (Group I) or conventional orthodontic therapy (Group II)".	Concealment of allocations prior to assignment was not described.	Blinding of participants and personnel during the interventions were not described.	Blinding of outcome assessment were not described.	Attrition and exclusions were not reported	Tooth movement: Outcome of the operated and nonoperated groups at all measurement times were reported incompletely, without standard deviations or p values. Probing depth: Tooth movement: Outcome of the operated and nonoperated groups at all measurement times were reported	
	Review authors' judgement	The study does not describe the method used to generate the randomised sequence	The study does not describe the method used to conceal the allocation sequence	It was impossible to blind participants in this study because of surgery intervention.	The study does not describe whether there was blinding of outcome assessment	The study does not describe Attrition and exclusions	Inadequate outcome reporting. The result of total treatment time, although it is mentioned in the results as evaluated with significant differences, no table of results regarding this variable is found in the article.	
	Evaluation	Unclear	Unclear	High	Unclear	Unclear	High	Unclear
Al-Naoum et al. 2014	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	" Split-mouth-design randomized controlled trial - The containers included 15 envelopes with the letter 'R' indicating the right-hand side and 15 envelopes with the letter 'L"	"Each patient was asked to pick an opaque sealed envelope from a container to allocate the surgical intervention side"	Blinding of participants and personnel during the interventions were not described.	The measures to define the speed of dental movement were taken directly in the patient.	A flow chart showed no lost to follow-up of patients recruted (Figure 1)	Outcome of the operated and nonoperated sides at all measurement times were reported	
	Review authors' judgement	Brief description of an adequate generation of a randomised sequence.	The opaque sealed enevelope method does not allow the operator or the participant to anticipate allocations prior to assignment.	It was impossible to blind participants in this study because of surgery intervention.	Detection bias due to knowledge of the allocated interventions by outcome assessors. It is impossible to perform a blinding of the evaluator because the measurements were performed clinically, where the scars of the gum are easily seen where the intervention was performed.	The study describes adequately Attrition and exclusions	Adequate outcome reporting.	
	Evaluation	Low	Low	High	High	Low	Low	Low
Aristizabal et	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**

al. 2016		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	"Patients were randomly divided into two groups: Periodontally Accelerated Osteogenic Orthodontics (PAOO) group (n= 5, mean age: 29.6±9.8 years) and Control Group (n= 5, mean age: 28.5±6.3 year"	Concealment of allocations prior to assignment was not described.	Blinding of participants and personnel during the interventions were not described.	Blinding of outcome assessment were not described.	"All patients completed the trial and received follow-up care"	Outcome of the operated and nonoperated groups at all measurement times were reported	
	Review authors' judgement	The study does not describe the method used to generate the randomised sequence	The study does not describe the method used to conceal the allocation sequence	It was impossible to blind participants in this study because of surgery intervention.	The study does not describe whether there was blinding of outcome assessment	All the patients completed the trail. Thera was no attrition in this study.	Adequate outcome reporting.	
	Evaluation	Unclear	Unclear	High	Unclear	Low	Low	Unclear
Abbas et al. 2012	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	Patients were randomly divided to two groups; group I (corticotomy group) in which Alveolar Corticotomies (ACS) were performed using PES and group II (non surgical group) in which non-surgical standard orthodontics technique was done	Concealment of allocations prior to assignment was not described.	Blinding of participants and personnel during the interventions were not described.	Blinding of outcome assessment were not described.	Attrition and exclusions were not reported	Tooth movement: Outcome of the operated and nonoperated groups at all measurement times were reported. Periodontal health: Outcome of the operated and nonoperated groups at all measurement times were not reported	
	Review authors' judgement	The study does not describe the method used to generate the randomised sequence	The study does not describe the method used to conceal the allocation sequence	It was impossible to blind participants in this study because of surgery intervention.	The study does not describe whether there was blinding of outcome assessment	The study does not describe Attrition and exclusions	The secondary result of periodontal health, although it is mentioned in the results as evaluated without significant differences, no table of results regarding this variable is found in the article.	
	Evaluation	Unclear	Unclear	High	Unclear	Unclear	High	Unclar
Aksakalli et al. 2015	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	" Split-mouth design, with the experimental quadrant selected by randomization"	Concealment of allocations prior to assignment was not described.	Blinding of participants and personnel during the interventions were not described.	"The examiner who was responsible for the measurements was blinded"	Attrition and exclusions were not reported	Outcome of the operated and nonoperated sides at all measurement times were reported	

	Review authors' judgement	The study does not describe the method used to generate the randomised sequence	The study does not describe the method used to conceal the allocation sequence	It was impossible to blind participants in this study because of surgery intervention.	The measurements were made in scanned models which allows the blinding of the evaluator, because he can not observe the scars in the gum left by the cut of the piezotomo	The study does not describe Attrition and exclusions	Adequate outcome reporting.	
	Evaluation	Unclear	Unclear	High	Low	Unclear	Low	Unclear
Charavet et al. 2016	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	"This study was designed as a randomized controlled clinical trial to compare conventional orthodontic treatment (control group) and piezocision-assisted orthodontic treatment (piezocision group)"	Concealment of allocations prior to assignment was not described.	Blinding of participants and personnel during the interventions were not described.	´´Following the alignment steps, impressions were taken, and a blinded senior orthodontist validated appliance removal or provided advice regarding further adjustments."	"All patients were followed until the completion of treatment. Two patients (1 in each group) failed to show up for the posttreatment CT scan and were excluded from the follow-up".	Tooth movement and periodontal health: Outcome of the operated and nonoperated groups at all measurement times were reported incompletely, without standard deviations or p values.	
	Review authors' judgement	The study does not describe the method used to generate the randomised sequence	The study does not describe the method used to conceal the allocation sequence	It was impossible to blind participants in this study because of surgery intervention.	Regarding the main variable (treatment time), the opinion of the end of a treatment was made by a blinded clinician who only evaluated the study models. But the study does not describe whether there was blinding of outcome assessment	The study describe that there was a complete follow-up of the sample of the patients, specifying that two of the patients were excluded in the follow-up and and because they were from different groups they did not alter the results.	Inadequate outcome reporting.	
	Evaluation	Unclear	Unclear	High	Unclear	Low	High	Unclear
Uribe et al. 2017	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS

	Support for judgement	"Randomization sequences were generated using Random Allocation Software program. Random block sizes of six and eight and allocation ratio of 1:1 were generated to ensure balanced numbers in each group "	" The allocation sequences were sealed around with aluminium foil in envelopes with identical appearance, and were stored in a box."	Blinding of participants and personnel during the interventions were not described.	"Patient codes were assigned to the models prior to measurement to ensure blinding of the evaluators. Two blinded outcome assessors, different from the study coordinator were calibrated in the assessment of the Little's irregularity index"	"The subject flow through the trial using a CONSORT diagram. Out of the 41 subjects enrolled in the study, six subjects did not receive the allocated intervention for different reasons such as patient not starting treatment (three subjects), periodontal disease after careful evaluation of records (two subjects) and change in the treatment plan (one subject) from a non-extrac- tion to an extraction approach. Three subjects were lost to follow up. Two control and one experimental subjects were excluded from the analysis due to insufficient initial irregularity index as determined by the outcome assessors, leaving a total of 29 subjects completing the study and analysed (16 experimental and 13 control)"	Outcome of the operated and nonoperated groups at all measurement times were reported		
	Review authors' judgement	Brief description of an adequate generation of a randomised sequence.	The opaque sealed enevelope method does not allow the operator or the participant to anticipate allocations prior to assignment.	It was impossible to blind participants in this study because of surgery intervention.	The study describes blinding of outcome assessment	The study describes adequately Attrition and exclusions	Adequate outcome reporting.		
	Evaluation	Low	Low	High	Low	Low	Low	Low	
Tunçer et al. 2017	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**	
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS	

	Support for judgement	"We conducted a randomized, single-centred, parallel-group, controlled trial" - Envelopes	"Randomization: Accomplished with opaque, sealed envelopes. But, the 'opaque-sealed envelope' technique was not used step-by-step as it is described in the literature"	Blinding of participants and personnel during the interventions were not described.	"Data assessment was blinded. Cephalometric analyses and dental cast measurements were performed by the principal investigator (N.I.T.) after being given research numbers by another investigator (A.A.O.). GCF samples were numbered accordingly and analysed by another blinded investigator (J.S.G.)".	Soon after the beginning of en-masse retraction, one patient was excluded from the study because of bad oral hygiene and noncompliance to the appointments. One patient meeting the eligibility criteria was included in the same group while patient recruitment was still proceeding and the final sample size was 30 at the end of retraction. Data of the excluded patient was not included in the assessment.	Outcome of the operated and nonoperated groups at all measurement times were reported	
	Review authors' judgement	Brief description of an adequate generation of a randomised sequence.	The opaque sealed enevelope method does not allow the operator or the participant to anticipate allocations prior to assignment.	It was impossible to blind participants in this study because of surgery intervention.	The study describes blinding of outcome assessment	The study describes adequately Attrition and exclusions	Adequate outcome reporting.	
	Evaluation	Low	Low	High	Low	Low	Low	Low

Alikhani et al. 2013	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	"Patients were randomly assigned to one of the study groups"	Concealment of allocations prior to assignment was not described.	"The subjects and the residents administering the treatment were aware of the group assignment and therefore were not blinded"	"The investigators performing the measurements and data analysis were blinded from the group assignments."	"Twenty patients were recruited and completed the study with no loss to follow-up.	Tooth movement and GCF: Outcome of the operated and nonoperated groups at all measurement times were reported incompletely, without standard deviationS.	
	Review authors' judgement	The study does not describe the method used to generate the randomised sequence	The study does not describe the method used to conceal the allocation sequence	It was impossible to blind participants in this study because of surgery intervention.	The study describes blinding of outcome assessment	The study describes adequately Attrition and exclusions	Inadequate outcome reporting.	
	Evaluation	Unclear	Unclear	High	Low	Low	High	Unclear
kundi 2018	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS

	Support for judgement	"28 adult patients with class II div I malocclusion were randomly allocated with the help of SPSS software to either perforation or conventional group for carrying out this randomized parallel group controlled trial in 1:1 ratio"	"The patients were randomly allocated by a sequence generated in SPSS with equal number of participants in each group, and the allocation was centrally concealed"	"Blinding of the patient and operator was not feasible and blinding was confined to analysis stage only"	"Blinding of the patient and operator was not feasible and blinding was confined to analysis stage only"	"56 canines in 28 patients of mean age 28.4 ± 4.2 years (age range 20-36 years) were followed for 28 days. There were no losses to follow up"	Outcome of the operated and nonoperated groups at all measurement times were reported	
	Review authors' judgement	Brief description of an adequate generation of a randomised sequence.	Allocation concealment described.	It was impossible to blind participants in this study because of surgery intervention.	The study describes blinding of outcome assessment	The study describes adequately Attrition and exclusions	Adequate outcome reporting.	
	Evaluation	Low	low	High	Low	Low	Low	Low
Khan et al. 2018	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	"The experimental side receiving MOP was randomly (coin toss) allotted either left or right side, while control side did not receive any MOP"	"The experimental side receiving MOP was randomly (coin toss) allotted either left or right side, while control side did not receive any MOP"	"The subjects and the residents administering the treatment were aware of the group assignment and therefore were not blinded"	"The investigators performing the measurements and data analysis were blinded from the group assignments".	30 patients were recruited and completed the study with no loss to follow-up.	Outcome of the operated and nonoperated sides at all measurement times were reported	
	Review authors' judgement	Brief description of an adequate generation of a randomised sequence.	The coin toss method does not allow the operator or the participant to anticipate allocations prior to assignment.	It was impossible to blind participants in this study because of surgery intervention.	The study describes blinding of outcome assessment	The study describes adequately Attrition	Adequate outcome reporting.	
	Evaluation	Low	Low	High	Low	Low	Low	Low
Alkebsi et al. 2018	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS

	Support for judgement	"The intervention was randomly allocated to either the right or left side with a 1:1 allocation ratio. The randomization was accomplished by using the permuted random block size of 2 with the random generation function in Excel (Microsoft, Redmond, Wash)"	"Subsequently, the random sequences to either the right or left were concealed in opaque envelopes and shuffled before the intervention to increase the unpredictability of the random allocation sequence. Each patient was asked to pick a sealed envelope to assign the surgical intervention to either the right or left side. Allocation concealment was aimed to prevent selection bias and protect the assign- ment sequence until allocation"	"Blinding of either patient or clinician was not possible"	"Blinding was ensured at the measurement stage (data collection), in which the investigator (A.A.) was blinded to where the MOPs were applied by coding all digital models"	"Three subjects were excluded after MOP intervention due to either irregular attendance or poor oral hygiene. During the analysis stage, there were 32 subjects"	Outcome of the operated and nonoperated sides at all measurement times were reported	
	Review authors' judgement	Brief description of an adequate generation of a randomised sequence.	The opaque sealed enevelope method does not allow the operator or the participant to anticipate allocations prior to assignment.	It was impossible to blind participants in this study because of surgery intervention.	The study describes blinding of outcome assessment	The study describes adequately Attrition	Adequate outcome reporting.	
	Evaluation	Low	Low	High	Low	Low	Low	Low

Leethanakula et al, 2014	Domain	**Selection bias**		**Performance bias**	**Detection bias**	**Attrition bias**	**Reporting bias**	**Other bias**
		RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER SOURCES OF BIAS
	Support for judgement	" This study was a split-mouth design in which the experimental side was allocated by randomization"	Concealment of allocations prior to assignment was not described.	Blinding of participants and personnel during the interventions were not described.	Blinding of outcome assessment were not described.	Attrition and exclusions were not reported	Outcome of the operated and nonoperated sides at all measurement times were reported	
	Review authors' judgement	The study does not describe the method used to generate the randomised sequence	The study does not describe the method used to conceal the allocation sequence	It was impossible to blind participants in this study because of surgery intervention.	The study does not describe whether there was blinding of outcome assessment	The study does not describe Attrition and exclusions	Adequate outcome reporting.	
	Evaluation	Unclear	Unclear	High	Unclear	Unclear	Low	Unclear

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2,3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 (Table 1)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1,3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3 (Table 1)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary table 1,2,3,4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3,4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3,4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3,4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4,5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	0
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	0
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5, (Figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-9 (Table 2)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5 (Table 4) (Supl. Table 5)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-9 (Table 2-3)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10 (Figure 2)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	0
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	0
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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