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Does the use of platelet-rich fibrin enhance the rate of orthodontic tooth movement? A systematic review and meta-analysis

Jitendra Sharan [a,*], Indumathi Shivakumar [b], Arunachalam Shivakumar [c], Vineet Kumar Kamal [d], Prabhat Kumar Chaudhari [e], Srikrishna Challasany [f], Anand Marya [g]

[a] Unit of Orthodontics and Dentofacial Orthopedics, Department of Dentistry, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India
[b] Department of Prosthodontics, Faculty of Dentistry, SEGi University, Selangor, Malaysia
[c] Division of Children & Community Oral Health, School of Dentistry, International Medical University, Kuala Lumpur, Malaysia
[d] Division of Epidemiology and Biostatistics, Indian Council of Medical Research-National Institute of Epidemiology, Chennai, India
[e] Department of Orthodontics and Dentofacial Orthopedics, Centre for Dental Education and Research, All India Institute of Medical Sciences, New Delhi, India
[f] Visakhapatnam, Andhra Pradesh, India
[g] Department of Orthodontics and Dentofacial Orthopedics, Faculty of Dentistry, University of Puthisastra, Phnom Penh, Cambodia

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ABSTRACT

Introduction: This review synthesizes the available evidence pertinent to the effect of platelet-rich fibrin on the rate of orthodontic tooth movement during comprehensive orthodontic treatment.
Method: This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. Nine electronic databases were searched until January 2024 without restrictions, followed by a hand search of the reference lists. Controlled randomized split-mouth human studies assessing the effect of platelet-rich fibrin on the rate of orthodontic tooth movement were included. All relevant data from the included studies were extracted and pooled for qualitative and quantitative analysis. Risk-of-Bias was assessed using the Cochrane Risk of Bias tool. The certainty of the evidence was graded using the Grading of Recommendations, Assessment, Development, and Evaluation tool.
Results: From 515 studies, eleven randomized clinical trials were included for qualitative analysis and nine for quantitative analysis. The certainty of the evidence for these studies was low to moderate. The overall risk of bias for most studies was of some concern. The pooled estimate of the data from ten studies has a mean revealed difference of 1.31 (0.13–2.48) at a 95 % confidence interval with significant heterogeneity.
Conclusions: This systematic review suggest that platelet-rich fibrin enhances the orthodontic tooth movement rate, but the evidence quality was moderate. Further, based on the currently available evidence, the effectiveness of platelet-rich fibrin on the acceleration of orthodontic tooth movement could not be fully established.
Trial registration: PROSPERO: (CRD42021261836).

1. Introduction

In most extraction or otherwise complicated cases, contemporary orthodontic treatment often requires two years or more for completion.[1,2] Long treatment duration for most patients is secondary to various biomechanical and biochemical events occurring simultaneously after the orthodontic force application. This leads to remodeling the periodontal ligament, supporting alveolar bone, and causing orthodontic tooth movement (OTM). In addition, applied orthodontic forces cause the biphasic process of bone resorption and deposition on the compression and tension sides of the alveolar bone, respectively. All these events are secondary to the alteration in the local blood flow, stasis of blood flow, and the release of various bioactive substances, which take sufficient time and occur in a planned manner, thus increasing the overall treatment time.[3,4] Also, lengthy orthodontic treatment can lead to white spot lesions, dental caries, periodontal diseases, root resorption, and psychological burnout.[5,6] Thus, various techniques and procedures to decrease the active orthodontic treatment duration could be of great

* Corresponding author. Unit of Orthodontics and Dentofacial Orthopedics, Department of Dentistry, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India.
E-mail addresses: jsbmds@gmail.com (J. Sharan), cherub2008@gmail.com (I. Shivakumar), sivlalith2004@yahoo.co.in (A. Shivakumar), vineetstats@gmail.com (V.K. Kamal), dr.prabhatkc@gmail.com (P.K. Chaudhari), orthodontist7@gmail.com (S. Challasany), amarya@puthisastra.edu.kh (A. Marya).

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importance for both the patient and the treating orthodontist.

Various techniques, such as physical, biomechanical, biological, and surgical, have been used with conflicting outcomes to reduce the duration of active orthodontic treatment.[7–12] Surgical methods alone (such as corticotomies and micro-osteoperforations) or combined with bioactive materials have been clinically proven to decrease the duration of orthodontic treatment.[13–17] However, these techniques might injure the hard and soft tissues due to their invasive nature. Further, bioactive chemicals such as hormones tend to produce various unwanted systemic effects, which is against the ethos of optimal treatment.

Many bioactive substances possess various limitations, such as the risk of an immune response, high cost, extreme recipient donor site pain, swelling, and ulceration. All these factors have led clinicians and researchers to consider biomaterials that can modulate the inflammatory response and enhance the healing process with no side effects. Over the past two decades, platelet derivatives have been widely used in oral health sciences.[18] Platelet-rich fibrin (PRF) is an autologous concentrate of platelets and leukocytes in a complex matrix. It is considered a potentially rich source of various growth factors (GFs) and a variety of cytokines, which get eluted from the fibrin matrix in a controlled manner over a period of time when it is placed in the biological system.[19] The PRF matrix contains leukocytes, platelets, and various cytokines, such as interleukin (IL)-1β, IL-6, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta1 (TGF-β1).[20] These growth factors accelerate and promote endothelial cell proliferation and differentiation pathways of osteoblasts, osteoclasts, and fibroblasts, leading to enhanced stimulation and remodeling of tooth-supporting structures.[20,21] Various studies have indicated that PRF promotes the healing of the wound and local defects and has a definitive role in orthodontic tooth movement.[17,22–26] Studies on humans to evaluate PRF and acceleration of OTM are recently reported in the literature.[22–29] There are contradictory observations by the researchers regarding the OTM; few studies are of the view that there is accelerated OTM[23,25,27,29,30]; on the other hand, few indicated no or very limited benefit of PRF application on OTM.[26,28,31,32] Considering the conflicting results of the published studies and the availability of very limited evidence on this aspect, a systematic review has been performed to analyze PRF's effectiveness on the acceleration of OTM critically. Therefore, this systematic review aimed to investigate whether the application of PRF enhances the rate of OTM.

2. Materials and methods

2.1. Protocol and registration

The PRISMA statement and guidelines were used to conduct the review.[33] The review protocol was registered in PROSPERO (CRD42021261836). Further, the review was approved by the Institute Review Board (T/IM-NF/Dental/221163).

2.2. Eligibility criteria

The PICOS format formulated the clinical question (Table 1). In addition, experimental prospective controlled studies involving healthy individuals undergoing active OTM were included. The assessment's primary outcome was comparing the OTM rate after the administration of PRF in the experimental site with the control site (i.e., without PRF).

2.3. Information sources and search strategy

PubMed, Scopus, Embase, Cochrane Central Registry of Controlled Trials (CENTRAL), Global Index Medicus, CINHAL, ProQuest Dissertations and Theses, ISRCTN Registry, and China National Knowledge Infrastructure were searched until January 2024. A detailed summary of the database search is elaborated in Table 2. No restriction was imposed on the language, status, or publication date. Further, the reference lists

Table 1
Eligibility criteria for the present systematic review.

Focus question	Does the use of platelet-rich fibrin (PRF) has any effect on the rate of orthodontic tooth movement?	
Domain	Inclusion criteria	Exclusion criteria
Participants	Subjects undergoing orthodontic treatment. (Males/Females/Both, Humans, Age range of 12–40 years, Class I or II malocclusion, full complement of permanent teeth except third molars)	- Any animal model used for any type of orthodontic tooth movement. - Human growing subjects, mixed dentition phase. - Any history of orthodontic treatment for active tooth movement. Radiographic evidence of severe bone resorption. - Subjects with craniofacial deformities or syndrome or any systemic disease affecting tooth movement. - Subjects with any blood dyscrasia.
Interventions	Orthodontic treatment with the use of platelet-rich fibrin. (Extraction treatment-Maxillary first premolars or all first premolars)	- PRF used with any other surgical techniques or biomaterials to enhance tooth movement.
Comparison	Subjects who underwent orthodontic treatment without PRF. (Before and after space closure, right vs. left side)	
Outcomes	Extent and rate of tooth movement (measured by any change in linear or rotational tooth movement in mm).	
Study design	Randomized controlled trial (Split mouth study/Case-control study using lateral cephalometric/Study model/Clinical/3D evaluation)	- Non-comparative studies. - Case reports, narrative reviews, case series, animal studies, letters to the editors, and opinion articles.

Table 2
Strategies for database search.

Database	Search Strategy	Hits
PubMed/Medline	("platelet-rich fibrin"[MeSH Terms] OR ("platelet-rich"[All Fields] AND "fibrin"[All Fields]) OR "platelet-rich fibrin"[All Fields] OR ("platelet"[All Fields] AND "rich"[All Fields] AND "fibrin"[All Fields]) OR "platelet rich fibrin"[All Fields]) AND ("tooth movement techniques"[MeSH Terms] OR ("tooth"[All Fields] AND "movement"[All Fields] AND "techniques"[All Fields]) OR "tooth movement techniques"[All Fields] OR ("orthodontic"[All Fields] AND "tooth"[All Fields] AND "movement"[All Fields]) OR "orthodontic tooth movement"[All Fields])	349
Scopus (Elsevier)	TITLE-ABS-Key ((("tooth movement" OR orthodontics*) AND ("platelet-rich fibrin"))	24
Embase, Cochrane Central Register of Controlled Trails (CENTRAL), Global Index Medicus (World Health Organization)	(orthodontics OR orthodontic*) AND (Tooth movement OR movement*) AND (platelet-rich fibrin)	44
CINAHL (Ebsco)	(MH Orthodontics + OR TX "tooth movement" OR TX orthodont) AND (MH Platelet-rich fibrin)	3
Dissertation Abstracts (ProQuest)	Orthodontic*, platelet-rich fibrin, tooth movement	91
ISRCTN Registry, CNKI,	Platelet-rich fibrin, tooth movement, orthodontic tooth movement	1

of the eligible studies were also hand-searched.

2.4. Study selection

Two authors (JS and IS) assessed the titles and abstracts of the retrieved studies. Any disagreement during the selection process was resolved by the author (AS).

2.5. Data collection and data items

Two reviewers (JS and IS) extracted the relevant data into a customized data collection form. The outline of the data collection form had author, year, study design, subject characteristics, intervention, control, sample size, participant age, PRF protocol, outcome assessed, follow-up, and conclusion.

2.5.1. Risk of bias (RoB) in individual studies

JS and IS independently assessed the RoB (Cochrane risk-of-bias tool: version 2).[34,35] It is an endorsed tool structured with a fixed set of bias domains and signaling questions, focusing on trial design, conduct, and reporting. Further, the summary of the RoB was noted in compliance with Sterne et al.,[32] and Higgins et al.[33]

2.6. Summary measures and synthesis of results

Continuous and categorical demographic and clinical variables data from included studies were measured. The outcome parameter (the rate of OTM) was converted to uniform units (per month) using a given estimate of outcome divided by total months. The heterogeneity was identified using I-squared (I^2) statistics (0–30 %, not important; 31–50 %, moderate; 51–80 %, substantial; 81–100 %, considerable). Using the random effect model, the pooled effect size was measured in terms of standardized mean difference (95 % CI) between the experiment and control group.

Additionally, the cause of heterogeneity was determined by incorporating covariates, such as age and gender, into the meta-regression model, taking into account the availability of data. A quantitative synthesis of results was carried out in this study as many assignments and pertinent information regarding the PRF were retrieved. This resulted in synthesizing the quantitative data, even though this was considered earlier. Due to fewer studies (only seven), the proposed sensitivity & subgroup analyses were not executed (StataCorp LLC, Texas, USA).

2.7. RoB across studies and additional analysis

The Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach used GRADEpro online software (https://gradepro.org) to appraise the quality of evidence from the retrieved studies.[36] Based on the assessment of the study design, risk of bias, inconsistency, indirectness, and the certainty of evidence level was derived. Assessment of publication bias was included when the outcome had more than 11 articles included for the quantitative analysis.

3. Results

3.1. Study selection

Five hundred and fifteen (515) studies were identified through database searching and three additional studies through manual search. Four hundred and three studies (403) were obtained after the removal of the duplicates. The records were further screened, and eleven studies were assessed for eligibility.[23–32,37–39] Out of these twelve studies, one study was excluded as it evaluated the rate of incisor retraction.[27] Thus, eleven studies were included for qualitative analysis (Fig. 1).[23–26,28–32,38,39] The Kappa statistics for inter-examiner reviewer agreement indicated an almost perfect agreement level (k = 0.90).

3.2. Study characteristics

All eleven included studies were randomized control trials (Table 3).[23–26,28–32,38,39] Six out of eleven studies used L-PRF (leukocyte platelet-rich fibrin),[23,24,26,28,29,31] and the remaining five used the i-PRF (injectable platelet-rich fibrin).[25,30,32,38,39] Maxillary first premolars

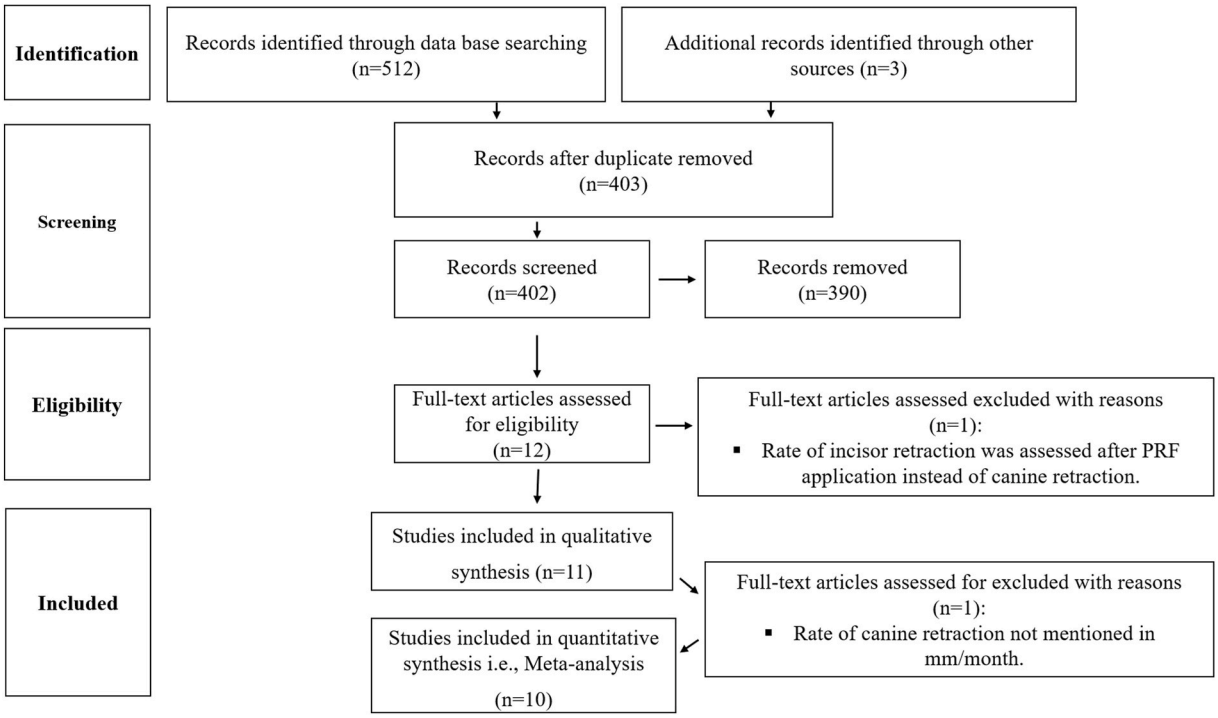


Fig. 1. Systematic search and selection strategy.

Table 3
Study characteristics (sample size, sex ratio, age group), intervention (orthodontic intervention), observation, comparison (platelet-rich fibrin), outcome (rate of tooth movement), and study design.

Study	Tehranchi et al.[23]	Nemtoi et al.[24]	Pacheco et al.[30]	Erdur et al.[25]	Zeitounlouian et al.[31,36]	Karcı et al.[37]	Gupta et al.[38]	Barhate et al.[26]	Krishna et al.[28]	Gupta et al.[29]	Ammar et al.[30]
Year	2018	2018	2020	2021	2021	2021	2022	2022	2023	2023	2023
Study design	RCT (split-mouth)	RCT (split-mouth)	RCT (split-mouth)	RCT (split-mouth)	RCT (split-mouth)	RCT (split-mouth)	RCT (split-mouth)	RCT (split-mouth)	RCT (split-mouth)	RCT (split-mouth)	RCT (three-arm randomized)
Interventions	Maxillary and mandibular first premolars extraction; Maxillary and mandibular or mandibular arch canine retraction using NiTi closed coil spring, force value not specified.	Symmetrical maxillary first premolars extraction, Maxillary canine retraction using NiTi closed coil spring, force value not mentioned.	Maxillary first premolars extraction, Maxillary canine retraction using elastic chain; 150 g.	Maxillary first premolars extraction; Maxillary canine retraction using NiTi closed coil spring; 150 g.	Maxillary first premolars extraction; Maxillary canine retraction using NiTi closed coil spring; 150 g.	Maxillary first premolar extraction, Maxillary canine retraction using closed coil spring; 150 g.	Maxillary first premolar extraction, Maxillary canine retraction using closed coil spring; 150 g.	Maxillary first premolar extraction, Maxillary canine retraction using closed coil spring; 150 g.	Maxillary first premolar extraction, Maxillary canine retraction using closed coil spring; 150 g.	Class II div. 1 or, Class I bimaxillary protrusion requiring fixed mechanotherapy with first premolar extractions. Maxillary canine retraction using closed coil spring; 150 g.	20 patients of Class II Div 1 malocclsuion requiring anterior retraction, requiring maxillary first premolars extraction. Maxillary canine retraction using closed coil spring; 150 g.
Control	Contralateral side of the maxillary and mandibular arch or mandibular canine retraction using equal force.	Contralateral side of the maxillary arch, Canine retraction using equal force.	Contralateral side of the maxillary arch, Canine retraction using equal force.	Contralateral side of the maxillary arch, Canine retraction using equal force.	Contralateral side of the maxillary arch, Canine retraction using equal force.	Contralateral side of the maxillary arch, Canine retraction using equal force.	Contralateral side of the maxillary arch, Canine retraction using equal force.	Contralateral side of the maxillary arch, Canine retraction using equal force.	Contralateral side of the maxillary arch, Canine retraction using equal force.	Contralateral side of the maxillary arch, Canine retraction using equal force.	20 patients with maxillary premolar extraction and canine retraction using the close coil spring and equal force, with out any intervention.
Sample size (Females/ Males)	8 (3/5)	20 (Sex distribution not mentioned)	17 (Sex not specified)	20 (8/12)	21 (15/6)	12 (7/5)	13 (5/8)	15 (15/0)	16 (16/0)	16 (9/7)	40 Sex distribution not specified in the control and i-prf groups.
Participant age in years (mean ±SD)	12–15 (17.37 ± 12.48)	12–20 (Mean ± SD not mentioned)	≥20 (33.59 ± 5.9)	≥20 (21.4 ± 2.9)	16–28 (20.85 ± 3.85)	14–22 (16.45 ± 0.27)	14–30 (20.6 ± 3.2)	18–25 (Mean ± SD not mentioned)	18–25 (Mean ± SD not mentioned)	17–25 (21.85 ± 2.45)	18–25
PRF protocol	2700 rpm, 12 min L-PRF	2700 rpm, 12 min L-PRF	2700 rpm, 14 min L-PRF	700 rpm, 3 min i-PRF	700 rpm, 3 min i-PRF	800 rpm, 3 min i-PRF	700 rpm, 3 min i-PRF	2700 rpm, 12 min L-PRF	2700 rpm, 12 min L-PRF	2700 rpm, 12 min L-PRF	700 rpm, 3 min i-PRF
Outcome assessed	Canine tooth movement, Dental casts measurements	Orthodontic tooth movement, Dental casts measurements.	Canine distalization, Clinical measurements using flexible tape.	Canine tooth movement, Dental casts measurements	Canine retraction, Dental casts	Canine distalization, Digital dental models and measurement using software	Canine tooth movement, Dental casts measurements	Canine distalization, Digital dental models and measurement using software	Canine distalization, Digital dental models and measurement using software	Canine tooth movement, Dental casts measurements	Canine distalization, Digital dental models and measurement using software
Follow up	Clinical evaluation:	Clinical evaluation: Before tooth	Clinical evaluation:	Clinical evaluation:	Clinical evaluation:	Clinical evaluation:	Clinical evaluation:	Clinical evaluation:	Clinical evaluation:	Clinical evaluation:	Clinical evaluation:

(*continued on next page*)

Table 3 (*continued*)

Study	Tehranchi et al.[23]	Nemtoi et al.[24]	Pacheco et al.[30]	Erdur et al.[25]	Zeitounlouian et al.[31,36]	Karcı et al.[37]	Gupta et al.[38]	Barhate et al.[26]	Krishna et al.[28]	Gupta et al.[29]	Ammar et al.[30]
	Before tooth extraction followed by 2nd,4th,8th, 10th,12th,14th, and 16th weeks post-extraction canine retraction.	extraction followed by 4th,8th,12th,16th, 20th, and 24th weeks post-extraction canine retraction.	Before tooth extraction followed by 1st,2nd,3rd,4th, and 5th months post-surgical procedure canine distalization.	Before tooth extraction followed by 1st,4th,8th, and 12th weeks post-extraction canine retraction.	Before tooth extraction followed by 1st,2nd,3rd,4th, and 5th month post-extraction canine retraction.	Before tooth extraction followed by every two weeks interval at 7-time points.	Before tooth extraction followed by	Before tooth extraction followed by 1st,2nd,4th, and 8th weeks post extraction canine retraction.	Before tooth extraction followed by 1st,2nd,4th, and 8th weeks post extraction canine retraction.	Before tooth extraction followed by recall visit at interval of 21 days for 5 months.	Assesment made at five time point: the beginning of tooth movement, and at 4, 8,12, and 16 weeks.
Study duration	4 months (16 weeks)	6 months (24 weeks)	5 months	3 months (12 weeks)	5 months	3 months	Not mentioned	8 weeks (2 months)	8 weeks (2 months)	5 months	16 weeks (4 months)
Conclusion	OTM: - Experimental group > Control group - **mm/month:** Not mentioned or derived	OTM: - Experiment group > Control group - **mm/month:** E: 0.52 C: 0.32	OTM: - Control site > Experiment site - **mm/month** E: 0.67 (95 % CI, 0.6–0.7 mm) C: 0.91 (95 % CI, 0.8–1 mm)	OTM: - Experiment site > Control site - **mm/month** E: 2.02 C: 1.30	OTM: - No significant change in the rate of tooth movement on the experiment and control group except at 2nd month over a period of 5th month - **mm/month** E: 0.78 ± 1.74 C: 0.79 ± 0.99	OTM: - Experiment group > Control group - **mm/month** (over 3 months) E: 0.94 C: 0.68	OTM: - Experiment group > Control group - **mm/month** E: 2.37 ± 0.56 C: 1.32 ± 1.32	OTM: - Experiment group > Control group. Small acceleration of canine retraction on experimental side occurred in 1st 4 weeks, following that canine movement was comparable in experimental and control group. - **mm/month** E: 1.22 ± 0.15 C: 1.04±0.00.	OTM: - Experiment group > Control group. Small acceleration of canine retraction on experimental side occurred in 1st 4 weeks, following that canine movement was comparable in experimental and control group. - **mm/month** E: 1.15 ± 0.17 C: 1.00 ±0.06.	OTM: - Experiment group > Control group. The rate of canine retraction was statistically greater on the experimental side only for first two months. - **mm/month** E: 1.28 ± 0.70 C: 1.11 ±0.51.	OTM: - Experiment group > Control group. The rate of canine retraction was statistically greater on the experimental side. i-PRF has a prolonged acceleration effect. - **mm/month** E: 0.87 ± 0.12 C: 1.36 ±0.32.

RCT: randomized control trial, PRF: platelet-rich fibrin, L-PRF: leukocyte platelet-rich fibrin, i-PRF: injectable platelet-rich fibrin, OTM: orthodontic tooth movement, E: experiment site, C: control site.

were extracted in all the studies,[24–32,38,39] except one study,[23] where all first premolars were extracted. For most of the included studies, the experiment lasted between 5 weeks and 24 weeks[23–26,28–32,38]; on the other hand, one study did not mention the duration.[39]

The participants were aged between 12 and 28 years. The sample size calculation was conducted for all the included studies.[23–26,28–32,38,39] The type of malocclusion was not mentioned in the two studies.[23,24] Only, three studies did not specify the gender.[24,30,31] Most of the studies used NiTi closed coil springs for tooth movement,[23–26,28–30,38,39] except one where the elastomeric chain was used.[31] The force level was kept at 150 g for most of the studies,[25,26,28–32,38,39] except for two, where it was not mentioned.[23,24] The rate of OTM was evaluated on dental stone models,[23–25,29–31,38] digital study models,[26,28,38] and clinical evaluation using flexible tape.[31]

3.3. RoB within studies

Fig. 2 depicts the summary of the ROB assessment. Two studies were assessed to have high RoB, mainly due to inadequate allocation concealment during randomization and outcome measurements.[24,39] Five studies had 'some concerns' (sequence generation, outcome measurement, results reporting).[23,29,31,32,38] Four studies had a low risk of bias.[25,26,28,30]

3.4. Effect of PRF on the rate of orthodontic tooth movement (results of individual studies)

Six studies demostrated efficacy of the application of PRF in enhancing the OTM.[23–25,29,38,39] Nemtoi et al.[24] reported OTM on the experiment and the control sides in the ratio of 1.63:1 over six months of study. The rate of OTM was derived from the difference between the extent of space available at the extraction site before and after the completion of the study. Erdur et al.[25] using the maxillary canine retraction model, observed a greater OTM on the experiment side over 12 weeks of study ($P < 0.001$). Gupta et al.[29] mentioned that the ratio of tooth movement on the experimental and control sides is 1.15:1 (Experimental side 1.28 mm/month and control side 1.11 mm/month). This accelerated tooth movement on the experimental side was observed only for first two month, following which the rate of orthodontic tooth movement on control and experimental sides was statistically non significant. Ammar et al.[30] made an observation that there was enhanced OTM on the experimental side compared to the control one, and it was in the ratio of 1.56 which was statistically significant. They also suggested that i-PRF had a prolonged accelerated effect on OTM. Karcı et al.[38] have observed tooth movement in the ratio of 1.38:1 (Experimental site 0.94 mm/month and control site 0.68 mm/month) over three months of study. Gupta et al.[39] have pointed out that a single i-PRF injection enhances tooth movement by 1.8 times on the intervention side ($p < 0.001$; experiment side 2.37 ± 0.56 mm/month; control side 1.30 ± 0.16 mm/month).

On the other hand, three studies have suggested almost similar extents of tooth movement on the control and experimental sides.[26,28,32,39] Barhate et al.[26] have observed that, maxillary canine retraction acceleration was only 0.35 mm more on the experimental side than the control side; this too was during the first 4 weeks, following which it was comparable on both sides. Krishna et al.[28] have observed that the extent of orthodontic tooth movement on the experimental and control sides were very close (it was statistically significant but clinically non significant) during the first 4 weeks. After 4 weeks the rate of tooth movement on the experimental and control sides were similar. Zeitounlouian et al.[32,37] found an almost similar rate of OTM in the experiment (0.78 ± 1.74) and control (0.79 ± 0.99) sides ($P = 0.383$). However, Pacheco et al.[31] reported that the amount of canine distalization was less in the PRF group compared to the control group over five months of the study period (PRF group 0.67, 95 % CI, 0.6–0.7 mm, Control group 0.90, 95 % CI, 0.8–1 mm, $P = 0.004$).

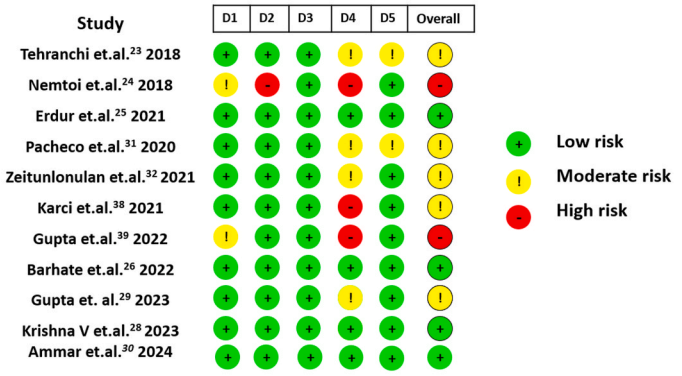
3.5. Data synthesis

The rate of tooth movement for the experiment group varied from 0.52 to 2.37 mm, and for the control group, it was 0.32–1.32. Eleven studies[23–26,28–32,38,39] were included for meta-analysis (Fig. 3). One study was excluded as it was not feasible to derive the amount of canine retraction (in mm/month).[23]

The pooled data from the ten studies[24–26,28–32,38,39] revealed an overall mean difference of 1.31 (95 % CI: 0.13 to 2.48) between the experiment and control group with high heterogeneity ($I^2 = 96.30$ %). The I^2 measures the percentage of total variability due to the treatment outcome of the included studies and heterogeneity seems to be very high (96.44 %). Meta-regression did not identify age and gender as important confounders. We cannot estimate the sensitivity analysis as only seven studies were part of the meta-analysis.

3.6. RoB across studies

The quality of evidence pertinent to the OTM evaluated in this systematic review was low. It was observed that inconsistency, indirectness, and RoB were rated high. This could be because one study had RoB



D1: Randomization process; D2: Deviations from the intended interventions, D3: Missing outcome data; D4: Measurement of the outcome; D5: Selection of the reported result.

Fig. 2. Summary of the Risk-of-Bias Assessment according to version 2 of the Cochrane risk-of-bias tool for randomized trials.

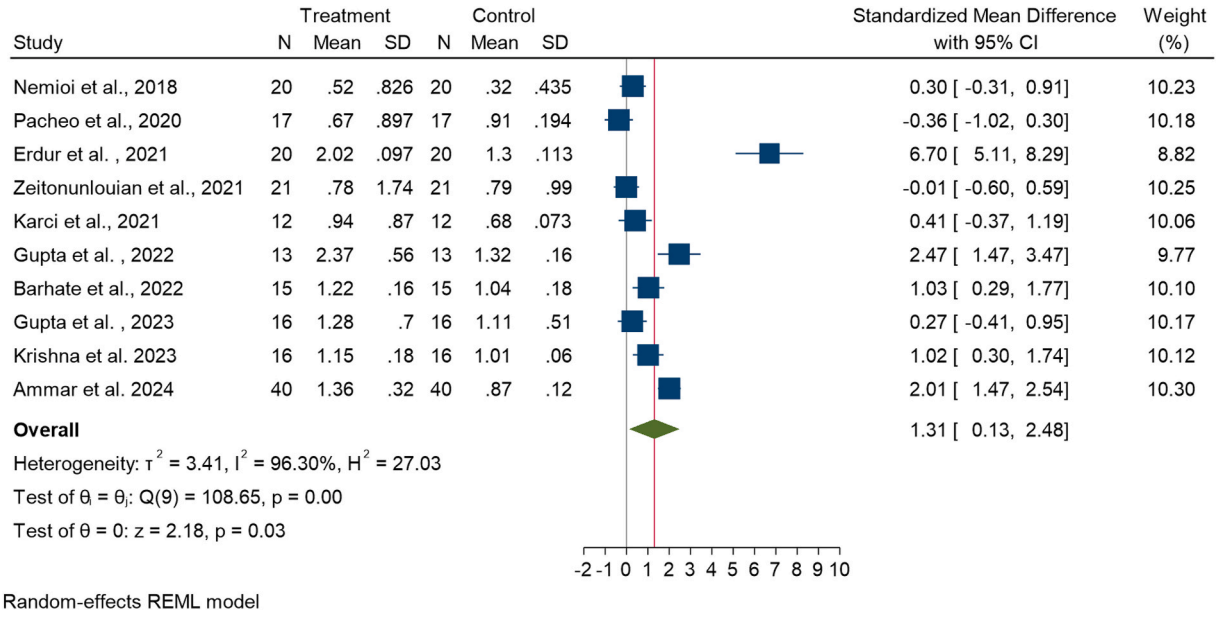


Fig. 3. Meta-analysis Forest plot of included studies (95% confidence intervals).

on the higher side, while four studies had some concern due to differences in the measurement of outcomes and reported results. Concerns regarding the small sample size and high ROB with evidence further downgraded between low to moderate for the final assessment.

Additionally, the publication bias was not observed. Further, the effect of PRF on the rate of OTM was moderate from GRADE. Such observations were due to the selection bias and the difference in the study outcome (Table 4).

4. Discussion

4.1. Summary of evidence

The meta-analysis revealed an overall mean difference of 1.31 (95 % CI: 0.13 to 2.48) for tooth movement in mm/month. The outcome was derived from the pooled data of the RCT on the human model. Six studies demonstrated relationship between the application of PRF (L-PRF/i-PRF) and the enhancement of OTM.[24,25,29,30,38,39] The conclusions of these studies agreed with Sar et al.[17] observation. On the other hand, Pacheco et al.[31] suggested that there is no benefit of using PRF, as the extent of OTM was more on the control than on the experimental site. A similar result was reported in an animal model, where the use of carbonate hydroxyapatite and PRF has shown a local reduction in alveolar bone remodeling.[40] Zeitounlouian et al.[32,37] reported an almost similar degree of OTM on both sites. The authors have suggested that the rate of canine retraction following PRF application was not significant between the control and the experimental sides except in the 2nd month over 5th months of study duration. Very similar views were proposed by Barhate et al.,[26] and Krishna et al.[28] they suggested that canine retraction on the experimental side was enhanced only by 0.35 mm and 0.28 mm respectively compared to the control side using L-PRF over 4 weeks; following this, the canine retraction was comparable. This leads to presume that the acceleratory effect of PRF on the OTM cannot be confirmed, but there was moderate evidence that the OTM can be enhanced by repeated application of PRF.

Studies have suggested that i-PRF contains more GFs than L-PRF, and the release of GFs from the fibrin matrix is more sustained in i-PRF over L-PRF.[20] Although there were variations in the GFs profile of PRFs (L-PRF and i-PRF), the superiority of any of them over the other in accelerating the OTM cannot be established in this study. One study pointed out that growth factors decrease bone turnover over and induce bone neoformation, thus decreasing the OTM.[31] In contrast, other studies suggest a positive enhancement in OTM with PRF usage.[24,25,30,39,41] Therefore, the therapeutic concentration range for

Table 4
Grade evidence profile for the quality of available evidence on the rate of orthodontic tooth movement for the RCT.

Quality assessment						Effect	Quality
Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other		
L-PRF (6)	Serious[a]	Not serious	Not serious	Not serious	None	- Tehranchi et al.[23]: Increased in EG - Nemtoi et al.[24]: Increased in EG - Barhate et al.[26]: Almost similar in CG and EG - Pacheco et al.[31]: Increased in CG - Krishna V et al.[28] : Almost similar in CG and EG - Gupta et al.[29]: Increased in EG	⊕⊕⊕◯[b] **Moderate**
i-PRF (5)	Serious[a]	Not serious	Not serious	Not serious	None	- Erdur et al.[25]: Increased in EG - Ammar et al.[30]: Increased in EG - Zeitonulouia et al.[32,36]: Almost similar in CG and EG - Karcı et al.[38]: Increased in EG - Gupta et al.[39]: Increased in EG	⊕⊕⊕◯[b] **Moderate**

L-PRF leukocyte platelet-rich fibrin, i-PRF injectable platelet-rich fibrin.
EG experiment group, CG control group.
[a] The overall results were based on few studies.
[b] Lack of randomization during sample allocation.

efficient, effective, and safe PRF application for accelerated OTM remains unclear.

4.2. Limitations and future directions

The limited availability of studies on this topic with a uniform outcome could be an inherent limitation. Studies with varied outcomes had to be interpreted cautiously in the same clinical scenario. Further, most studies had concerns about the RoB, and overall quality was low. Additionally, most of the included studies had a smaller sample size, which poses a risk to the quality of evidence. So, more high-quality studies with a standardized study design emphasizing optimization of PRF concentration for enhancement of OTM should be conducted to have sufficient clinical data for the effective and efficient application of PRF.

5. Conclusions

There is moderate evidence with respect to enhanced orthodontic tooth movement rate and the use of platelet-rich fibrin based on the ROB assessment.

Author contributions

Concept - J.S.; Design - J.S., I.S.; Supervision - J.S., I.S., A.S.; Materials - J.S., I.S., A.S.; Data Collection and/or Processing - J.S., I.S., A.S., P.K.C., A.M.; Analysis and/or Interpretation - J.S., I.S., V.K.K., A.S.; Literature Review – J.S., A.S., P.K.C., A.M; Writing - J.S., I.S., A.S., V.K.K; Critical Review – J.S., I.S., A.S., P.K.C., V.K.K., A.M. all authors contributed to the article and approved the submitted version.

Consent for publication

Not applicable.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Protocol and registration

The protocol was registered before the study in the accessible PROSPERO database (CRD42021261836).

Ethics approval and consent to participate

This paper did not use experimental data from human subjects. The Institute Review Board approved the review (T/IM-NF/Dental/221163).

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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