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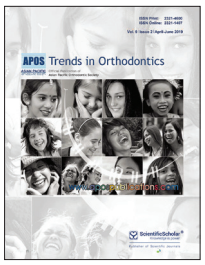

Review Article

Platelet-rich derivatives for accelerating the rate of orthodontic tooth movement - a systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this systematic review and meta-analysis was to report on the effects of using platelet-rich derivatives on the rate of tooth movement.

Material and Methods: Both electronic and manual searches were performed with specific eligibility criteria based on population, intervention, comparison, outcome, and study design. Risk of bias (RoB) assessment was done using the Cochrane RoB tool 2, the data were pooled and analyzed using review manager 4.5, and certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach. Two independent reviewers performed the study selection, data extraction, and analysis. Nine studies were included for qualitative analysis and two of them were subjected to meta-analysis.

Results: The standard mean difference for the rate of canine distal movement with platelet-rich derivatives was not significantly higher than controls at any of the time intervals ($P > 0.0001$). Rotation of canines, molar mesialization, and pain scores were not affected by the administration of platelet-rich derivatives for accelerating tooth movement. A moderate to high RoB was noted in the included studies and the certainty of the available evidence as assessed by the GRADE approach was moderate.

Conclusion: The included studies presented with high heterogeneity and more high-quality studies with strict protocols are needed. Even though individual studies report significant acceleration of tooth movement following administration of PR derivatives, moderate certainty of evidence suggests no acceleratory effect on tooth movement.

Keywords: Platelet-rich derivatives, Accelerated orthodontics, Platelet-rich plasma, Platelet-rich fibrin, Rate of tooth movement

INTRODUCTION

Orthodontic treatment takes a long duration to complete and can increase the risk of root resorption, white spot lesions, periodontal complications, and dental caries in patients.[1] Clinicians and researchers have always attempted methods to accelerate tooth movement and achieved varying degrees of success. Various surgical and non-surgical approaches have been tried and tested to accelerate tooth movement.[2] Surgical methods such as corticotomy have been proven to be successful in reducing the duration of tooth movement.[3] Surgical methods

involving osteotomies, and corticotomies involving elevation of mucoperiosteal flap elevations are considered more invasive by clinicians and are also associated with injuries to the soft and hard tissues.[4-7]

Biological agents such as Vitamin D, parathyroid hormone, and prostaglandins have also been used to accelerate tooth movement. However, the existing literature regarding these agents presents conflicting results[8] and systemic administration of these agents can also result in side effects.[8,9] Minimally invasive procedures such as micro osteo perforations (MOPs) using the Propel device and recently mini-implant aided MOPs are used to accelerate tooth movement and reported to be successful by individual authors.[10] But a recent systematic review reported that MOPs have a statistically significant but clinically not very substantial effect in accelerating tooth movement.[11]

Platelet-rich derivatives include platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and leukocyte-PRF. All of these are derived from the patient's blood sample. PRP is an autologous concentration of platelets in a small volume of plasma and is rich in autologous growth factors.[12] The growth factors present in PRP can cause both osteoblastic and osteoclastic activity which in turn leads to alveolar bone remodeling and thus can potentially accelerate orthodontic tooth movement.[13] Similarly, PRF is a second-generation platelet containing biomaterial and has potential applications in wound healing. PRF traps platelets and cytokines in a fibrin gel.[13,14] PRF mainly consists of a fibrin matrix rich in platelet and leukocyte cytokines such as IL-1, -4, and -6, and growth factors such as transforming growth factor beta 1, platelet-derived growth factor, and vascular endothelial growth factor.[15] The tissue regeneration property of PRF can, therefore, be used for alveolar socket preservation post-orthodontic extraction and to induce bone remodeling.[16]

Human clinical trials have been carried out in recent times to assess the effectiveness of PRF and PRP for accelerating tooth movement. A systematic review has been performed on the effectiveness of PRP in animal subjects[6] but no systematic review involving human trials has been reported.

Objective

Therefore, the aim of this review is to analyze the existing literature on the effect of all platelet-rich derivatives (PRP, PRF, and LPRF) on tooth movement in orthodontic subjects.

MATERIAL AND METHODS

Protocols and registration

This review has been registered via PROSPERO international register for systematic reviews. This systematic review was prepared according to the Cochrane Handbook for Systematic Review of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[17-19]

Eligibility criteria

The population, intervention, comparison, outcome, and study design format was used to phrase the clinical question along with inclusion and exclusion criteria randomized clinical trials involving healthy patients undergoing active orthodontic treatment were included in the study. The primary outcome assessed was the amount of tooth movement and the secondary outcomes were the effect on canine rotation, molar mesialization, and pain scores [Supplementary Table 1].

Information source and search strategy

PubMed, Cochrane Central Register of Controlled Trials, Latin American and Caribbean Health Sciences Literature, and Google scholar databases were ***searched without time restrictions until APRIL 2021.*** The search strategies applied for all these databases are summarized in [Supplementary Table 1]. The search was carried out independently and also in duplicate. The references of the included studies were also searched for any relevant studies meeting the inclusion criteria.

Study selection

The selection of individual studies was done by two reviewers (DK and RKJ) independently based on the eligibility criteria. A full text reading of the studies meeting the inclusion criteria was then carried out. ***The 2 reviewers were not blinded to the authors, institutes, and research results***. Any disagreements were solved by a third reviewer (AMG) and the entire process was reviewed again.

Risk of bias (RoB) in individual studies

The Cochrane RoB2 tool was used for assessment of the RoB across the studies.[20] The tool assesses the risk of the included studies based on five domains: bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results. This process was carried out independently by 2 authors (DK and RKJ) and duplicated. The third author was involved in reviewing the assessment done by the first two authors (AB).

Data collection and data items

Two reviewers (DK and RKJ) were involved in extracting the relevant data from the studies which met the inclusion criteria. The data items were selected in adherence to

Table 1: Characteristics of included studies.

Author and year of study	Study design	Sample size Gender Dropouts	Groups	Outcomes assessed	Statistics used	Method of retraction used	Tools and landmarks used for assessment
Erdur *et al*., 2021	Split Mouth RCT	20 M: 8 F: 12	Intervention: Intraligamentary injections of i-PRF Control: No intervention	Primary: Rate of canine movement Secondary: Cytokine levels in GCF	One way analysis of variance (ANOVA and Student *t*-test), repeated measure ANOVA	0.22 MBT prescription with TAD's assisted retraction using 150 g force Niti coil springs on a 0.017" X 0.025" stainless steel wire	Measurements made on dental casts using digital calipers from midpoints of lines over the marginal ridge of the canine and lateral teeth
Karakasli *et al*., 2021	RCT	40 M: 17 F: 23	Intervention: PDL injections of i-PRF Control: No intervention	Primary: Rate of incisor movement	Student *t*-test and one way ANOVA	0.22 MBT prescription with TAD's assisted retraction using 150gm force Niti coil springs on a 0.019" X 0.025" stainless steel wire	Measurements were made on Study models using digital calipers. The horizontal distance between the mid-marginal ridges of adjoining teeth was recorded
Zeitounlouian *et al*., 2021	Split Mouth RCT	21 M: 6 F: 15	Intervention: Submucosal injection of i-PRF Control: No intervention	Primary: Rate of canine movement Secondary: Rate of canine rotation and loss of molar anchorage	Student *t*-test	0.22 MBT BRACKET PRESCRIPTION WITH 150gm force applied with e chains on a 0.019" X 0.025" stainless steel wire	Measurements were made on images of study models where software to measure the distance between the cusp tip of upper canine and medial end of the third palatal rugae ed
Ali *et al*., 2020	Split mouth RCT	18 M: 0 F: 18	Intervention: Submucosal injection of i-PRP Control: No injection	PRIMARY- the amount of tooth movement	Student *t*-test	0.22 MBT prescription with TAD's assisted retraction using 150gm force Niti coil springs on a 0.017" X 0.025" stainless steel wire	Measurements were made on scanned intraoral images.

(Contd...)

Table 1: *(Continued)*.

Author and year of study	Study design	Sample size Gender Dropouts	Groups	Outcomes assessed	Statistics used	Method of retraction used	Tools and landmarks used for assessment
Nemtoi *et al*., 2018	Split mouth RCT	20 F: 11 M: 9	Intervention: Placement of PRF plugs in sockets Control: No intervention	Primary: Amount of tooth movement Secondary: Bone regeneration	Mean and SD	0.22 MBT prescription with closed Niti coil springs on a 0.016" X 0.022" stainless steel wire	Measurements were made on study models using a flexible ruler. The horizontal distance between the mid-marginal ridges of the adjoining teeth was recorded
Pacheo *et al*., 2020	Split mouth RCT	21 F: 12 M: 5 DROPOUTS: 4	Intervention: Placement of LPRF membranes in sockets Control: No intervention	Primary: Rate of tooth movement Secondary: Change in inclination	Wilcoxon signed rank test	0.22 MBT BRACKET PRESCRIPTION WITH 150gm force applied with e chains using 0.020"stainless steel wire	Intraoral measurements using a flexible ruler. the distance from the dental midline under the brackets from the mesial surface of the canines and the maxillary central incisors to was recorded
El-Timamy *et al*., 2020	Split mouth RCT	16 F: 15 DROPOUTS: 1	Intervention: I-PRP with Cacl2 Control: Only Cacl2 injection	Primary Outcome: Rate of tooth movement Secondary Outcome: Pain assessment	Independent *t*-test and paired *t*-test	0.22 Roth prescription with TAD's assisted retraction using 150gm force Niti coil springs on a 0.019" X 0.025" stainless steel wire	Measurements were made by superimposing scanned intraoral images A visual analog scale was used for pain assessment
Arci *et al*., 2021	Split mouth RCT	12 M: 5 F: 7	Intervention: I-PRP Control: No intervention	Primary: Cephalometric measurements, amount of Canine distalization, canine rotation, molar mesialization transverse changes	Wilcoxon signed rank test, Chi-square test, and Mann-Whitney U test	0.22 MBT prescription with TAD's assisted retraction using 150gm force Niti coil springs on a 0.019" X 0.025" stainless steel wire	Measurements were made by superimposing scanned images of dental casts

(Contd...)

Table 1: *(Continued).*

Author and year of study	Study design	Sample size Gender Dropouts	Groups	Outcomes assessed	Statistics used	Method of retraction used	Tools and landmarks used for assessment
Angel *et al.*, 2021	Split mouth RCT	10	Intervention: I-PRP Control: No intervention	Primary: Rate of maxillary canine movement Secondary: Levels of osteoprotegerin (OPG and soluble receptor activator of nuclear factor-j ligand (sRANKL) in the gingival crevicular fluid	Mann Whitney U test and paired *t*-test	0.22 MBT prescription with TAD's assisted retraction using 150gm force Niti coil spring on a 0.019" X 0.025" stainless steel wire	Measurements were made by superimposing scanned images of dental casts

previously developed and piloted forms of data extraction for a systematic review. The data collected included: Author and year of study, study design, subject characteristics, intervention methods and protocol, control group, intervals of outcome assessment, and results obtained.

Summary measures and synthesis of results

The outcome measure for meta-analysis in this review was the rate of canine tooth distal movement. Studies included in the meta-analysis reported on the rate of canine distal movement at 4, 8, 12, and 16 weeks with injectable platelet-rich derivatives and compared with untreated controls. Random effects meta-analysis was carried out and a standard mean difference with 95% confidence intervals were used to measure and compare the outcome between the two groups.

Level of evidence

The certainty of the scientific evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADEPro) guidelines. Amount of tooth movement was the primary outcome and the studies were assessed for their design, RoB, inconsistency, indirectness, imprecision, and publication bias if any.

RESULTS

Study selection

A total of 275 published studies were identified through a search of various databases. Out of these studies, 16 duplicate studies were excluded and 259 studies were screened by two reviewers. Out of 259 studies, 250 were excluded after reading titles and abstracts. Nine studies were assessed for eligibility and after reading the full texts all nine studies were included for qualitative assessment and two studies were included for quantitative analysis. The methodology of the electronic database search is represented in [Figure 1].

Characteristics of the included studies

The characteristics of each included study are mentioned in [Table 1]. All included studies in this systematic review were split-mouth clinical trials except for the study by Karakasli *et al.* which was a randomized control trial.[21] A total of 133 patients were enrolled in split-mouth trials and 40 patients were enrolled in the RCT by Karakasli *et al.* Out of the included studies, four were carried out over 12 weeks.[21-24] Two studies were carried out over a period of 5 months.[25,26] The studies by El-Timamy *et al.* and Tehranchi *et al.* were carried out over 4 months.[27,28] The study by Nemtoi *et al.* was carried out for 6 months.[16]

Four out of the nine studies included iPRF,[21,23,24,26] two studies used iPRP,[22,27] and the remaining used LPRF membrane and PRF plugs as intervention.[16,25,28] In the studies using i-PRP, the administration was done at 0, 3, and 6 weeks by El-Timamy *et al.*[27] and only once before retraction by Ali *et al.*,[22] Erdur *et al.*, and Karakasli *et al.* administered PRF twice immediately after extraction of premolar teeth and during the 2nd week of distalization.[21,23] Zeitounlouian *et al.* administered i-PRF twice, just before refraction and 4 weeks later.[26] Karci *et al.* administered i-PRF only once before canine distalization[24] and in the studies by Nemtoi *et al.,* Pacheo *et al.,* and Tehranchi *et al.* PRF plugs and LPRF membranes were placed in the extraction sockets immediately after extraction of premolars.[16,25,28] All included studies reported on the amount of canine distal movement except the study by Karakasli *et al.,* in which incisor distal movement was measured. Canine rotation was reported in

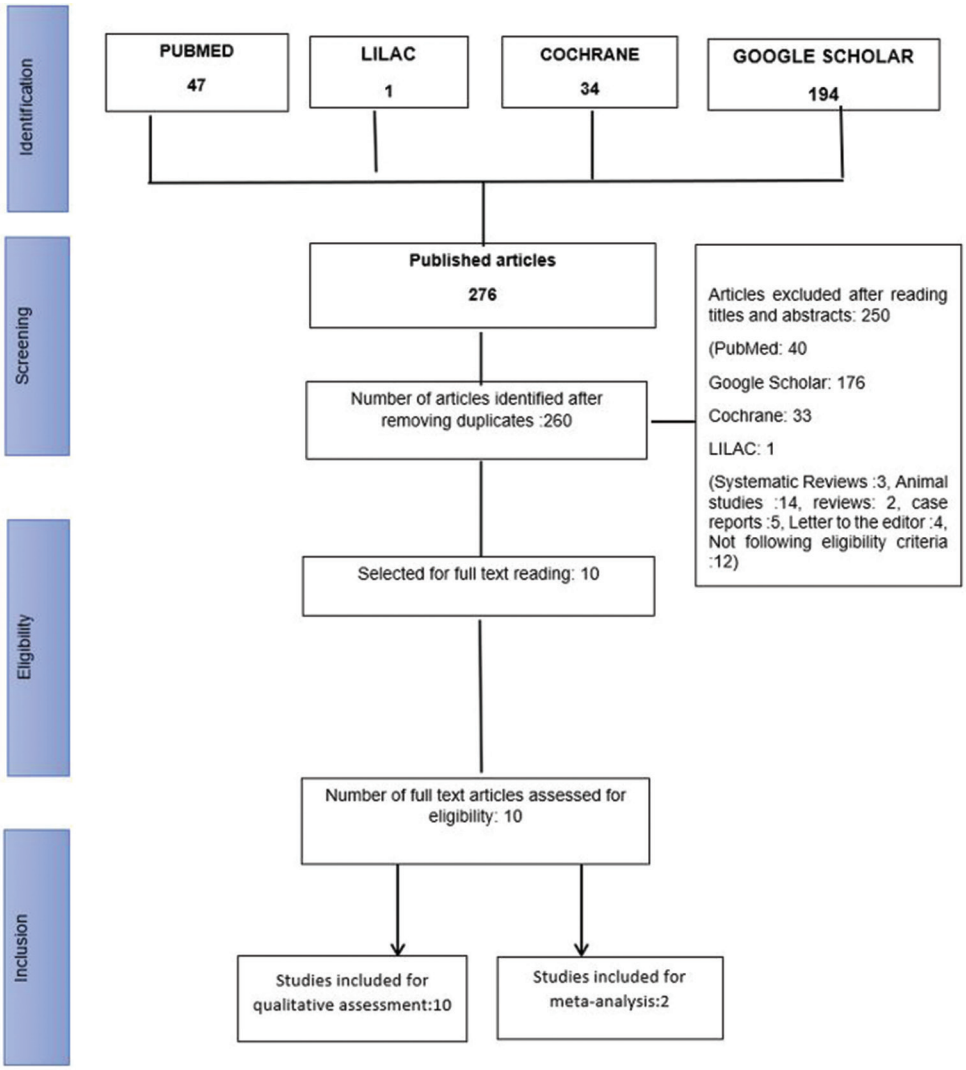

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for selection of the studies.

three studies,[23,26,27] molar mesialization in two studies,[24,26] and the study by El-Timamy *et al*. reported pain scores.

RoB assessment of included studies

The RoB in the included studies is summarized in [Figure 2]. On overall assessment, two studies presented with a high RoB[16,25] six had some concerns[21-24,26,28] and only one study had a low RoB.[27] For bias due to the randomization process four studies had some concerns,[21-23,26] one study reported high RoB as the method used for random sequence generation was not described,[16] and four studies had a low RoB.[24,25,27,28]

For bias due to deviations from the intended interventions six studies had a low RoB,[21-24,26,27] two studies had some concerns[16,28], and the study by Pacheo *et.al* had a high RoB as the dropout rate was significantly high and may affect the outcome assessed.[25]

Eight studies had a low risk for bias due to missing outcome data[16,21-24,26-28] and the study by Pacheo had some concerns.[25] For bias in the measurement of the outcome, four studies had low RoB[25-27] and five had some concerns.[16,21-24] For bias in the selection of the reported results, seven studies reported a low risk[21-27] and two studies reported some concerns.[16,28]

Results of individual studies

Results of the variables assessed in the individual studies are mentioned in [Table 2]. Out of the nine included studies six studies confirmed an overall acceleratory effect of platelet rich derivatives on the rate of tooth movement. Five out of the six studies reported significant acceleration of tooth movement with PRF[16,21,23,24,28] and one study reported the same with PRP.[22] The Trial by El-Timamy *et al*. reported that PRP accelerated tooth movement only at the end of

8 weeks and Zeitounlouian *et al*. reported PRF accelerated tooth movement at the end of 8 weeks only.[26,27] Pacheo *et al*. reported a decrease in the rate of tooth movement with LPRF.[25]

Synthesis of results

The studies included in the meta-analysis had either low RoB or some concerns, involved only injectable derivatives, and evaluated the outcome at specific time intervals. The outcome measure was the rate of canine distal movement reported in the included studies at the 4th, 8th, 12th, and 16th weeks. Quantitative evaluation was performed with an inverse-variance random-effects meta-analysis with standard mean difference keeping in mind the differences in the methodology, measurement methods, and heterogeneity of the data.

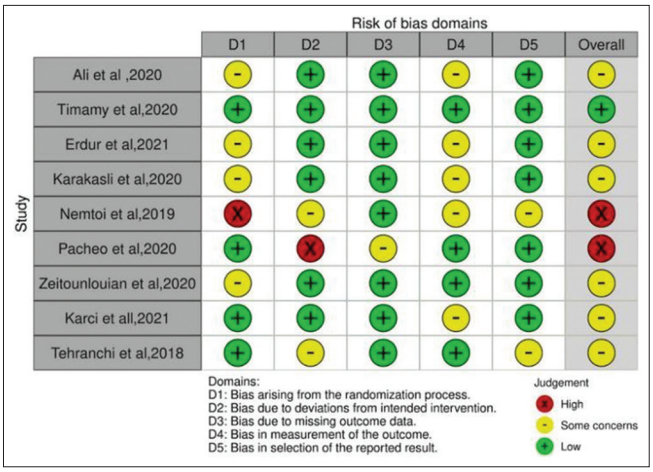

Figure 2: Risk of bias assessment of individual studies included in the systematic review using risk-of-bias-2 tool.

The results of the Meta-analysis at the 4th, 8th, and 12 weeks included the studies by Zeitounlouain *et al.* and El-Timamy *et al.*[23,26,27] At 4th week, there was no significant acceleration in the rate of canine distal movement with platelet-rich derivatives ($P > 0.0001$) and a moderate heterogeneity was reported (I^2 56%, $Tau^2 = 0.14$ $P < 0.00001$) [Figure 3]. The results of the subgroup meta-analysis in the 8th week showed no significant difference in the rate of canine distal movement between intervention and control ($P > 0.0001$) with a low heterogeneity ($I^2 = 12\%$, $Tau^2 = 0.01$) [Figure 3]. The results of the subgroup meta-analysis in the 12th week revealed no significant difference in the amount of canine distal movement between intervention and control. ($P > 0.0001$) and there was a substantial heterogeneity ($I^2 = 80\%$, $Tau^2 = 0.45$, $P > 0.00001$) [Figure 3]. The results of the subgroup meta-analysis at the 16th week showed that the rate of canine distal movement did not significantly increase with platelet-rich derivatives ($P > 0.0001$) and no heterogeneity was noted ($I^2 = 0\%$, $Tau^2 = 0.00$ $P < 0.00001$) [Figure 3].

The overall synthesis of results for the pooled effect at all-time intervals revealed no significant difference in the rate of canine distal movement between intervention and control ($P > 0.0001$) with a low heterogeneity ($I^2 = 36\%\%$, $Tau^2 = 0.06$, $P > 0.00001$).

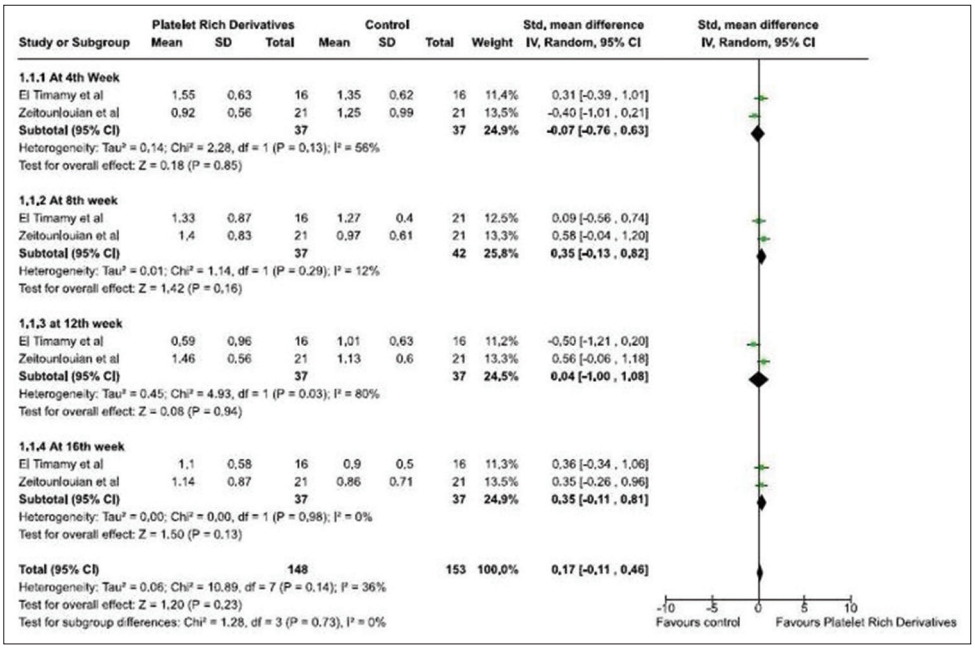

Figure 3: Forest plots for rate of tooth movement at 4th (a), 8th (b), 12th (c), and 16th (d) weeks of intervention of platelet-rich derivatives.

Table 2: Results of the included studies.

Author and year of study	Primary outcome assessed	Results		Inference
Karakasli *et al*., 2021	Amount of incisor tooth distal movement	Intergroup comparison Intragroup comparison between left and right sides at all-time intervals	*P*=0.05 *P*<0.05 *P*>0.05	I-PRF can be effective in the acceleration of tooth movement
Nemtoi *et al*., 2018	Amount of movement	Intervention group: Distance between adjacent teeth Immediately after extraction: 5 mm After retraction: 1.9 mm Control group: After extraction :4.8 mm After retraction :2.9 mm	*P*=0.05 *P*=0.006	PRF may accelerate orthodontic tooth movement
El-Timamy *et al*., 2020	Rate of Canine distal movement	Intervention: 4.53±1.12 Control: 4.53±1.12	*P*=0.05 *P*<0.05 at 8 weeks *P*>0.05 overall	PRP showed a positive potential to increase the rate of tooth movement when injected in the first 2 months. Repeated injections of PRP to maintain a steady rate of accelerated tooth movement need further research
Pacheo *et al*., 2020	Rate of Canine distal movement	Intervention: 0.668 mm Control: 0.909 mm	*P*=0.05 *P*<0.05	The use of L-PRF reduced the rate of distalization and changes in the inclinations of the maxillary canines in comparison to the control group
Erdur *et al*., 2021	Rate of canine tooth movement	Intervention: 6.06±0.20 Control: 3.89±0.34	*P*=0.01 *P*<0.001	iPRF was is safe and effective as a modality to accelerate tooth movement
Ali *et al*., 2021	Rate of canine retraction	Intergroup comparison	*P*=0.0001 *P*<0.0001	PRP accelerates tooth movement.
Zeitounlouian *et al*., 2021	Rate of canine retraction Molar mesialization	Intervention: 3.90±1.36 Control: 3.94±1.12 Intervention: 1.64±0.74 Control: 1.41±0.80	*P*=0.05 *P*<0.05 at 8 weeks *P*>0.05 overall	The rates of canine movement after the injection of platelet-rich fibrin were not greater on the experimental than on the control side except in the 2nd month No significant difference between intervention and control
Arci *et al*., 2021	Amount of canine distalization Amount of Molar mesialization	Intervention: 2.83±0.21 Control: 2.04±0.22 Intervention: 0.64±0.05 Control: 0.68±0.082	*P*=0.05 *P*<0.05 *P*>0.05	PRF accelerated tooth movement No significant difference between intervention and control
Tehranchi *et al*., 2018	Amount of tooth movement	Intergroup comparison.	*P*=0.006 *P*=0.006	Application of LPRF may aid in increasing orthodontic tooth movement
Angel *et al*., 2021	Rate of canine distalization	Intervention: 3.19±0.27 Control: 2.30±0.2	*P*=0.0001	During the 60 day observation period, it was found that submucosal injection of PRP significantly increased tooth movement

Canine rotation was reported in three studies,[23,26,27] molar mesialization in two studies[24,26] and the study by El-Timamy *et al*. reported pain scores. No significant differences between intervention and control for these secondary outcomes were reported.

Assessment of certainty of evidence

Regarding the effect of platelet-rich derivatives on the rate of orthodontic tooth movement, the quality of the available evidence was assessed by the Grading of Recommendations

Assessment, Development, and Evaluation (GRADE) approach using the GRADEpro guideline development tool.[29] The certainty of the evidence for the effect of platelet-rich derivatives on canine distal movement at the 4th, 8th, 12th, and 16th weeks was found to be "moderate" due to some concerns for the presence of heterogeneity and a wide variance effect in some of the studies - contributing to a risk of inconsistency within the studies [Figure 4].

DISCUSSION

In the recent past, non-surgical methods of increasing the rate of orthodontic tooth movement and reducing treatment time have gained popularity. Since surgical procedures could be invasive and come with the risk of causing injury to the hard and soft tissues the use of non-surgical methods is furthermore highlighted. Platelet-rich derivatives are of great interest to researchers and their role in accelerating orthodontic tooth movement is extensively being assessed both in animal and human studies. Both PRP and PRF are used extensively in dental practice and research but their use in orthodontics has been in accelerating tooth movement as they are rich in growth factors. They contain similar quantities of the growth factors but in PRF they are released more slowly. PRF is more effective in bone regeneration because of its longer duration of action than PRP.[30] The major disadvantage of these agents is the blood collection and the advantage is that they are non-invasive and economical.[13]

Summary of evidence

Most of the included studies in this review reported an acceleration of tooth movement with any of the platelet-rich derivatives used but the included studies had significant differences in the method of preparation, concentrations, delivery methods, frequency of administration, measurement methods, and time of evaluation. These differences also render it difficult to compare the clinical studies and pool them together for quantitative analysis.

Nevertheless, a random-effects meta-analysis was performed involving studies in which only injectable platelet-rich derivatives (iPRP and iPRF) were used and the rate of canine distal movement was reported at the end of 4, 8, 12, and 16 weeks. The standard mean difference was used to account for the different measurement methods used.

The results of the meta-analysis revealed no significant effect of platelet-rich derivatives on accelerating the rate of tooth movement at all-time intervals ($P > 0.0001$). The highest standardized mean difference between the intervention and control groups was 0.35 (–0.13, 4.47) at the 8th and 16th weeks and it was statistically not significant.

Certainty assessment							Summary of findings				
							Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Control	With Platelet Rich Derivatives		Risk with Control	Risk difference with Platelet Rich Derivatives
Rate of tooth movement - At 4th Week											
74 (2 RCTs)	not serious	serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	37	37	-	-	SMD **0.07 lower** (0.76 lower to 0.63 higher)
Rate of tooth movement - At 8th week											
74 (2 RCTs)	not serious	serious [a]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	42	37	-	-	SMD **0.35 higher** (0.13 lower to 0.82 higher)
Rate of tooth movement - at 12th week											
74 (2 RCTs)	not serious	serious [a]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	37	37	-	-	SMD **0.04 higher** (1 lower to 1.08 higher)
Rate of tooth movement - At 16th week											
74 (2 RCTs)	not serious	serious [a]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	37	37	-	-	SMD **0.35 higher** (0.11 lower to 0.81 higher)

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

Explanations

a. presence of inconsistency due to heterogeneity between studies

Figure 4: Level of evidence of the results obtained assessed using GRADEPro for the amount of tooth movement with the intervention of Plasma rich derivatives at 4th (a), 8th (b), 12th (c), and 16th (d) weeks.

The study by Karci *et al*. reported on iPRF as the intervention but was not involved in the meta-analysis as it reported on the canine distal movement at the end of 12 weeks only.[24] Similarly, the study by Erdur *et al*. also reported on iPRF but we decided not to include this study in the meta-analysis since certain methodological differences contributed to a very significant increase in the heterogeneity. Furthermore, the rate of canine distalization as reported by Erdur *et al*. was very high in comparison to the other trials included in this systematic review.[23] The results of this review are consistent with the findings of the recent review on animal studies done by Li *et al*.[6] in which the acceleratory effect of PRP on the rate of tooth movement in animal models could not be confirmed. No meta-analysis was, however, performed in that review due to high heterogeneity among the included studies.

The systematic review by Arqub *et al*. on the effect of biological substances on the rate of tooth movement concluded that the effect of PRP and its derivatives to increase the rate of tooth movement is inconsistent which is similar to the findings of our review.[31] They also highlighted the limitations of using PRP as it cannot be maintained in an active state for a long time. Since this review was on all biological agents for accelerating tooth movement, all relevant studies on platelet-rich derivatives were not specifically analyzed. This review included both split-mouth studies and only one parallel arm RCT, and only the split-mouth studies were included in the meta-analysis supported by a recent study done by Smail-Faugeron *et al*. who concluded that split-mouth studies can be considered for meta-analysis.[32] Secondary outcomes evaluated in the present review were canine rotation, molar mesialization, and pain scores. No significant difference between the intervention and control groups for canine rotation and molar mesialization was reported in the included studies.

Another systematic review performed in the past by Francisco *et al*. reported that PRF can improve alveolar cleft construction and orthodontic tooth movement; however, it included only two studies, neither of which used i-PRF as an intervention.[33]

El-Timamy *et al*. assessed pain using a visual analog scale-based questionnaire given to and responses were collected weekly once after giving PRP injection till the 7th week and reported no significant differences in pain scores between the intervention and control group.

Factors affecting the primary outcome

Acceleration of tooth movement is dependent on many factors and one of them is subject-related factors such as age, the jaw involved, and the type of malocclusion. All included studies mostly enrolled adult patients and the interventions were administered only in the maxillary jaw, except for the study by Tehranchi *et al*. where an intra-group comparison between upper and lower arches was done and revealed no significant difference between the two. In none of the included studies, age or malocclusion related differences in response to the administered platelet-rich derivative were reported.

As it has been pointed out previously, the type of the derivative and its concentration, method, and frequency of administration can affect the rate of tooth movement. A significant acceleration of tooth movement 2 months after starting canine retraction was noted by Zeitounlouain *et al*. and El-Timamy *et al*. in their studies, but no such effect was noted in the results of quantitative analysis. A cumulative effect of the sequential injections can be a reason for this transient acceleratory effect as stated by the authors as they had administered the injections at 0.3 and 6 weeks and 0.4 weeks, respectively.

Other effects of platelet-rich derivatives

Erdur *et al*. in their study reported on the levels of inflammatory markers following administration of iPRF for an acceleration of canine distal movement. They concluded that the mean values of IL-1b, MMP-8, and RANKL were high significantly in the iPRF group and there was a positive correlation between the levels of these cytokines and the acceleration of orthodontic tooth movement. None of the included studies measured root resorption, and bone density changes following administration of platelet-rich derivatives.

Limitations

An overall moderate certainty of the evidence is one limitation of this review and this can be attributed to confounding factors. Furthermore, the majority of studies included reported some concerns in the RoB assessment limiting the validity of their results. Another major limitation of this review is that only a few studies were included in the meta-analysis as most of them had methodological heterogeneity making it difficult for us to pool them together. The studies included also had a less overall sample size which is another major limitation of this review. Further well-designed studies with strict protocols are needed to strongly recommend the use of platelet-rich derivatives in clinical practice.

CONCLUSION

- The evidence available suggests a moderate certainty (Grade pro approach) about the non-acceleratory effect of platelet-rich derivatives on tooth movement
- The results of the individual studies should be interpreted carefully as they were inherent with a moderate to high RoB and a high heterogeneity even though they reported an acceleratory effect with platelet-rich derivatives.

Quantitative analysis failed to report any significant acceleration in the rate of canine distal movement with iPRP or iPRF and did not have any effect on the rotation of canine teeth or mesial movement of molars.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

Author Nikhilesh R. Vaid is the Emeritus Editor-In-Chief of the journal.

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SUPPLEMENTARY TABLE

Supplementary Table 1: Inclusion and exclusion criteria for the present systematic review.

Domain	Inclusion criteria	Exclusion criteria
Participants	Healthy human subjects undergoing active orthodontic treatment with fixed appliances -MBT or Roth prescription	• Animal subjects undergoing orthodontic treatment • Human subjects after cessation of orthodontic treatment • Unhealthy subjects or subjects with systemic illness
Intervention	Local administration of platelet-rich derivatives – Platelet-rich plasma, platelet-rich fibrin, leukocyte platelet-rich fibrin	• Studies using interventions like corticotomies, micro-oesteoperforations, piezocisions, the use of low-level energy lasers, and vibrations • Studies using systemic administration of biological agents like Vitamin D • Studies using platelet-rich derivatives for outcomes other than to assess orthodontic tooth movement (wound healing, periodontal procedures, cleft lip, and palate) • Studies using local administrations platelet-rich derivatives to assess outcomes other than the rate of tooth movements like root resorption and density of alveolar bone
Comparison	Placebo intervention or no intervention	
Outcomes	PRIMARY OUTCOME: rate of orthodontic tooth movement	• Qualitative assessments regarding the rate of orthodontic tooth movement • Assessments regarding outcomes other than the rate of tooth movement • Inadequate definition of outcomes
Study design	Randomized clinical control trials	• Studies without placebo or control group • *In vitro* or *ex vivo* studies • *In silico* studies • Case reports • Structured reviews • Systematic reviews and meta-analysis • Case series • Animal trials • Opinion articles • Letters from editor