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Efficacy of various Platelet concentrates on the rate of Orthodontic tooth movement – A Systematic Review and Meta-Analysis.

Pavithranand Ammayappan*[1], Prabhu Manickam Natarajan[2], And Vijayadhith C[3]

[1]*Professor and Head, Department of Orthodontics and Dentofacial Orthopedics, Indira Gandhi Institute of Dental Sciences, Sri Balaji Vidyapeeth (Deemed-to-be) University, Pondicherry, India.*
[2]*Assistant Professor in Periodontics, College of Dentistry, Ajman University, Ajman, United Arab Emirates.*
[3]*Professor and Head, Department of Orthodontics, Priyadarshini Dental College & Hospital, Tiruvalur, Chennai, India*

Abstract: With increased interest in reducing the average duration of Orthodontic treatment, various techniques for accelerating tooth movement have been extensively researched. Studies have shown conflicting results with various Platelet Concentrates (PCs). Hence this review aimed to evaluate and gather evidence of the effectiveness of Platelet concentrates (PRP/PRF) during orthodontic extraction space closure about the space closure rate and the time required for and the angular measurements of the tooth movement during space closure. The electronic databases of Cochrane CENTRAL, PubMed, Scopus, Web of Science, Embase, and Google Scholar were searched up to June 2021. The criteria for selection were Randomised Controlled Trials (RCTs) comparing the use of PCs with that of no intervention/placebo during canine retraction or retraction of anterior teeth. All other studies were excluded. Two reviewers performed the entire process of study selection, extraction of data, and quality assessment independently. Cochrane's ROB2 tool was used for quality assessment in the studies selected. The quantitative analysis of the studies was performed with the use of Review Manager (RevMan5). Eight RCTs met the inclusion criteria and were included for the qualitative synthesis in this review. Of these, five RCTs were included in the quantitative analysis. The results indicated an insignificant increase in the rate of tooth movement with the administration of the PCs (0.13 mm more Tooth movement; 95% CI = -0.17 – 0.43; p = 0.40). No differences were also found in the change of canine inclination and amount of canine rotation. Quantitative synthesis of the selected five studies (3 studies had a low Risk of Bias) reveals no statistically significant difference in the rate of tooth movement with the use of PCs. The results of this analysis should be interpreted with caution owing to the existence of heterogeneity. Limited evidence suggests an actual reduction in the overall treatment duration. Future studies should be aimed at standardizing the protocol for preparing and administering the PCs. This review did not receive any funding.Trial registration number: PROSPERO CRD42021241221

Keywords: Accelerated Orthodontics, Platelet concentrates, PRP, PRF, space closure, Canine retraction, Distallisation of Canines, Systematic Review, Meta-analysis.

***Corresponding Author**

Pavithranand Ammayappan , Professor and Head, Department of Orthodontics and Dentofacial Orthopedics, Indira Gandhi Institute of Dental Sciences, Sri Balaji Vidyapeeth (Deemed-to-be) University, Pondicherry, India.

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1. INTRODUCTION

Globally, there has been a steady increase in adults seeking Orthodontic treatment. It could be attributed to the factor that many of them might not have had the opportunity to have or were denied treatment during their childhood; additionally, many might not have been satisfied or might have had a relapse of their previous orthodontic treatment[1] Although no statistically significant difference in the treatment duration between adults and adolescents[2] exists, it is still one of the chief concerns of adults for commencing treatment, even though the duration of the treatment is related to both professional expertise and patient compliance. As there is evidence that longer treatment duration is associated with increased dissatisfaction[3] and greater susceptibility to iatrogenic complications[4], it would be beneficial to reduce the treatment duration. To address those concerns, many techniques have been developed, may it be ways of reducing friction using biological or surgical approaches, device-assisted treatment, pharmacological agents[5–7], or a combination of the above. Of late, there has been an increased interest in using various forms of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) for their role in reducing the overall duration of orthodontic treatment. That is because these platelet-based concentrations (PCs) are a good source of growth factors that help accelerate the healing and regeneration of the tissues involved[8,9]. Therefore, they were used extensively in various disciplines of medicine and surgery[10] before their introduction to dentistry. However, varying results have been demonstrated with the use of these Platelet concentrates, in both animal studies and human trials, ranging from an increased rate of tooth movement[11–15] to no difference[16]with its use and even a decrease[17,18] in the actual rate of tooth movement. Hence there is an absence of consensus and clear evidence. Therefore, while platelet concentrates are seen as potentially advantageous agents in various other medical disciplines, and realizing that their proper use can shorten the orthodontic treatment time, it is essential to examine the evidence systematically. Therefore, this systematic review was performed to evaluate and gather evidence of the effectiveness of Platelet concentrates (PRP/PRF) during orthodontic extraction space closure about the space closure rate and the time required for and the angular measurements of the tooth movement during space closure.

2. METHODS

2.1 Protocol and registration

The current Systematic Review and Meta-analyses were registered in the PROPERO database [CRD42021241221] and were done following the guidelines of the Cochrane Handbook for Systematic Reviews of Intervention[19] and are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines[20]. This research did not receive any specific funding.

2.2 Eligibility criteria

2.2.1 Study design

Only Randomized controlled trials (RCTs) were included in the present systematic review.

2.2.2 Participants

Patients undergoing Orthodontic treatment with pre-adjusted edgewise appliance with extractions of first bicuspids as part of their treatment in either the Maxillary arch or in both arches. The treatment plan also involved the use of Periodontally Accelerated Osteogenic Orthodontics (PAOO) for the retraction of canines or en-masse retraction of the anterior teeth.

2.2.3 Intervention

Use various Platelet concentrates forms (PRP, PRF, etc.)

2.2.4 Comparison

Placebo or no intervention

2.2.5 Primary outcome

Measure the rate of space closure.

2.2.6 Secondary outcome

Assess the treatment duration required for the closure of the extraction space and the change in angular measurements of the tooth movement.

2.2.7 Exclusion criteria

Nonrandomized prospective clinical trials, retrospective studies, case reports, review articles, and animal studies.

2.3 Sources, search strategy, and study selection

Two reviewers (PA and PM) independently searched the electronic database (PubMed, Scopus, Web of Science, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar) from March to June 2021. There were no restrictions in the year of study publication or study designs. Hand-screening the reference lists of relevant journals and the included studies was also carried out. Two reviewers (PM and VC) also performed the Risk of bias. Attempts were made to contact the corresponding authors by mail in case of any missing information. The resolution of disagreements (if present) between the two reviewers was addressed by a third reviewer (PA).

2.4 Data extraction

Data extraction from the included studies was undertaken from a predetermined template. It included the study details (article name, first author, year of publication), study design, sample size, age and gender, anchorage preparation, space closure mechanics and the arch involved, type of Intervention used, frequency of Intervention, type of fixed appliance, type of archwire used for space closure/retraction, force delivery mechanism, and magnitude, the timing of extraction, the outcome of treatment (primary and secondary outcomes, assessment time points, rate

of canine retraction, time taken for space closure, angular measurements of retracted tooth/teeth, statistical significance of the reported data). These were collected by two reviewers independently (PA and PM).

2.5 Risk of bias assessment

Two reviewers (PM and AV) independently assessed the included studies' quality. The revised Cochrane risk-of-bias tool for randomized trials (RoB2) was used to assess the bias in the findings of the RCTs. This revised tool is structured into five domains to assess the bias which may be introduced into the result. The five domains are:

1. Bias arising from the randomization process;
2. Bias due to deviation from intended interventions;
3. Bias due to missing data;
4. Bias in measurement of the outcome;
5. Bias in the selection of the reported result.

The studies were assessed to be of low, high Risk of bias or some concerns based on the Risk of bias judgments of individual domains through algorithms that map the responses to the signaling questions for each domain. In addition, the study was given an overall high-risk score if (i) one of the domains was judged to be at high risk of bias or (ii) if multiple domains had some concerns.

2.6 Quality of the evidence

The Grading of Recommendations, Assessment, Development, and Evaluation [GRADE] approach was used to evaluate the quality of evidence. This approach weighs up the body of evidence on the extent to which one can be confident that an estimate of the effect (or association) is correct. The summary of the quality of evidence was generated by using the GRADEpro platform (https://gdt.gradepro.org/app/#organizations). The assessment of the quality of evidence is generated by taking into consideration various factors like the Individual study limitations (Risk of Bias), the inconsistency of the result (heterogeneity of the study), the indirectness of the evidence, imprecision, and the presence of publication bias in the studies selected for the systematic review. The quality of the evidence is then rated down one or two levels based on the presence of the factors mentioned above.

2.7 Summary measures and synthesis of the results

The results of the studies were combined using the reported means, sample size, and standard deviations into a standardized mean with a 95% calculated Confidence Interval (CI) in anticipation of possible differences in the time points when measurements were made. If sufficient homogeneity existed among the selected studies, they were synthesized using the Review Manager (RevMan) ([Computer program] Version 5.4. The Cochrane Collaboration, 2020) for quantitative analysis and forest plots generated. A qualitative synthesis was performed in case it was not feasible to combine the studies. A random-effects model accounted for the possible heterogeneity in the studies and patient characteristics. The heterogeneity of the studies was analyzed statistically by the chi-square-based Q statistic method and the I^2 test, wherein a score of less than 30% and a score of more than 50% corresponded to low and high heterogeneity, respectively.

2.8 Additional analyses

Sensitivity analysis was performed to detect the impact of studies with a high risk of bias on the overall results.

3. RESULTS

3.1 Study selection and characteristics

A total of 1148 articles were retrieved from the various search engines (Fig.1), of which 847 studies were screened after eliminating the duplicates. Based on the relevance to the protocol of the current review, 828 articles were excluded. Full-text articles from 19 studies were further assessed, and 11 were excluded. Eight studies[12–17,21,22] met the inclusion and exclusion criteria and were included in this qualitative analysis. The studies were further grouped based on the intervention agent and control group. Seven of the included studies were of split-mouth design involving retraction of canines. One was a parallel-group RCT[21] in which the rate of retraction of the maxillary incisors was evaluated. Of the eight included studies, only Tehranchi et al.[13] evaluated the canine retraction in both maxillary and mandibular arches. In contrast, the other studies evaluated the retraction rate of the maxillary canines. The frequency of administration of PCs varied from a single intervention in three studies[12,13,17], thrice in two studies[14,16,21], and twice in three studies[15,22]; the timing of the second and third administration of the PCs was also not constant. The period of the studies, too, varied across the studies, the minimum being 4 weeks by Karakasli et al. [21] followed by three months(14,15), four months(13,22), five months[16,17] and by Nemtoi et al. [12] up to 6 months. (Table.1) The canine retraction was carried out on 0.016" x 0.022" SS in three studies(12,13,15), 0.017" x 0.025" SS in two(14,22), 0.019" x 0.025" SS by Zeitounlouian et al. (16) and on 0.020" SS by Reyes Pacheco et al. [17]. The force delivery system used were NiTi closed coil springs in seven studies of which five[14–16,21] of the studies used a constant force of 150 gm per side. In contrast, in the other two studies[12,13], no information was provided on the force used for retraction. In the study by Reyes Pacheco et al. [17], they used an e-chain for retraction with a force of 150 gms. TADs / Miniscrews were the sources of anchorage in four studies[14,15,21,22], TPA in the study by Zeitounlouian et al. [16], and the three studies revealed no information on their anchorage preparation. The measurement of canine retraction was performed with the use of digital calipers on dental models in three studies[13,14,21]and with a ruler by Nemtoi et al. [12] wherein they measured the amount of extraction space closure, one study[17] measured the canine retraction using a flexible ruler from the midline of the arch running labially to the mesial of the canine, Zeitounlouian et al. [16] performed measurements using a cephalometric software application, while El-Timamy et al. [22] performed the measurements on the scanned models using a software application and finally, Karci et al.[15] superimposed the digital models to assess the canine movement.

3.2 Risk of bias within included studies

The present systematic review included 8 RCTs for the qualitative analysis. Three RCTs were found to have a low risk of bias[14,16,22] and four were assessed to have some concerns[13,15,17,21] due to the lack of blinding of the assessors. On the other hand, one RCT was found to have a high risk of bias[12], as there was no information regarding randomization and blinding of the study, including that of the assessor. Figures 2 & 3 represent the summary of the qualitative analysis as the traffic light plot and the summary plot, respectively. As blinding the operator and participants was not feasible, this was not considered in assessing the Risk of Bias arising from the randomization process.

3.3 Results of individual studies, meta-analysis, and additional analysis

Based on the Intervention used, the studies were subdivided into four groups. The results were summarized (Table. 2). Since each study evaluated the rate of canine retraction at different time points, we combined the values of the different time points to standardize the rate of tooth movement per month. We entered the obtained mean value into the meta-analysis using a statistical website (https://www.statstodo.com/CombineMeansSDs.php).
The method that was used to combine the means and standard deviations of 2 groups was according to the algorithm described by the Cochrane handbook[19], and as follows:

$$\textbf{Combined mean} = \frac{(n_1 m_1 + n_2 m_2)}{n_1 + n_2}$$

$$\textbf{Combined SD} = \sqrt{\frac{(n_1-1)SD_1{}^2 + (n_2-1)SD_2{}^2 + \frac{n_1 n_2}{n_1+n_2}(m_1^2 + m_2^2 - 2m_1 m_2)}{n_1 + n_2 - 1}}$$

Where:

n_1 = number of samples of 1st time point
n_2 = number of samples of 2nd time point
m_1 = mean value of 1st time point
m_2 = mean value of 2nd time point
SD_1 = standard deviation of 1st time point and
SD_2 = standard deviation of 2nd time point

When more than two values were to be combined, the first two values were combined; first, the results were combined with the third value, then sequentially combined with each of the following values of each time point. As the standard deviations were not retrievable from the study by Nemtoi et al. (12), the combined means were calculated and not included in the meta-analysis.

3.4 Group 1a – i-PRF versus No Intervention

Three studies evaluated the use of i-PRF (injectable-platelet-rich fibrin), of which two[15,16]had evaluated the rate of canine distallisation and one(21) on Incisor retraction. Among the studies which evaluated the rate of canine retraction, Zeitounlouian et al.[16] found no statistically significant difference among the experimental and control groups over five months (mean rate: 1.12 ± 0.74 mm/month and 1.09 ± 0.7 mm/month, respectively) except during the second month where the canine retraction was found to be significantly higher in the experimental group, while Karci et al.[15]showed an increased rate of canine retraction ($p < 0.05$) in the experimental group than on the control side (mean rate: 0.943 ± 0.07 mm/month and 0.68 ± 0.07 mm/month respectively). Karakasli et al. [21], on evaluation of the rate of retraction of the maxillary incisors, found a significantly higher ($p < 0.05$) rate of tooth movement in the experimental group than in the control. As this study[21] evaluated the maxillary incisors' retraction rate, they were not included in the meta-analysis.

3.5 Group 1b – i-PRF versus Placebo

One study[14] compared the effectiveness of i-PRF against a placebo and found a statistically significant increase in the rate of canine retraction with the use of i-PRF than on the control side (1.52 ± 0.49 mm/month and 0.97 ± 0.38 mm/month respectively). The results of the meta-analysis comparing the rate of canine retraction with the use of i-PRF (n = 53) showed a statistically significant difference in the tooth movement when compared with the control group (n = 53; weighted mean difference [WMD] = 0.03; 95% CI = 0.09 – 0.53; p = 0.006; Fig. 4).

3.6 Group 2 – L-PRF versus No Intervention

Pacheco et al. (17) showed a statistically significant decrease in the rate of canine retraction with the use of L-PRF (Leukocyte-platelet-rich fibrin) compared to the control side. The standard deviation of the results was calculated from the provided Confidence Interval using the formula described in the Cochrane Handbook(19);

$$\textbf{SD} = \frac{\sqrt{n} * (CI_{upp\ limit} - CI_{low\ limit})}{3.92}$$

Where;

n = Sample size
$CI_{upp\ limit}$ = upper limit of the provided Confidence Interval
$CI_{low\ limit}$ = lower limit of the provided Confidence Interval
3.92 = the value used when the CI of the study is set at 95%

In contrast, Tehranchi et al. (13) 's study evaluated the space closure rate and showed a significantly higher rate (p = 0.006) on the experimental side. However, since they did not evaluate the rate of canine distilization separately, it was not included in the meta-analysis.

3.7 Group 3 – PRF plug versus No Intervention

Nemtoi et al. (12) also assessed the rate of space closure as a whole. They reported a significantly higher rate (p=0.006) with the experimental group compared to the control group when evaluating the use of PRF plugs placed into the extraction sockets; this study was also not included in the meta-analysis as they did not evaluate the rate of canine retraction separately.

3.8 *Group 4 – PRP versus Placebo*

One RCT(22) was identified where they had used PRP for accelerating the tooth movement and showed a significantly higher rate of tooth movement on the experimental side for the first two months (p = 0.049), after which the rate was significantly lesser on the intervention side (p = 0.02) after the cessation of PRP injections. When analyzing the meta-analysis (Fig. 4) of all the Platelet concentrates put together, the results showed no significant difference in the rate of tooth movement (WMD = 0.13; 95% CI = -0.17 – 0.43; p = 0.40) with the use of Platelet concentrates (PRF/PRP), again possibly due to the presence of high heterogeneity (I^2 = 94%).

3.9 Secondary outcomes

3.9.1 Canine inclination

Two studies evaluated the difference in the change of the inclination of the canines after retraction. While Reyes Pacheco et al. [17] found a statistically significant difference in the amount of change in inclination of the canine between the control and experimental groups (8.57° ± 3.07° and 5.81° ± 3.09° respectively, p = 0.001), and they also added that there was a low correlation between the rate of movement and the change in inclination of the canines for the control and experimental groups, Karci et al.[15] found no significant difference in the inclination of the canines between the experimental and control groups. The meta-analysis (Fig. 5) revealed no significant difference in the amount of canine inclination following retraction of the canines between the use of PRF and control (n = 29; weighted mean difference [WMD] = -0.99; 95% CI = -4.20 – 2.22; p = 0.55)

3.9.2 Canine rotation

Karci et al. (15), Zeitounlouian et al. (16), and El-Timamy et al. (22) evaluated the extent of canine rotation following retraction between the experimental and control groups and found no statistically significant difference among the two groups (p = 0.175, 0.655 and 0.710 respectively)

3.9.3 Treatment duration

Only one study was identified, Zeitounlouian et al. [16]assessed the overall duration of canine retraction. They found it statistically insignificant between the experimental and control groups (3.28 ± 1.00 months and 3.57 ± 1.16 months, respectively).

3.9.3 Sensitivity Analysis

The impact of individual studies on the overall results was assessed, and RCTs with a high risk of bias were not included in the meta-analysis. The increase in the confidence of the results was observed with the removal of these studies (Fig. 6); the heterogeneity was assessed using I^2, chi-squared and Tau-squared tests.

3.9.4 Quality of the evidence

The assessment of the present meta-analysis using the GRADE system revealed a low quality of evidence for the primary outcome (rate of canine distalization), which is represented in Table. 3. As far as the secondary outcomes considered, the quality of evidence was moderate for the change in canine inclination, and canine rotation and evidence were high (only one study evaluated this outcome) for reducing the treatment duration with the use of Platelet concentrates. All of the above secondary outcomes were statistically non-significant.

Table 1. Study characteristics (Study design, retraction mechanics, type and frequency of PC administered, outcome measures)

Study	Study design	Sample Size	Age (yrs)/ Gender	Mechanotherapy	Anchorage preparation	Force delivery	Type of tooth movement, Arch included	Type of Intervention	Frequency of Intervention	Assessment Time points	Primary Outcome	Secondary Outcome
Nemtoi 2018	Split mouth Clinical Trial	n=20	12 – 29 Boys, 11 Girls	MBT prescription, 0.022" slot. Retraction on 0.016 x 0.022" SS Archwire	Not mentioned	NiTi closed coil spring Force level not mentioned	Canine retraction Maxillary arch	PRF in extraction socket vs. no intervention	Once, at the time of extraction	Once every four weeks for six months	Bone regeneration	Rate of Orthodontic tooth movement
Tehranchi 2018	Split mouth RCT	n=15	12 – 25 Five males Three females	Roth prescription, 0.022" slot. Retraction on 0.016 x 0.022" SS Archwire	Not mentioned	NiTi closed coil spring Force level not mentioned	Canine retraction. Extraction after leveling and aligning Both arches	L-PRF in extraction socket vs. no intervention (?)	Once, at the time of extraction	Once in 2 weeks for four months	Amount of Orthodontic tooth movement	-
Reyes Pacheco 2020	Split mouth RCT	n=17	20 – 45 Five males 12 females	MBT prescription, 0.022" slot. Retraction on 0.020" SS Archwire	Not mentioned	Elastic chain 150 g	Canine retraction. Extraction after leveling and aligning Maxillary arch	L-PRF membrane in extraction socket vs. no intervention	Once, at the time of extraction	Once a month for five months	Distalization rate	Canine inclination
Erdur 2021	Split mouth RCT	n=20	21.4 ±2.98 men 12 women	MBT prescription, 0.022" slot. Retraction on 0.017 x 0.025" SS Archwire	Miniscrew	NiTi closed coil spring 150 g	Canine retraction. Extraction after leveling and aligning Maxillary arch	i-PRF 4 ml vs placebo	Once after extraction 2nd Intervention after two weeks of retraction	T0, T1 - 1st week T2 - 4th week T3 - 8th week T4 - 12th week	Distalization rate	Inflammatory cytokines
El-Timamy 2020	Split mouth RCT	n=15	15 women	Roth prescription, 0.022" slot.	Miniscrew Indirect anchorage	NiTi closed coil spring 1.5 N	Canine retraction	PRP injections with 10% $CaCl_2$ vs	injected on 0th, 21st, 42nd day	Once a month for four months	Rate of canine retraction	Pain

				Retraction on 0.017 x 0.025" SS Archwire			Not mentioned Maxillary arch	placebo ($CaCl_2$)			Canine rotation	
Zeitounlouian 2021	Split mouth RCT	n=21	16 – 28 6 Men 15 women	MBT prescription, 0.022" slot. Retraction on 0.019 x 0.025" SS Archwire	TPA	NiTi closed coil spring 150 g	Canine retraction. Extraction after leveling and aligning Maxillary arch	i-PRF vs no intervention	Once at the time of extraction 2nd Intervention after one month	Once a month for five months	Rate of canine retraction	Rate of molar anchorage loss, Canine rotation
Karci 2021	Split mouth Parallel group RCT	n=12	14 – 22 7 Girls 5 Boys	MBT prescription, 0.022" slot. Retraction on 0.016 x 0.022" SS Archwire	Miniscrew	NiTi closed coil spring (9 mm) 150 g	Canine retraction followed by Levelling and aligning Maxillary arch	i-PRF vs no intervention Peizocision vs no intervention	Once at the time of extraction, after 2 weeks, and after 4 weeks.	Once every 2 weeks for 3 months	Rate of canine distalization	Cephalometric parameters, Canine rotation, molar mesial movement. Periodontal parameters
Karaksali 2021	Parallel group RCT	n=40	Study group – 21 ± 1.35 12 women, 8 men Control group – 20.4 ± 1.56 11 women, nine men	0.022" slot. Retraction on 0.019 x 0.025" SS Archwire	TAD	NiTi closed coil spring 150 g	Incisor retraction Maxillary arch	i-PRF vs no intervention	Once at the time of retraction of Incisors 2nd Intervention after two weeks of retraction	Once a week for four weeks	Rate of Incisor retraction	Angulation change of Incisors

Table 2. Results of selected RCTs (space closure)

Study (Author / Year)	Timing of extraction	Reported measurement of space closure	Calculated Rate of Canine retraction/space closure (mm / month) ± SD	Result of study p-value
Nemtoi 2018	Unclear	**PRF** – before the start of space closure – 5 mm After six months of retraction – 1.9 mm **Control** – before the start of space closure – 4.8 mm After six months of retraction – 2.9 mm	**PRF** - 0.52 **Control** – 0.32	The experimental group with PRF showed a higher rate of Orthodontic tooth movement than the control group p = 0.006
Tehranchi 2018	After leveling phase	**Not retrievable**	Not retrievable	The experimental group with PRF showed a higher rate of Orthodontic tooth movement than the control group p = 0.006
Reyes Pacheco 2020	After leveling phase	**L-PRF** – mean value – 0.668 mm Min value – 0.40 mm Max value – 0.88 mm **Control** – mean value – 0.909 mm Min value – 0.44 mm Max value – 1.16 mm	**L-PRF** – 0.668 ± 0.11 **Control** – 0.909 ± 0.21	The experimental group with PRF showed a lower rate of Orthodontic tooth movement than the control group p = 0.004
Erdur 2021	After levelling phase	**i-PRF** T_0-T_1 – 0.73±0.11 (T_0 – before extraction, T_1 – first week) T_1-T_2 – 1.56±0.08 (T_2 – at fourth week) T_2-T_3 – 1.90±0.1 (T_3 – at eighth week) T_3-T_4 – 1.88±0.11 (T_4 – at 12th week) T_0-T_4 – 6.06±0.29 **Control** T_0-T_1 – 0.35±0.08 (T_0 – before extraction, T_1 – first week) T_1-T_2 – 1.08±0.1 (T_2 – at fourth week) T_2-T_3 – 1.23±0.12 (T_3 – at eighth week) T_3-T_4 – 1.23±0.13 (T_4 – at 12th week) T_0-T_4 – 3.89±0.34	**i-PRF** – 1.5175 ± 0.4874 **Control** – 0.9725 ± 0.3822	The experimental group with PRF showed a higher rate of Orthodontic tooth movement than the control group p < 0.001
El-Timamy 2020	Not mentioned	**PRP** T_0-T_1 – 1.55±0.63 (First month) T_1-T_2 – 1.33±0.87 (Second month) T_2-T_3 – 0.59±0.96 (Third month) T_3-T_4 – 1.10±0.58 (Fourth month) **Control** T_0-T_1 – 1.35±0.62 (First month)	**PRP** – 1.1425 ± 0.8376 **Control** – 1.1325 ± 0.5631	Rate of canine retraction more with PRP during the first month while it was lesser than the control during the third month. P < 0.05 While there was no statistical difference during the other two months of evaluation

		T_1-T_2 – 1.27±0.40 (Second month) T_2-T_3 – 1.01±0.63 (Third month) T_3-T_4 – 0.90±0.50 (Fourth month)		
Zeitounlouian 2021	After levelling phase	**i-PRF** T_0-T_1 – 0.92±0.56 (First month) T_1-T_2 – 1.40±0.83 (Second month) T_2-T_3 – 1.46±0.56 (Third month) T_3-T_4 – 1.14±0.87 (Fourth month) T_4-T_5 – 0.68±0.55 (Fifth month) **Control** T_0-T_1 – 1.25±0.99 (First month) T_1-T_2 – 0.97±0.61 (Second month) T_2-T_3 – 1.13±0.60 (Third month) T_3-T_4 – 0.86±0.71 (Fourth month) T_4-T_5 – 1.23±0.31 (Fifth month)	**i-PRF** – 1.12 ± 0.7371 **Control** – 1.088 ± 0.6927	No statistical difference between the groups. p=0.918
Karci 2021	On the day of bonding	**i-PRF** mean value – 2.83 mm standard deviation – 0.21 Min value – 1.79 mm Max value – 4.24 mm **Control** means value – 2.04 mm standard deviation – 0.22 Min value – 1.08 mm Max value – 3.99 mm	**i-PRF** ~ 0.943 ± 0.07 **Control** ~ 0.68 ± 0.073	The experimental group with PRF showed a higher rate of Orthodontic tooth movement than the control group p = 0.011
Karaksali 2021	After leveling phase Incisor retraction was initiated after canine retraction.	*Right side* *Left side* **i-PRF** T_1-T_0 – 0.14 ± 0.03 0.14 ± 0.04 (First week) T_2-T_1 – 0.11 ± 0.03 0.11 ± 0.04 (Second week) T_3-T_2 – 0.14 ± 0.03 0.13 ± 0.04 (Third week) T_4-T_3 – 0.11 ± 0.03 0.10 ± 0.03 (Fourth week) **Control** T_1-T_0 – 0.08 ± 0.02 0.08 ± 0.03 (First week) T_2-T_1 – 0.07 ± 0.02 0.07 ± 0.02 (Second week) T_3-T_2 – 0.07 ± 0.02 0.06 ± 0.01 (Third week) T_4-T_3 – 0.08 ± 0.02 0.07 ± 0.02 (Fourth week)	**i-PRF** – 0.5 ± 0.11 (right side) / per week 0.48 ± 0.12 (left side) / per week **Control** – 0.3 ± 0.06 (right side) / per week 0.28 ± 0.17 (left side) / per week	The experimental group with PRF showed a higher rate of Orthodontic tooth movement than the control group p < 0.001

Table 3. GRADE Summary of Findings: Do PCs, when compared to no intervention/placebo increase the rate of orthodontic tooth movement, influence the inclination and rotation of the canines and decrease the treatment duration.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platelet concentrates**	**no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Rate of Canine distalization												
7	randomized trials	serious [a]	serious [b]	not serious	not serious	none	101	101	-	SMD **0.01 SD higher** (0.35 lower to 0.09 higher)	⊕⊕◯◯ Low	
Change in inclination of Canine												
2	randomized trials	serious	not serious	not serious	not serious	none		-			⊕⊕⊕◯ Moderate	
Amount of Canine Rotation												
2	randomized trials	serious	not serious	not serious	not serious	none		-			⊕⊕⊕◯ Moderate	
Treatment time reduction												
1	randomized trials	not serious	not serious	not serious	not serious	none		-			⊕⊕⊕⊕ High	

CI: confidence interval; SMD: standardized mean difference

3.9.5 Explanations

a. one of the included studies had a high risk of bias owing to a need for more information regarding the randomization process and the blinding done.
b. presence of heterogeneity
c. the studies had an unclear risk of bias, as there was no information regarding the blinding of the assessor.

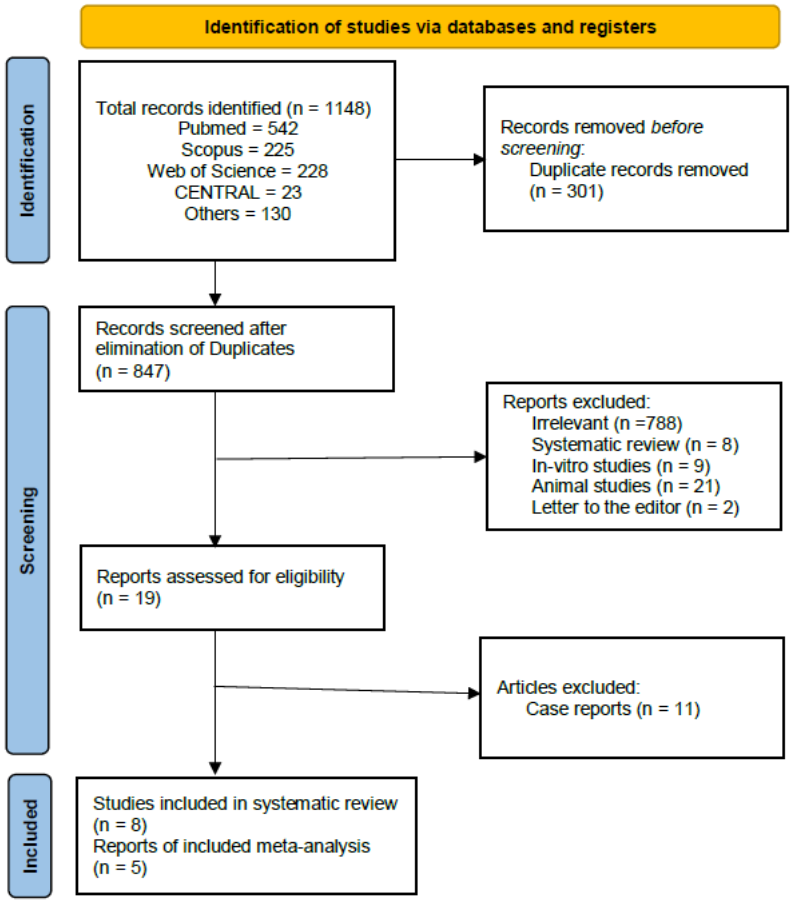

Fig. 1 PRISMA flow chart depicting the literature search

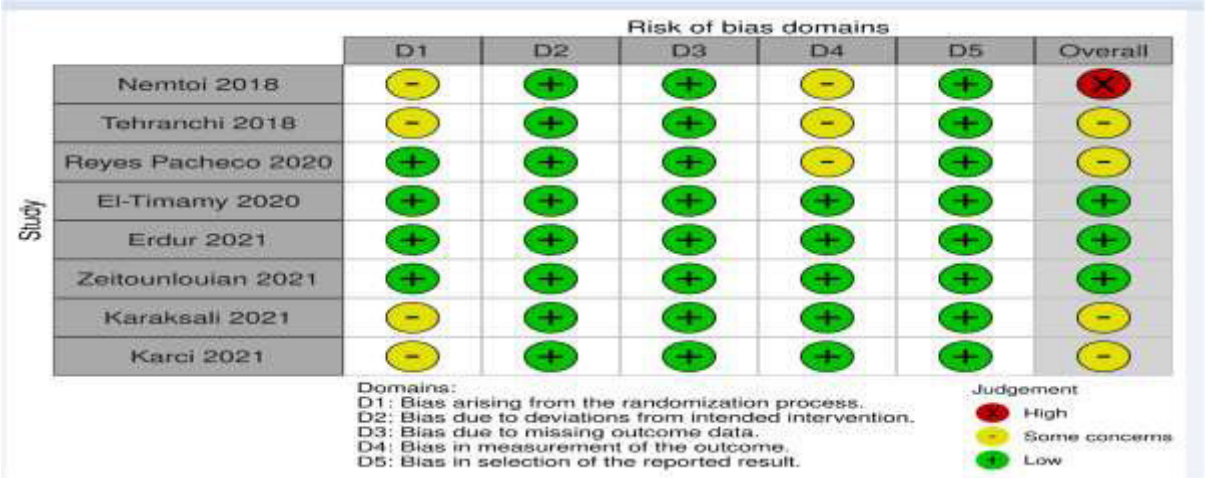

Fig. 2 RoB traffic plot

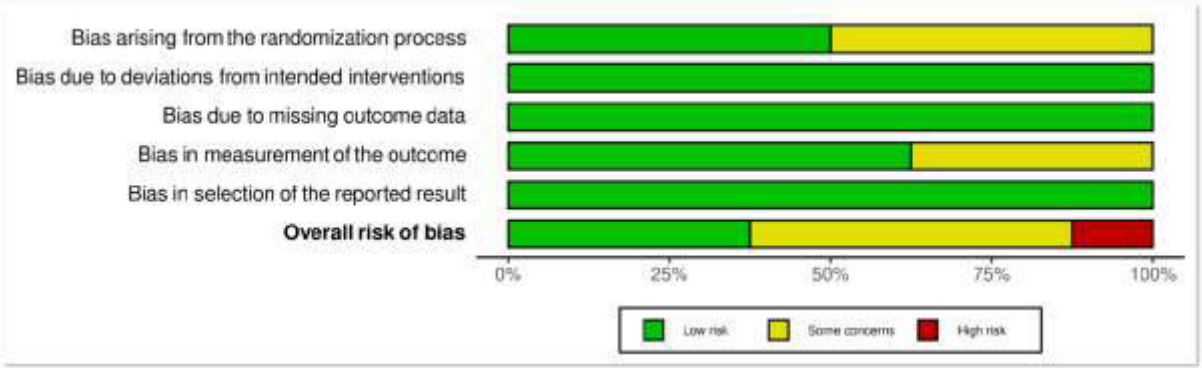

Fig. 3 Summary plot of overall Risk of Bias in each field

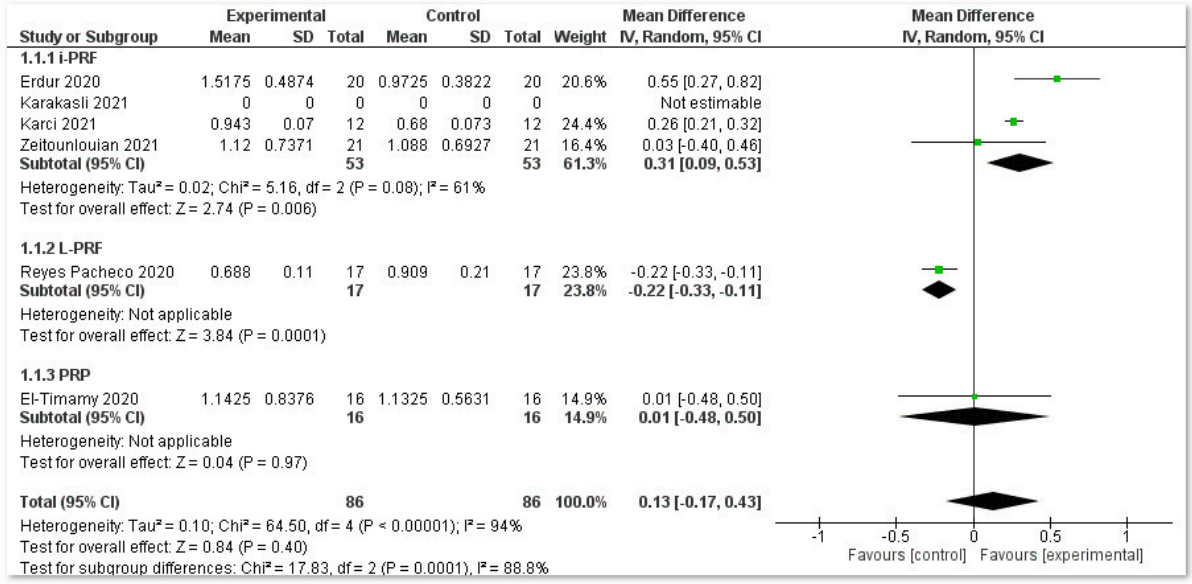

Fig. 4 Meta analysis-comparison of the rate of Canine retraction

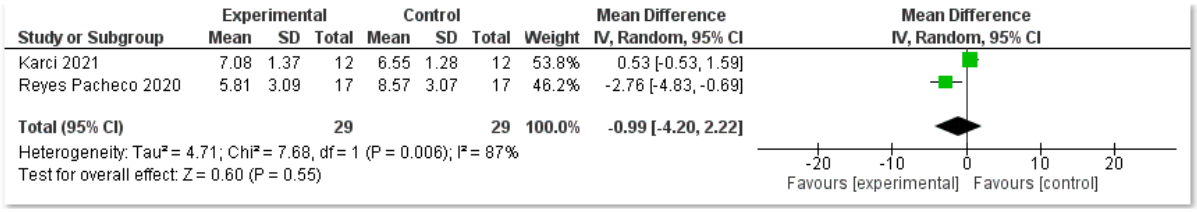

Fig. 5 Meta-analysis- change in Inclination of canine

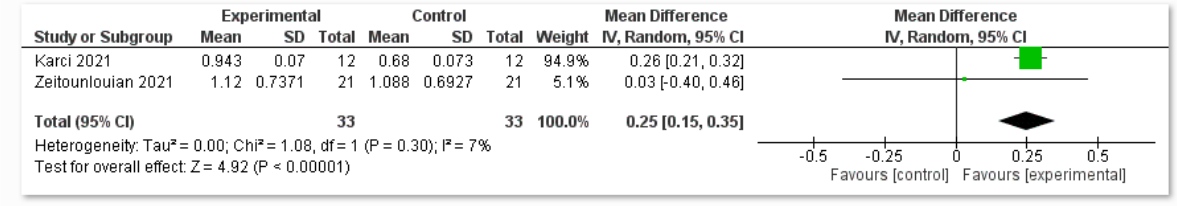

Fig. 6 Sensitivity analysis rate of Canine retraction[1]

4. DISCUSSION

At the time of the commencement of this review, there were no registered systematic reviews in the PROSPERO database to the best of our knowledge, evaluating the Platelet concentrates' ability to accelerate the orthodontic tooth movement. Of late several RCTs have evaluated the efficiency of these substances on orthodontic tooth movement but have

differing results. Other systematic reviews[23] investigated the efficiency of locally injected biological substances or animal studies[24], which cannot be directly extrapolated to human studies. Hence, this systematic review was designed to assist the orthodontist in deciding whether the various platelet concentrates are justifiable to accelerate the tooth movement and help reduce the treatment duration.

5. RATE OF CANINE RETRACTION

From the selected studies, the use of PRP/PRF has modified the rate of space closure. However, the rate of canine retraction could have been more consistent across the studies due to the different protocols adhered to or the frequency at which they were administered. Among the five selected RCTs in the quantitative analysis, only two studies[14,15]showed a statistically significant increased rate of canine distalization. These studies had multiple administrations of i-PRF, twice by Erdur et al. [14] and thrice by Karci et al.[15], which was attributed as the reason for the increased rate of tooth movement by the authors. Although Zeitounlouian et al. [16] and El-Timamy et al. [22] also had multiple administrations of PRF (twice) and PRP (thrice), respectively, they did not show a significant difference in the rate of canine retraction. El-Timamy et al. have shown that the rate of retraction was higher in the initial days of injection (PRP administered thrice, at 0, 3, and 6 weeks) and reported a reduction after three months of the final administration of PRP and Zeitounlouian et al. had reported an increased rate of canine distalization during the 2nd month. No significant difference later on; the reason the rate of tooth movement decreases after a period might be due to a difference in the release of the growth factors responsible for the tooth movement to occur[25–27]. It could also be the reason for the conclusion of the increased rate of canine retraction in the studies by Erdur et al. and Karci et al., as they evaluated only for three months, in contrast to the studies by El-Timamy et al. and Zeitounlouian et al. who evaluated for a period of four and five months respectively, where probably after the cessation of administration of the PRF, the increased rate of canine retraction started to reduce after the exhaustion of the growth factors responsible for tooth movement.

On the other hand, Nemtoi et al, Tehranchi et al. and Reyes Pacheco et al. [12.13.17]administered PRF once in the extraction socket; the latter two studies found a negative influence on the rate of tooth movement, while the former one found a clinically insignificant increase in tooth movement (0.2mm). Although Nemtoi et al.[12] reported an increased rate of movement, the study evaluated the rate of extraction space closure in contrast to other studies evaluating canine retraction; hence, it cannot be emphasized that the real increase in the rate of tooth movement is due to the canine retraction, as there was no mentioning of the anchorage preparation in their study.

Even though Karakasli et al.[21] have reported on incisor retraction, there was no difference in the rate of tooth movement compared with other studies. Again, the reported statistically significant increased rate of retraction of the incisors could be due to the repeated administration of the PRF and the relatively short study duration of only four weeks.

Whether repeated injections of these Platelet concentrates are warranted to sustain the increased rate of tooth movement needs further investigation. However, this is indeed true that all studies included in this study showed only a minuscule difference between the test and control groups, even though there was a statistical difference. As rightly pointed out by Zeitounlouian et al. [16], there is a main disadvantage in all these studies as they are conducted with very small sample sizes. Further, the reason for heterogeneity in results must be analyzed. Concerning the set of selected papers in this study, two studies (Nemtoi et al. [12] and Tehranchi et al. [13] did not report force level. Still, other studies reported similar force levels of 150-152 grams. Hence, the force level may not have influenced the current perspective. However, Erdur et al. [14] reported that bone density, age, and other patient-specific factors might influence the results. It will be more pronounced due to the smaller sample size. Therefore, in the selected studies, there is high heterogeneity in the age of samples, which is a confounding factor.

6. LIMITATIONS

Although no language restrictions were applied, due to the lack of proper means for translation, only the English-language publications were included, due to which data from other language publications could have been missed in this systematic review and meta-analysis. Heterogeneity was also identified in the preparation and administration of the PCs, which might have impacted the results of the included studies. Also, there is a large amount of heterogeneity in the age of subjects, besides the smaller sample size. Since there were differences in the measurement of the primary outcomes in each study, it was standardized by arriving at a mean retraction rate using statistical tools.

7. RECOMMENDATIONS

From the results of this review, we can recommend future studies to standardize the methodology of preparation of the different PCs and their route of administration. Future studies could also be directed using mini-screws/TADs for anchorage reinforcement with en-masse retraction for maximum anchorage cases. From the evidence gathered in this review, well-designed RCTs need to improve the quality of evidence. Limited research on the efficacy of various Platelets concentrates on the rate of orthodontic tooth movement is available. Some studies have suggested that using platelet-rich plasma (PRP) may accelerate orthodontic tooth movement and improve the rate of bone remodeling. Still, more research is needed to confirm these findings. However, the results of such studies have been inconclusive and vary widely. It is important to note that orthodontic treatment is a complex process influenced by many factors, and individual responses to treatment can vary. Therefore, more well-designed and controlled studies are needed to fully understand the potential role of Platelet concentrates in orthodontic treatment.

8. CONCLUSIONS

While this systematic review has focused on the use of PCs (PRP/PRF) for accelerating tooth movement, the results of participant reports are not clinically significant.

- Insufficient evidence exists for these agents' use for accelerating tooth movement.
- Moderate quality of evidence suggests no difference in the change of inclination or the extent of canine rotation with the use of PCs.
- Limited high-quality evidence from only one study shows no reduction in the treatment duration with the use of PCs.
- There is limited evidence on whether multiple administrations of PCs would be required, albeit minimally invasive, to accelerate tooth movement.
- Therefore, within the said limitations, the use of large-scale use of PRP/PRF cannot yet be recommended as it requires studies with a larger population and with homogenous age groups.

9. ABBREVIATIONS

PCs: Platelet Concentrates; PRP: Platelet-rich plasma; PRF: Platelet-rich fibrin; i-PRF: injectable-platelet-rich fibrin; L-PRF: Leukocyte-platelet-rich fibrin; RCT: Randomized controlled trial; TAD: temporary anchorage device; CI: Confidence interval

10. DECLARATIONS

Ethics approval and consent to participate – not applicable
Consent for publication – not applicable
Availability of data and material – the data and materials have been included in the paper
Competing interests – None
Funding – None
Acknowledgments – None

11. AUTHORS CONTRIBUTION STATEMENT

PA and VC designed the study and developed the protocol. PA and PM did a literature search, and study selection—PM and VC did the Risk of Bias assessment. PA was the third reviewer. PA and PM carried out data extraction. VC was involved in the GRADE assessment and assisted PA and PM in the manuscript preparation. All authors were involved in the data interpretation. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none.

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