

PLATELET RICH DERIVATIVES FOR ACCELERATION OF ORTHODONTIC TOOTH MOVEMENT: A SYSTEMATIC REVIEW OF RCTS.

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Abstract

BACKGROUND: Platelets Rich Plasma (PRP) therapy has been in use for periodontal healing as it speeds up the process thereby reducing time also injection of high concentration PRP could accelerate orthodontic tooth movement via decreasing alveolar bone volume density on paradental tissues in a transient way.

AIM: The aim of this review is to systematically report and appraise the current evidence on the effectiveness of platelet rich derivatives in accelerating orthodontic tooth movement.

MATERIALS AND METHODS: The reporting of this systematic review was according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement. Detailed search strategies were prepared and 3 electronic databases were searched for the eligibility criteria. The Cochrane Collaboration's Risk of Bias tool was used for qualitative assessment of the included studies.

RESULTS: 4 studies satisfying the selection criteria were included. All of the 4 studies reported significant acceleration of tooth movement with platelet rich derivatives. 1 study reported high risk of bias and 3 studies reported unclear risk of bias.

CONCLUSION: The available literature suggests acceleration of tooth movement with plasma rich derivatives but the quality of evidence is moderate to low and hence more high quality RCTs are needed.

KEYWORDS: I-PRF;LPRF;PRP;CaCl₂;Accelerated tooth movement.

INTRODUCTION:

Orthodontic tooth movement happens with remodeling of the bone which involves a complex process of bone deposition and resorption(1).It was observed that there was some amount of trauma to the periodontium when orthodontic forces were applied even if the force levels were light and continuous. Acceleration of tooth movement is required in many clinical situations and many methods. Long-term orthodontic care with fixed appliances is often linked to an increased risk of negative side effects such as enamel demineralization(1,2). Apart from optimising the treatment process, efforts have been made to speed up alveolar bone remodelling, which is critical for faster orthodontic tooth movement. Pharmaceuticals(3) and numerous physical(3,4) (3–5)(3–6) approaches have been used to do this.

Nowadays there is a new way of treatment called the Platelets Rich Plasma (PRP) which was invented in the 1970s and first used in Italy 17 years later in a medical major surgery (open heart) PRP therapy has been in use for periodontal healing as it speeds up the process thereby reducing time(7). Also, injection of high concentration PRP could accelerate orthodontic tooth movement via decreasing alveolar bone volume density on paradental tissues in a transient way(7,8).

Systematic review on piezotony by Hoffman et al in 2017 has reported the evidence for an acceleration of tooth movement in the human is low(9). Another SR on low level laser therapy and corticotomy by Gkantidis et al in 2014 has reported that low level laser therapy and corticotomy are effective(10). There are no systematic reviews at present reporting on platelet rich derivatives for acceleration tooth movement.

The multitude of growth factors within the PRP that has the potential to stimulate both osteoblastic and osteoclastic activities together with its rich content of cytokines that have a major role during orthodontic tooth movement throughout mediating differentiation, activation and survival of all bone cells, supported the idea that PRP could have a possible effect on orthodontic tooth movement(8). Platelets are responsible for storing intracellular

mediators and cytokines, and after aggregation, they release their granule material. This process is most active in the first hour, and cytokine and growth factor synthesis can last up to seven days(11).In the surrounding media, more than 800 distinct proteins are secreted(12).chondrocytes(12–14), tendon cells(15), mesenchymal stem cells from various origins(16)(17),chondrocytes(17,18), osteoblasts(19)(20), fibroblasts(21), and endothelial cells have a paracrine impact(21,22). Tissue repair is aided by cell regeneration, angiogenesis, and cell migration(8).Accordingly, the current study was designed to examine clinically and histologically the possible effects of Platelet rich derivatives on the rate of orthodontic tooth movement.The aim of this review is to systematically report and appraise the current evidence on the effectiveness of platelet rich derivatives in accelerating orthodontic tooth movement.

PICO ANALYSIS:

P-Human subjects undergoing treatment with fixed appliances

I-Local or systemic administration of biological agents(I-PRF,LPRF,PRP and CaCl₂)

C-Placebo intervention or no intervention

O-Data on the rate of orthodontic tooth movement.

MATERIALS AND METHODS:

The reporting of this systematic review was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.The selection of articles for this systematic review were done based on the eligibility criteria mentioned in Table 1.

Search strategy and information of sources:

Detailed search strategies were developed and appropriately revised for each database, considering the differences in controlled vocabulary and syntax rules. The following electronic databases were searched: MEDLINE (Pubmed, Appendix 1, from 1946 to October 30th, 2020), Google Scholar, the Cochrane Oral Health Group's Trials Register.(Table 2)

Unpublished literature was searched on ClinicalTrials.gov, the National Research Register, and Pro-Quest Dissertation Abstracts and Thesis database. The search attempted to identify all relevant studies irrespective of language. The reference lists of all eligible studies were hand-searched for additional studies.

Screening and selection of studies:

The selection criteria that were applied for the inclusion of articles in the review are represented in (Table 1). A study was judged eligible when it included two treatment arms that are platelet rich derivatives and no treatment which none of the exclusion criteria fulfilled. After removal of internal and external duplicates, articles were screened on the basis of title, abstract, and full-text. When titles and abstracts were insufficient to decide, the full text of the article was acquired. The sequential selection of studies was undertaken by following the prisma protocol.(Figure 1)

Risk of bias (quality) assessment:

The Cochrane Collaboration's Risk of Bias tool was used to assess sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases involved in the included randomized controlled trials. Risk of Bias assessment was done individually by two authors (KR, RKJ). Disagreements were resolved by joint discussion with the third author (SRL). The authors of the included studies were contacted for clarification if required.

Data Analysis

A narrative description of the findings of all the included studies was provided, aiming at the stability of the treatment and patient perception. The primary outcome (the rate of orthodontic tooth movement) as reported in all three articles was subjected to qualitative analysis using the Review Manager Software (RevMan, Version 5.4, Copenhagen, The Cochrane Collaboration).

RESULTS:

Description of Included Studies

A total of 3457 records were identified based on preliminary web search. After the removal of duplicates, 1494 studies were obtained. After going through the full text articles,983 studies were further excluded based on the inclusion and exclusion criteria. A Total of 4 studies were included in this systematic review for qualitative analysis. All of the four studies were split mouth RCTs and they reported that the rate of tooth movement was increased when plasma rich derivatives like PRP,PRF or iPRF were used as an intervention when compared to

the untreated side. The study design, characteristics of participants, comparison groups, follow-up period, and the outcomes of the included studies are presented in (Table 3).

Risk of bias/methodological quality of included 3 studies

Out of the four included studies one study reported with high risk of bias and three studies reported unclear risk of bias. Incomplete outcome data and selective reporting was not mentioned in the studies by Tehranchi et al(23). Allocation concealment reported unclear risk of bias by Nemtoi et al(24) and Erdur et al(25). Incomplete outcome data reported unclear risk of bias by Timamy et al(26).

Qualitative analysis of the primary outcomes:

All the four included studies checked on the rate of tooth movement (Erdur et al, Nemtoi et al, Tehranchi et al and Timamy et al) reported significant results (<.05).

Qualitative analysis of the secondary outcomes:

Erdur et al checked on IL-1b, MMP-8 and RANKL levels at T0, T1 & T2 and reported significant result (<.05). Timamy et al checked on pain assessment.

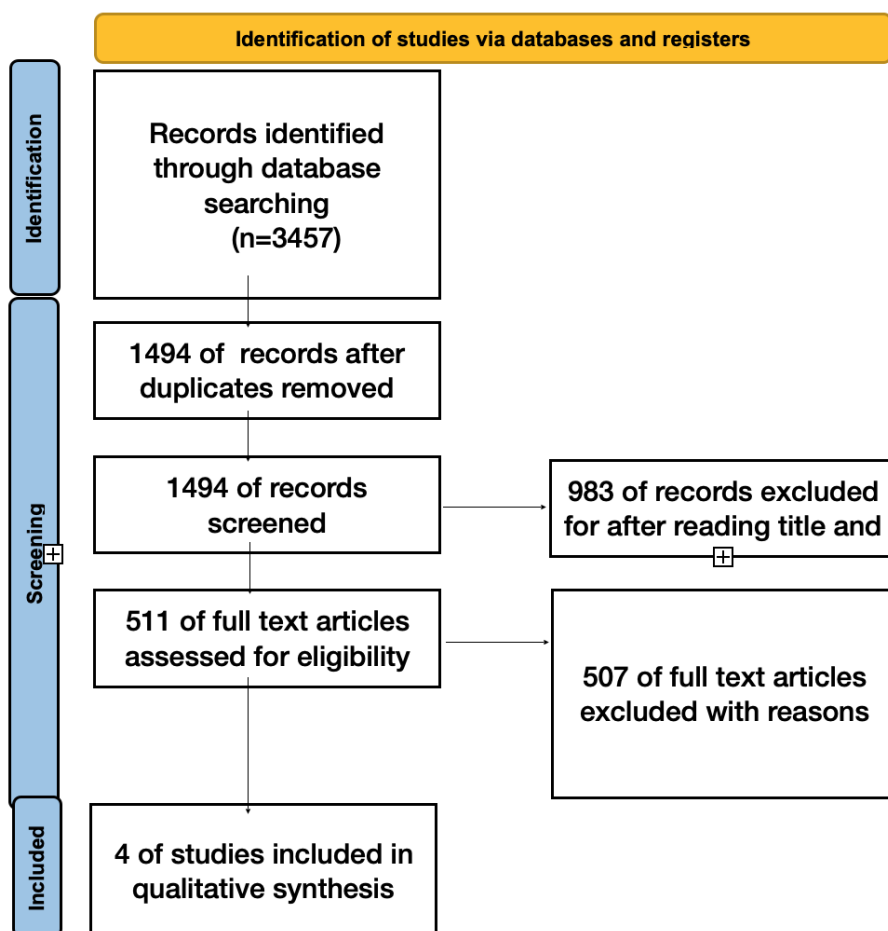


Figure 1-Prisma flowchart

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Erdur et al,2021	+			+	+		+
Nemtoi et al,2018	+		+	+	+		+
Tehranchi et al,2019	+	+	+	+	-	+	+
Timamy et al,2021	+	+	+	+		+	+

Figure 2- cochrane ROB for bias assessment of included studies

DOMAIN	INCLUSION CRITERIA	EXCLUSION CRITERIA
Participants	Human subjects undergoing treatment with fixed appliances	-Animal subjects undergoing orthodontic treatment . -Human subjects after cessation of orthodontic treatment or unhealthy subjects with systemic diseases or syndromes.
Interventions	Local or systemic administration of biological agents(I-PRF,LPRF,PRP and CaCl ₂)	-Studies using intervention used to decelerate orthodontic tooth movement . -Studies using interventions like corticotomies, micro osteoperforation, piezocision, the use of low-level energy laser and vibration) -Studies reporting the use of bisphosphonates, non-steroidal anti-inflammatory drugs(NSAIDS), immunosuppressants and anticancer drugs
Comparison	Placebo intervention or no intervention	
Outcomes	Data on the rate of orthodontic tooth movement	

Study design	Randomized control trials	-studies without control or placebo group. -In vitro or ex vivo studies. -Case reports, structured reviews, systematic reviews and meta-analyses, case series, animal studies, opinion articles, and letters from editor
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Table 1-Eligibility criteria for selection of studies

DATABASE	SEARCH STRATEGY	HITS
Pubmed/Medicine	Search: (((((Orthodontic tooth movement) OR (tooth movement)) OR (orthodontic) AND ((fha[Filter]) AND (clinicaltrial[Filter] OR systematic review[Filter]))) AND ((Platelet rich plasma) OR (platelet rich fibrin)) OR (leukocyte platelet rich plasma) AND ((fha[Filter]) AND (clinicaltrial[Filter] OR systematic review[Filter]))) AND ((Humans) NOT (Animals) AND ((fha[Filter]) AND (clinicaltrial[Filter] OR systematic review[Filter]))) AND ((fha[Filter]) AND (clinicaltrial[Filter] OR systematic review[Filter]))) AND (("1960/01/01"[Date - MeSH] : "2021/2/10"[Date - MeSH])) Filters: Abstract, Clinical Trial	1449
Google Scholar	“orthodontic tooth movement” “tooth movement” “platelet rich plasma” “platelet rich fibrin” “leukocyte platelet rich plasma” “human” “not animal”	336
Cochrane	“Orthodontic tooth movement” “platelet rich plasma” “platelet rich fibrin” “leukocyte platelet rich plasma”	1672

Table 2 - Databases searched with keywords

Author and year of study	Study design	Sample size	Groups (intervention and control group)	Outcomes assessed	Statistics used	Tools used for assessment
Erdur et al,2021(1)	split mouth RCT	25 patients	Intervention group -i-PRF injected intraligamentary Control group	Rate of tooth movement Cytokines level	Student t-test and one-way analysis of variance (ANOVA) Repeated-measure ANOVA	study model measurements -distance between the midpoints of the vertical lines drawn from the Incisal edge to the cervical line over the marginal ridge of the lateral and canine teeth.
Nemtoi et al,2018(27)	split mouth RCT	20 patients	Intervention group -PRF plugs were placed in socket Control group	Rate of tooth movement	Mean and SD	Study model measurements - distance between the adjacent teeth.
Tehranchi, et al,2019 (1,28)	split mouth RCT	8 parts	GRP 1- immediate placement of LPRF in the extraction socket. Group 2- secondary healing.	Rate of tooth movement	Mean and SD Independent sample t-test	study model measurements- distance between marginal ridges of the adjacent teeth every two weeks

Tim Amy et al,2021(26)	split mouth RCT	16 patients	Grp 1-PRP injected intraligamental in the middle, distobuccal and distopalatal areas with submucosal injection buccally and palatally with CaCl ₂ Group 2-CaCl ₂ injection	Rate of tooth movement. Pain assessment	Paired t-test	digital models superimposed using 3 shape analyser software . Visual analogue scale
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Table 3-Characteristics table of the included studies

Author and year of study	Outcomes assessed	Results Mean	P value	Inference
Erdur et al,2021	Rate of tooth movement IL-1b,MMP-8 and RANKL levels at T0,T1 & T2	Intervention group- 6.06 +0.29 Control group 3.89 +0.34	T test <.001 ANOVA <.001 Repeated measures<.001 Pearson correlation<.001	I prf accelerates tooth movement Inflammatory cytokines expressed
Nemtoi et al,2018	Rate of tooth movement	Intervention group-Mean value started at 5mm and ended at 1.9mm after 6 months. Control group-Mean value started at 4.8mm and ended at 2.9 after 6 months	Mean and standard deviation-0.0006	PRF may accelerate tooth movement
Tehranchi,et al,2019	Rate of tooth movement	Intervention group-mean-6.65 SD-0.834 Control group-Mean-6.76 SD-0.763	Independent sample t-test Experimental group-0.94 Control group-0.77	LPRF may accelerate tooth movement
Tim Amy et al,2021	Rate of tooth movement. Pain assessment	T0: Intervention group-1.55+0.63 Control group-1.35+0.62 T1: Intervention group-0.59+0.96 Control group-1.01+0.63 T2: Intervention group-4.57+1.32 Control group-4.53+1.12	Paired t test: T0-0.049 T1-0.772 T2-.020	PRP did not exhibit long term acceleration effect

Table 4-Results of the included studies

DISCUSSION:

This review aimed to systematically report and appraise the current evidence on the effectiveness of platelet rich derivatives in accelerating orthodontic tooth movement. Qualitative analysis of the primary outcomes showed that all the four included studies checked on rate of tooth movement (Erdur et al, Nemtoi et al, Tehranchi et al and Timamy et al). All of the four studies were split mouth RCTs and they reported that the rate of tooth movement was increased ($p < .05$) when plasma rich derivatives like PRP, PRF or iPRF were used as an intervention when compared to the untreated side.

Risk of bias assessment (also known as "quality evaluation" or "critical evaluation") helps to ensure that evidence synthesis results and findings are transparent. Each included study in your review is usually subjected to a risk of bias evaluation(29). All four studies had low risk of bias for random sequence generation bias, blinding of outcome assessment and other bias. For allocation concealment bias Nemtoi et al and Erdur et al showed unclear bias, blinding of participation and personnel bias Erdur et al showed unclear bias. For incomplete outcome data bias Tehranchi et al showed high risk bias and Timamy et al showed unclear risk of bias and for selective reporting bias Nemtoi et al and Erdur et al showed unclear risk of bias. Qualitative analysis of the secondary outcomes showed that Erdur et al checked on IL-1 β , MMP-8 and RANKL levels at T0, T1 & T2 and reported significant results ($< .05$). Timamy et al checked on pain assessment. Erdur et al also reported that i-PRF increased the expression of inflammatory cytokines, indicating osteoclastic activity and a faster rate of tooth movement. During the entire follow-up period, the canine on the study side moved almost twice as much as the canine on the control side. Nemtoi et al reported that PRF application in the extraction socket has been shown to have a beneficial effect on bone regeneration and orthodontic tooth movement.

Rashid et al reported that in the animal investigation (mongrel dogs), local injections of PRP resulted in faster orthodontic tooth movement with no clinical or microscopic side effects(30). Akbulut et al reported that At day 3, the rats in the platelet-rich plasma group had less tooth movement than the control rats. On day 14, all groups showed the most tooth mobility. At day 14, however, there was no statistical significance between the groups. There were no significant differences in osteoclast and osteoblast cells in either group or at any time(31). Güleç et al reported that study done on rats after injecting both moderate and high quantities of PRP into the paradental tissues may help to speed up orthodontic tooth movement by temporarily increasing osteoclastic activity and decreasing alveolar bone density(32). Nakornnoi et al reported that at all times, the L-PRP group had considerably more cumulative tooth movement. On days 0–7 and 7–14, however, a significantly higher rate of tooth movement was observed. On days 7 and 14, the number of osteoclasts in the L-PRP group grew considerably(33).

Shirude et al reported that low-level laser therapy showed increased rate of tooth movement than micro-osteoperforations, vibrations and photobiomodulation were the most successful non-invasive therapies(34). Gkantidis et al reported that Low laser therapy and corticotomy have some evidence of effectiveness, although interseptal bone reduction has weak evidence, and photobiomodulation and pulsed electromagnetic fields have extremely weak evidence(10). Alfawal et al reported that the evidence for the effectiveness of minimally invasive surgically accelerated orthodontics is weak (MISAO). Although the current study found that MISAO can aid in the speeding up of canine retraction, more research in this area is needed before it can be suggested in routine clinical practice(35).

Timamy et al reported that on the intervention side, there was a 15% increase in canine retraction in the first month and a 5% increase in the second month. Tehranchi et al reported that The experimental groups had a smaller gap between mid-marginal ridge points of crowns adjacent to extraction sites, indicating that LPRF application in the extraction socket could accelerate orthodontic tooth movement, including anchorage loss of posterior teeth.

Preparation of i-PRF as follows :

Each patient had a venous blood sample drawn with a 30-mL injection syringe into 10-mL i-PRF tubes without anticoagulant and centrifuged at 700 rpm for 3 minutes at room temperature with a Choukroun PRF Duo Centrifuge. In dental injectors, the i-PRF derived from the upper liquid layer was put. The amount of i-PRF was standardised as 4 mL and was injected intraligamentally into the distobuccal and distopalatal side of the canine tooth (2 mL for each side) (2 mL for each side). Local anaesthetic was used to control pain before the injection of platelet-rich fibrin (PRF). I-PRF was given to the study group twice: immediately after premolar extraction and again at the end of the second week of distalization. On the opposing side served as control side.

Preparation of PRP:

The double-spin process was used to make PRP. The intervention side was anaesthetized for 15 minutes with 2% mepivacaine and a vasoconstrictor. PRP was administered intraligamentally in the middle, distobuccal, and distopalatal portions of the distal surface of the canines (5 units each), as well as submucosal injections buccally and palatally, into hens (5 units each area). The same volume of 10% CaCl₂ solution was infused immediately after the PRP injection to activate the PRP. The intervention side received injections at 0, 21, and 42 day intervals. The control group was sedated and given 25 units of 10% CaCl₂ according to the same procedures and at the same time as the intervention group.

Preparation of LPRF:

A 10 mL syringe is used to collect whole venous blood from the brachial vein. The blood was taken and deposited symmetrically in two sterile vacutainer tubes (9 mL) without anticoagulant in the centrifuge apparatus. The intraspinal tubes were immediately centrifuged (PCO2 Process) at 2700 rpm for 12 minutes, resulting in three layers: red blood cells at the bottom, straw-colored cellular plasma at the top, and fibrin clot and platelets in the intermediate portion. The upper straw-colored layer was removed, and the middle fraction, which was LPRF, was collected 2 mm below the bottom dividing line. Following centrifugation, fibrinogen, which is initially concentrated in the upper section of the tube, is mixed with circulating thrombin to produce fibrin. In the middle of the tube, between the red corpuscles at the bottom and the acellular plasma at the top, a fibrin clot forms. The fibrin mesh traps a large number of platelets.

The release of growth and healing factors peaks about 7 days after buccal vestibular mucosal injection in rat models, according to in-vitro and in-vivo studies. However, this accelerating trend was only temporary, and it seemed to fade away over the next 2–3 weeks(36). An in vivo study revealed that a new PRF formulation (A-PRF, i-PRF) induced significantly higher growth factor release over time and had a steady release of growth factors up to about 1 week. For these reasons, we chose to use i-PRF in this study to reduce treatment time by increasing tooth movement(37). The rate of canine retraction between the two sides was not significantly different in the last month of the study period. Aboul-Ela et al reported that on the control side, the rate of canine retraction was significantly higher than on the experimental side(38).

CONCLUSION:

Even though all of the 4 studies included in this review reported significantly increased rate of tooth movement following administration of platelet rich derivatives, 1 study reported with high risk of bias and 3 studies reported unclear risk of bias, hence, the results should be interpreted with caution.

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Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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