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Do platelet concentrates accelerate orthodontic tooth movement?: a systematic review

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ABSTRACT

Purpose: Surgical techniques in orthodontics have received widespread attention in recent years. Meanwhile, biomaterials with high molecular content have been introduced, such as platelet concentrates (PCs), which may accelerate orthodontic tooth movement (OTM) and reduce periodontal damage. The present systematic review aimed to answer the following PICO question: "In patients in whom orthodontic surgical techniques are performed (P), what is the effectiveness of using PCs over the surgical site (I) when compared to not placing PCs (C) to achieve faster tooth movement (O)?"
Methods: A search was performed in 6 databases. The criteria employed were those described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses declaration. The present review included studies with a control group that provided information about the influence of PCs on the rate of OTM.
Results: The electronic search identified 10 studies that met the established criteria.
Conclusions: The included studies were very diverse, making it difficult to draw convincing conclusions. However, a tendency was observed for OTM to be accelerated when PCs were used as an adjuvant for canine distalization after premolar extraction when distalization was started in the same session. Likewise, studies seem to indicate an association between PC injection and the amount of canine retraction. However, it is not possible to affirm that the use of PCs in corticotomy shortens the overall treatment time, as this question has not been studied adequately.

Trial Registration: PROSPERO Identifier: CRD42021278542

Keywords: Orthodontics; Orthodontic space closure; Platelet-rich fibrin; Platelet-rich plasma; Tooth movement techniques

INTRODUCTION

Orthodontic treatment with fixed appliances lasts, depending on the severity of the malocclusion, more than 1 and a half years on average, with substantial variation among studies and reported treatment periods ranging from 14 to 33 months [1]. This often exceeds patients' expectations. For instance, when adolescent patients were asked how long they would like their orthodontic treatment to last, 40.8% said that they would prefer for it to last for less than 6 months and 33.2% indicated that their preference would be for a treatment duration between

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6 and 12 months. In contrast, 42.9% of adult patients asked the same question responded that they would prefer a period of 6 to 12 months, while 26.5% indicated a preference for 12 to 18 months [2]. Shorter treatment times would both increase patient satisfaction and reduce the risk of patient noncompliance and treatment-related complications, such as periodontal problems, root resorption, white spots, and carious lesions [3].

Surgical methods are the most commonly used techniques for accelerating tooth movement, since they hasten healing and enhance the progression of regional regeneration processes. This is known as the regional acceleratory phenomenon (RAP) [4-7]. In this regard, some procedures have been developed, such as tooth extraction, which both creates space and triggers the RAP [8], and periodontally accelerated osteogenic orthodontics (PAOO). PAOO includes bone corticotomy and bone grafting procedures [9], which shorten orthodontic treatment by improving bone remodeling, preserving the cortical bone or even increasing its thickness, and accelerating orthodontic tooth movement (OTM). Due to its benefits, the RAP has also been introduced for younger patients, such as adolescents [10].

Movement of the teeth with orthodontic forces depends on bone remodeling, which is associated with the activity of inflammatory markers, the quality and quantity of bone turnover, and the balance between osteoclastic and osteoblastic activity [11]. Therefore, OTM is an aseptic inflammatory process, consisting of an acute and then transitory chronic inflammation phase. The use of platelet concentrates (PCs), as biomaterials with high molecular content that promote bone regeneration, angiogenesis, and wound healing, may be of interest in orthodontics [12].

Many types of PCs have been described, and there has long been a lack of consensus regarding terminology. The current classification system is based on dividing the many available products into 2 main families: platelet-rich plasma (PRP) and platelet-rich fibrin (PRF). These families can then be subdivided based on their fibrin architecture and cell content into pure (P-PRP or P-PRF) or leukocyte-rich (L-PRP or L-PRF) formulations [13].

The present systematic review aimed to determine whether PCs are useful in orthodontics to achieve a faster OTM. The secondary objective was to determine how PCs influence other orthodontic and/or periodontal parameters.

MATERIALS AND METHODS

Protocol

This systematic review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14], and it was recorded in PROSPERO (registration number: CRD42021278542).

Focused question

The aim of this study was to answer the following PICO (P = population; I = intervention; C = comparison; and O = outcome) question:

> In patients in whom orthodontic surgical techniques are performed (P), what is the effectiveness of using PCs (I) when compared to not placing PCs (C) to achieve faster tooth movement (O)?

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The secondary objectives were to determine how PCs influence other orthodontic and/or periodontal parameters.

Eligibility criteria

Based on the study objectives, the eligibility criteria were predefined.

Inclusion criteria

The studies had to be investigations with a split-mouth design or control group versus an experimental group (PCs in RAP)—that is, 1) randomized clinical trials (RCTs), controlled clinical trials (CCTs), observational studies, multicenter studies, comparative studies or doctoral theses; 2) published in English or Spanish; and 3) performed only in humans. We also included studies in which bone substitutes were used, either in combination with PCs or as a control group. The following types of PCs were considered: PRF, PRP, L-PRF, L-PRP, A-PRF (advanced-PRF), P-PRF, P-PRP, and plasma rich in growth factors (PRGF). Procedures to trigger the RAP could be performed in any location of the mandible and/or the maxilla.

Exclusion criteria

The following studies were excluded: 1) studies that did not use PCs for the RAP, 2) experimental laboratory studies, 3) animal studies, 4) duplicate articles, 5) systematic reviews and meta-analyses; 6) book or chapters of books, 7) letters to the editor, 8) comments, 9) reviews, 10) case reports, 11) unpublished articles, and 12) articles whose main topic was not a comparison between PCs and other approaches for the acceleration of OTM.

Information sources and search strategy

A comprehensive search of the literature was conducted in the following databases: MEDLINE (via PubMed), Web of Science, Scopus, LILACS, and Google Scholar. A search for unpublished studies (the gray literature) was conducted in the OpenGrey database. The search was independently performed by 2 researchers (AOSP and SHL). It was not time-restricted and was updated to September 2021. Medical Subjects Headings (MeSH) terms, keywords, and other free terms were used with the Boolean operators (OR, AND) to combine searches, as follows: (corticotomy OR corticotomy orthodontic OR corticotomy assisted OR corticotomy assisted orthodontic OR corticotomy-facilitated orthodontics OR regional acceleratory phenomenon OR segmental corticotomy OR accelerated osteogenic orthodontics OR periodontally accelerated osteogenic orthodontics) AND (platelet concentrates OR platelet-rich fibrin OR PRF OR fibrin mesh OR platelet-rich plasma OR PRP OR leukocyte platelet-rich fibrin OR advanced platelet-rich fibrin OR A-PRF OR L-PRF OR leukocyte platelet-rich plasma OR L-PRP OR pure platelet-rich fibrin OR P-PRF OR pure platelet-rich plasma OR P-PRP OR plasma-rich in growth factors OR PRGF OR injectable platelet-rich fibrin OR i-PRF OR growth factors OR platelet-derived growth factors). The same keywords were used for all search platforms following the syntactic rules for each database.

Study records

Two researchers (AOSP and SHL) independently compared their results to ensure completeness and removed duplicates by using Covidence (an online tool that streamlines parts of the systematic review process). The full titles and abstracts of the remaining papers were then screened individually. Finally, the full-text articles to be included in this systematic review were selected according to the criteria described above. Disagreements on eligible studies to be included were discussed with a third researcher (JGJHS), and a consensus was reached. The reference lists of the included studies were also reviewed to identify other

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studies potentially meriting inclusion. Agreement between reviewers was measured with the kappa coefficient. The results were also expressed as the concordance between reviewers (%).

Risk of bias in individual studies

Data collection was conducted using a pre-determined table designed in advance of the assessment of the resulting articles. Two independent reviewers (AOSP and SHL) evaluated the methodological quality of eligible studies following the Joanna Briggs Institute (JBI) Critical Appraisal Tool for RCTs and Quasi-Experimental Studies (experimental studies without random allocation) [15], which incorporates 13 and 9 domains, respectively. The studies were assessed as low-quality (a score of 0–7 or 0–5, respectively) or as high-quality (8–13 or 6–9, respectively). When there were disagreements between the 2 reviewers, a third author (JGJHS) was involved.

RESULTS

Study selection

The search strategy resulted in 208 results, of which 194 remained after removing duplicates. Then, 2 independent researchers (AOSP and SHL) reviewed all the titles and abstracts and excluded 174 papers that were outside the scope of this review. Thus, we obtained 20 potential references. After reading the full texts of those 20 papers, 10 were discarded for not having a control group (n=1), for studying an irrelevant intervention (n=3), for having an inappropriate study methodology (n=1), for being case reports or case series (n=3), or for being reviews of the literature (n=2). Therefore, 10 studies were included in this systematic review (**Figure 1**)

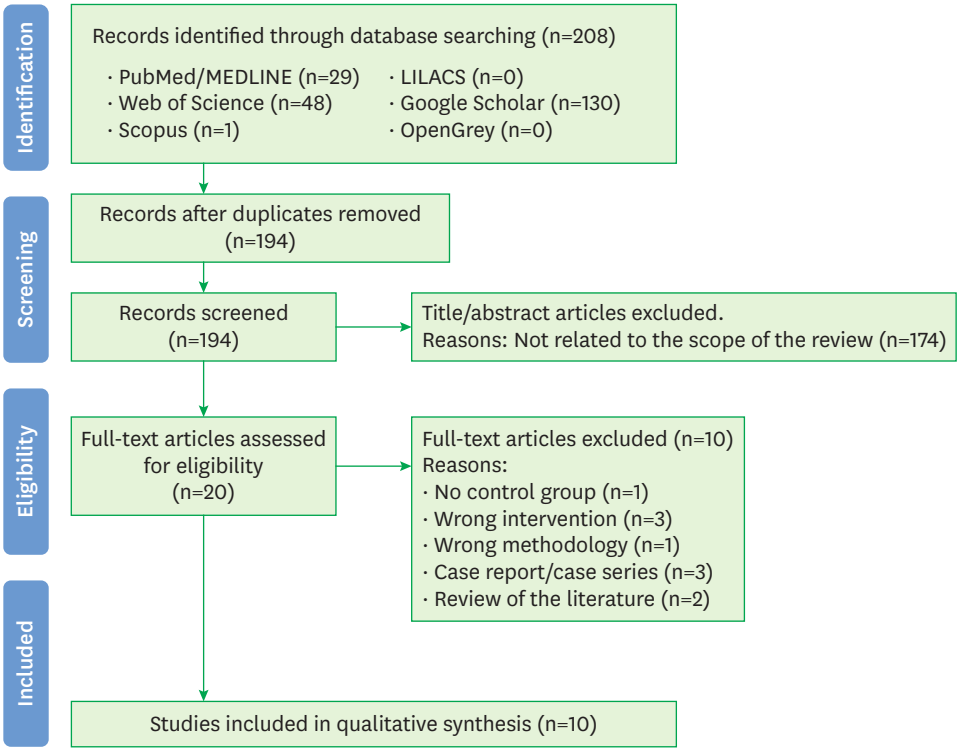

Figure 1. PRISMA flow diagram of the search processes and results.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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[7,9,11,12,16-21]. There was 90.81% concordance between the 2 authors (AOSP and SHL), with a kappa coefficient of 0.600 (standard error [SE]=0.09; 95% confidence interval [CI], 0.419–0.781) for titles and abstracts, and 95% concordance with a kappa coefficient of 0.898 (SE=0.099; 95% CI, 0.703–1.093) for full-text articles, respectively. Thus, the concordance was deemed to be good for titles and abstracts and very good for full-text articles.

PCs were used in 3 different ways: (1) over the buccal bone plate after corticotomy, and (2) for canine retractions, i) injected submucosally in liquid form, or ii) placed as a membrane in the alveolar socket after first premolar extraction. The main findings of each treatment modality are described below.

PCs in corticotomy

Study characteristics

Two CCTs published in 2019 [7] and 2020 [16] were included, with a mean follow-up of 6 months (**Table 1**). Neither studied the influence of PCs on the overall treatment time. Only Gonen et al. [7] (2019) compared the mean duration of treatment between both corticotomy patient groups and a retrospective group of patients who underwent non-extractive orthodontic treatment of class I malocclusion (11 months vs. 27.30 months, respectively; $P<0.001$). The primary outcome in both studies was the influence of a PC (specifically, PRF) on vestibular buccal bone thickness (BBT) and additionally, its influence on periodontal assessments. In both studies, PRF membranes were applied over the buccal plate in the test group versus a control group [7,16] and, in 1 of the studies, there was a second test group in which corticotomy was performed with a bone graft (BG) [7].

Patients' characteristics

Corticotomies were studied in class I patients with moderate crowding who had been previously treated without extractions [7] and in patients with maxillary protrusion who needed extraction of the maxillary first premolars [16]. These studies included a total of 50 patients. Twenty patients were controls (40%), 20 patients were treated with corticotomy +

Table 1. Results from studies in which PCs were used over the buccal bone plate after corticotomies

Author(s)	Year	Type of study	Sample size (patients)		Age (yr)	Sex	Follow-up (mo)	Malocclusion	Type of PC	Protocol	Surgical procedure		Overall treatment time
			PCs	Non-PCs							Control group	Test group	
Ahmed et al. [16]	2020	CCT	10	10	18–25	Female (n=20)	6	Maxillary protrusive patients which needed extraction of maxillary 1st PMs	PRF membranes	UNS	Piezocision guided by 3D surgical template	Piezocision guided by 3D surgical template. A bovine xenograft (400–800 μm) was mixed with plasma. A PRF membrane was attached underneath the mucosa.	Not studied by the authors.
Gonen et al. [7]	2019	CCT	10	10 BG, 10 control group	15.17	Female (n=24), Male (n=6)	6	Class I patients with moderate crowding who were previously treated without tooth extractions	PRF membranes	2,700 rpm, 12 min	Flapless corticotomy	Flapless corticotomy + BG Flapless corticotomy + PRF membranes	Mean treatment time was significantly lower in corticotomy patients vs. the own historic group of patients who underwent non-extraction orthodontic treatment (11 mo vs. 27.3 mo, respectively; $P<0.001$).

PC: platelet concentrate, CCT: controlled clinical trial, PMs: premolars, PRF: platelet-rich fibrin, UNS: unspecified by authors, BG bone graft, rpm: revolutions per minute.

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PRF alone (n=10 patients; 20%) or combined with BG (n=10 patients; 20%), and 10 patients (20%) were treated with corticotomy + BG [7]. The maxillary arch was studied in the first study [7], and both arches were studied by Ahmed et al. [16]. Forty-four patients were female (88%) and 6 were male (12%). The mean age was 15.17±0.17 years in the study of Gonen et al. [7], while Ahmed et al. presented an age range of 18 to 25 years [16].

PC types and protocols

Both studies used PRF membranes. The PRF protocol was described only by Gonen et al. [7]; in their study, the blood samples were centrifuged at 2,700 revolutions per minute (rpm) for 12 minutes. Neither study specified how many PRF membranes were used.

Surgical technique

The surgical technique differed between these 2 studies. Gonen et al. [7] elevated mucoperiosteal flaps to perform combined vertical and horizontal corticotomies. The patients' samples were divided into 3 groups: in group 1 (control), only corticotomies were performed (n=10); in group 2, a bovine-derived hydroxyapatite ceramide BG (0.5–1 mm granule size) mixed with 1 ampule of clindamycin was applied (n=10); and in group 3, PRF membranes were applied to the corticotomy region (n=10). In contrast, Ahmed et al. [16] used a flapless technique and performed only vertical corticotomies. Their patient sample was divided into 2 groups: group 1 (control) treated with piezocision corticotomy alone (n=10); and group 2 (test) treated with corticotomy and BG (bovine xenograft [400–800 μm particle size] + plasma) protected with PRF membranes underneath the mucosa, over the alveolar buccal plate (n=10).

Periodontal assessments

1. BBT

Comparing BBT between the studies was difficult given their heterogeneity. Both studies used measurements of sagittal cone-beam computed tomography (CBCT) views. Ahmed et al. [16] measured BBT in millimeters, while Gonen et al. [7] calculated changes in square pixels (px^2).

The BBT in the maxilla was studied by both authors. Gonen et al. [7] reported an increase in BBT in the control (1,356.90±3,412.48 px^2) and both test groups (corticotomy + BG=12,607.10±7,647.85 px^2; corticotomy + PRF=6,159.20±908.35 px^2) compared with the baseline. This increase was significantly higher in both test groups versus the control group (P<0.05 and P=0.0004, respectively), and a significant difference was also found between the test groups (P<0.05). Ahmed et al. [16] measured BBT at 3, 6, and 9 mm from the cementoenamel junction (CEJ) in CBCT sagittal views. Mean BBTs of 0.93±0.047 mm at baseline, and 0.73±0.094 mm at 6 months (P<0.05) were observed in the control group; therefore, the associated bone loss was −0.20 mm. In the test group, an increase of +0.42 mm was observed. In this group, the BBT was 0.95±0.150 mm at baseline and 1.37±0.27 mm at 6 months (P<0.05).

Gonen et al. [7] studied the BBT in the mandible only. They observed bone loss at the end of treatment compared with baseline in the control group (−1,349.30±2,255.33 px^2). The greatest increase in BBT occurred in the group in which corticotomy + BG was performed (14,536.80±8,704.54 px^2), followed by the corticotomy + PRF group (5,774.20±2,744 px^2). These differences were statistically significant between all groups (P<0.05).

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2. Plaque index
The plaque index was only studied by Gonen et al. [7]. The plaque index score of the patients significantly increased from baseline to 6 months and the end of orthodontic treatment in the control group (corticotomy alone) and both test groups (corticotomy + PRF, and corticotomy + BG).

3. Pocket depth (PD)
PD was assessed in both studies [7,16]. In Gonen et al. [7], a significant increase in the control group at 6 months and at the end of treatment was observed compared with baseline. In the 2 test groups, a significant increase in PD was observed at 6 months compared with baseline, but at the end of orthodontic treatment, the PD scores were similar to baseline. Ahmed et al. [16] observed a significant reduction in the PD in the control group and in the test group (corticotomy + PRF + BG). These scores were 2.50±1.00 mm at baseline and 1.70±0.92 mm at 6 months (P=0.015), with a PD reduction of 0.8 mm. In the test group, PD was 2.90±0.98 mm at baseline and 2.00±0.32 mm at 6 months (P=0.015), for a PD reduction of 0.90 mm. The difference in PD reduction between the groups was not statistically significant (P>0.05).

4. Bleeding on probing (BP)
BP was examined by both studies [7,16]. Although the BP score significantly increased 6 months after orthodontic treatment when compared with baseline, there was no significant difference between the BP score at the end of orthodontic treatment compared with baseline in the control group. The BP score significantly increased in the corticotomy + BG group at 6 months and at the end of orthodontic treatment when compared with baseline [7]. The BP score significantly increased in the PRF group at 6 months of orthodontic treatment when compared with baseline.

Meanwhile, Ahmed et al. [16] did not observe significant differences in BP in the control group between baseline and the end of treatment (at 6 months), while the corticotomy + PRF + BG group showed a significant decrease (control: 0.30±0.81 and 0.25±0.78; P=0.726 vs. test: 0.30±0.57 and 0.16±0.40; P=0.01, respectively).

5. Width of the keratinized gingiva (KG)
The width of the KG was only studied by Gonen et al. [7]. In the control group and in the corticotomy + BG group, the widths of KG at the upper and lower incisor teeth were significantly lower at the end of treatment than at baseline. In the PRF group, however, no statistically significant difference was observed in the width of KG over time. The width of KG in the upper incisor area was significantly lower in the corticotomy + BG group than in the corticotomy + PRF group (P=0.04).

PCs for canine retractions: PCs in post-extraction sockets

Study characteristics
Two RCTs [19,20] and 1 CCT [18] with a split-mouth design (1:1) published in 2018 (n=2) [18,20] and 2020 (n=1) [19] were included. The follow-up periods were 4 [20], 5 [19], and 6 months [18] (**Table 2**).

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Table 2. Results from studies in which PCs were placed in alveolar sockets

Author(s)	Year	Type of study	Sample size (patients/ sockets)	Age (yr)	Sex	Follow-up (mo)	Malocclusion	Orthodontic treatment	Type of PC	Protocol	Retraction rate			Comments
											Control side	Test side	*P*-value	
Reyes Pacheco et al. [19]	2020	Split-mouth RCT (1:1)	17/42	33 (20–45)	Female (n=12), Male (n=5)	5	Class I (n=14) or Class II division 1 (n=3) requiring extraction of maxillary 1st PMs.	15 days after 1st PM extractions, a 0.008-in ligature wire was placed from the 1st M to the 2nd PM as an anchor unit. The distalization of the canines were performed using the 0.020-in SS archwire. All the arches had an omega loop mesial to the 2nd M and were tied back. Elastic chains were placed between the 2nd PM and the canine to apply a force of 150 g.	L-PRF membranes	2,700 rpm for 14 min	0.90 mm/mo (0.44–1.16)	0.67 mm/mo (0.40–0.88)	0.004[a]	None.
Nemtoi et al. [18]	2018	Split-mouth CCT (1:1)	20/40	16.43 (12–20)	Female (n=11), Male (n=9)	6	Severe crowding of protrusion requiring maxillary 1st PMs extractions	After extraction of 1st PMs, the teeth adjacent to the defect were pulled together by a Ni-Ti closed-coil spring with constant level of force. A piece of 0.016×0.022-inch SS wire was used as the main arch wire.	PRF plug	2,700 rpm for 12 min	0.32 mm/mo	0.52 mm/mo	0.006[a]	None.
Tehranchi et al. [20]	2018	Split-mouth RCT (1:1)	8/30	17.37±12.48 (12–25)	Female (n=3), Male (n=5)	4	Severe crowding of protrusion requiring 1st maxillary and/or mandibular PM extractions	After 1st PM extractions, the teeth adjacent to the socket were pulled together by a Ni-Ti closed-coil spring with a constant level of force. A piece 0.016×0.022-inch SS wire was used as the main arch wire.	L-PRF membranes	2,700 rpm for 12 min	Upper arch: 6.96±0.695 mm (1.74 mm/mo) Lower arch: 6.58±0.819 mm (1.65 mm/mo)	Upper arch: 6.76±0.538 mm (1.69 mm/mo) Lower arch: 6.56±1.06 mm (1.64 mm/mo)	0.558 0.969	In spite of a lack of StS differences in overall retraction rate, in all time points the mean linear measurements between mid-marginal ridges of teeth adjacent to extraction sides were less in L-PRF group vs. control (*P*=0.006[a])

PC: platelet concentrate, RCT: randomized clinical trial, CCT: controlled clinical trial, PMs: premolars, M: molars, UNS: unspecified by authors, rpm: revolutions per minute, Ni-Ti: nickel-titanium, SS: stainless steel, L-PRF: leukocyte-rich platelet-rich fibrin, StS: statistically significant.
[a]Statistically significant difference compared to the baseline.

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Patient characteristics

In total, 45 patients and 112 sockets were studied. Twenty-six female patients (57.78%) and 19 male patients (42.22%) were included. The mean ages of the patients included in the studies were 16.43 years (range 12 to 20 years) [18], 33 years (20–45) [19], and 17.37±12.48 years [20].

In 2 studies, the treatment was performed only in the maxilla [18,19]. Tehranchi et al. [20] assessed both the maxillary and mandibular arches in 7 patients and only the mandibular arch in 1 patient.

The studies focused on patients with severe crowding and/or upper incisor protrusion requiring first premolar extraction (28 patients [62.22%]; 70 sockets [62.50%]) [18,20] and patients with class I or class II division 1 requiring extraction of the maxillary first premolars (17 patients [37.78%]; 42 sockets [37.50%]). All first premolars extracted were maxillary, except in 1 study [20], in which maxillary and mandibular first premolars were extracted in 7 patients, while in 1 patient, only the mandibular first premolars were extracted.

PC protocols

All 3 studies used PRF. The manufacturing protocols described for producing it were 2,700 rpm centrifugation for 12 minutes [18,20] or 14 minutes [19]. PRF was used to fill post-extraction sockets on the test sides in the form of plugs [18] or membranes [19,20].

Rate of canine retraction

In studies where canine distalization was started immediately after first premolar extraction, the canine retraction rate was higher in the PRF groups than in controls [18,20]. Nemtoi et al. [18] reported retraction rates of 0.52 and 0.32 mm/month, respectively (P=0.006). Tehranchi et al. [20] observed that, in all follow-up visits (every 2 weeks for 4 months), the mean linear measurements between the mid-marginal ridges of teeth adjacent to the extraction sites were lower in the PRF group than in the control group, meaning that the teeth moved faster than they did on the control sides (P=0.006). Contrarily, Reyes Pacheco et al. [19] found a significantly higher canine retraction rate on the control sides (0.23 mm/month), but they started canine distalization 15 days after first premolar extraction (control sides: 0.90 mm/month [0.44–1.16]; L-PRF sides: 0.67 mm/month [0.40–0.88]; P=0.004). At 5 months, a difference of 1.20 mm favoring the control sides was observed.

Other parameters

1. Canine rotation/inclination

This parameter was evaluated only by Reyes Pacheco et al. [19]. The mean canine inclination on the test side was 5.80°, whereas on the control side it was 8.50° (P=0.001). Thus, there was more retroclination of the canine on the test side (PRF) at the end of distalization.

2. Buccal bone density (BBD)

This parameter was assessed only by Nemtoi et al. [18], using CBCT examinations at 2 months after the extraction of each maxillary first premolar. BBD was classified into 4 groups: D1, homogeneous cortical bone with bone density of more than 1,250 Hounsfield units (HU); D2, thick cortical bone with marrow cavity (850–1,250 HU); D3, thin cortical bone with dense trabecular bone of good strength (350–850 HU); and D4, very thin cortical bone with low-density trabecular bone of poor strength (less than 350 HU). D1 was observed on 14 test sides (70%) and 9 control sides (45%); D2 on 3 (15%) versus 5 (25%) sides, respectively; D3 on 2 (10%) versus 2 (10%) sides; and D4 on 1 (5%) vs. 4 (20%) sides. They

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concluded that, after 2 months, improved bone regeneration was observed in patients who received PRF in the extraction socket.

PCs for canine retractions: injection of PCs

Study characteristics

All 5 included studies were comparative split-mouth RCTs that compared submucosally injected PCs [9,11,12,17,21]. One study evaluated PC injection and/or piezocision on the test sides, while in both groups the other side of the maxillary arch served as a control. This can be considered a double split-mouth RCT [17]. All of these studies were published in 2021 (n=4) [11,12,17,21] or 2020 (n=1) [9]. Two studies were published by the same research group using the same patients, but each study analyzed different outcomes [12,21]. If those are considered a single study, 80 patients were included in these studies, with mean follow-up periods of 3 [11,17], 4 [9], and 5 months [12,21] (**Table 3**).

Patient characteristics

Patients with class II division I malocclusion requiring first premolar extraction [11,12,21] or with severe/moderate crowding or protrusion requiring first premolar extraction were included [9,17]. The mean ages of the included patients were 18.00±3 years [9], 20.85±3.85 (range, 16–28 years) [12,21], 21.40±2.90 years [11], and 16.45±0.27 years in the PRF group and 16.84±0.33 years in the piezocision group [17]. Fifty-six patients were female (70%) and 24 were male (30%).

PC protocols

In 4 of the 5 included studies, injected PRF (i-PRF) was used [11,12,17,21]. Only El-Timamy et al. [9] used injected PRP. Only i-PRF protocols were described: 700 rpm for 3 minutes [11,12,21] or 800 rpm for 3 minutes [17]. After centrifugation, the yellow-orange top portion of the tube was collected to obtain i-PRF. In studies where i-PRF was used, it was injected intraligamentarily [11] or infiltratively [12,17,21] through the attached gingiva. El-Timamy et al. [9] injected PRP intraligamentarily and infiltratively. A total of 0.25 mL of PRP was injected [9] versus 2.50 to 4 mL of i-PRF [11,12,21]. The number of injections was 2 [11,12,21] to 3 [17] for i-PRF and 5 for PRP [9]. Moreover, the PC injections were repeated 2 [11,12,21] to 3 times [9,17]. Only 2 studies injected a placebo on the control side [9,11]. A more detailed description is presented in **Table 4**.

Rate of canine retraction

This parameter was assessed by all 5 studies [9,11,12,17,21], and all of the studies reported an increase in the canine retraction rate. Erdur et al. [11] and Çağlı Karcı and Baka [17] found a statistically significant increase in the canine retraction rate in the i-PRF group compared with the control group (6.06±0.29 mm vs. 3.89±0.34 mm; P=0.001 [11] and 3.47±0.25 mm vs. 2.73±0.25 mm; P=0.49 [17], respectively). In both studies, the i-PRF injections were started immediately after first premolar extractions and were repeated at 2 weeks [11] or at 4 and 8 weeks [17]. In the other studies, specifically those of Zeitounlouian et al. [12,21] and El-Timamy et al. [9], an increase in the canine retraction rate was observed in the test group compared with the control group, but without significant differences (23.89±7.04 mm vs. 22.83±6.71 mm; P=0.0655 [12,21] and 4.57±1.32 mm vs. 4.53±1.12 mm; P=0.895 [9], respectively). In these studies, PC injections (i-PRF [12,21] and PRP [9]) were started 2 weeks after the premolar extractions and were repeated at 3 [9], 4 [12,21] or 6 weeks [9]. The amount of closure of the extraction diastema was statistically significantly greater with the use of PCs in all studies. El-Timamy et al. [9] observed that, at the third month, a statistically

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Table 3. Characteristics from studies in which PCs were injected for canine distalization

Author(s)	Year	Type of study	Sample size (patients)	Age (yr)	Sex	Follow-up (mo)	Malocclusion	Orthodontic treatment	Type of PC	Protocol
Erdur et al. [11]	2021	Split-mouth RCT (1:1)	20	21.40±2.90	Female (n=12), Male (n=8)	3	Class II division I malocclusion requiring maxillary 1st PM extractions	Microscrews were placed bilaterally between maxillary 2nd PMs and 1st Ms for skeletal anchorage. Then, 1st PMs were extracted and canine distalization was conducted using 150 g Ni-Ti closed-coil springs.	i-PRF	700 rpm, 3 min The contralateral side received an injection of a placebo.
Zeitounlouian et al. [12,21]	2021	Split-mouth RCT (1:1)	21	20.85±3.83 (range 16–28)	Female (n=15), Male (n=6)	5	Class II division I malocclusion requiring maxillary 1st PM extractions	Maxillary 1st PM were extracted, and a transpalatal arch was inserted to preserve the transverse dimension. 15 days after 1st PMs extraction, canine distalization was conducted using a 150 g Ni-Ti closed-coil springs along with i-PRF injections.	i-PRF	700 rpm, 3 min
Çağlı Karcı and Baka [17]	2021	Double split-mouth RCT	24 PRF group (n=12), piezocision group (n=12)	16.45±0.27 in PRF group; and 16.84±0.33 in piezocision group.	Female (n=14), Male (n=10)	3	Class II with dentoalveolar protrusion or moderate crowding, requiring maxillary 1st PM extractions	Miniscrews (1.6×10 mm) were placed bilaterally between maxillary 2nd PMs and 1st Ms for skeletal anchorage. After PMs extraction, canine distalization was conducted using 150 g Ni-Ti closed-coil springs along with i-PRF injections.	i-PRF	800 rpm, 3 min
El-Timamy et al. [9]	2020	Split-mouth	15	18±3	Female (n=15)	4	Severe crowding of protrusion requiring maxillary 1st PM extractions	Two mini-screws (1.6×8 mm) were placed bilaterally between the maxillary 2nd PMs and 1st Ms for skeletal anchorage. Ni-Ti closed-coil springs delivering a retraction force of 1.5 N[12] following the injection of the PRP on the test side.	PRP	Double-spin technique. After PRP injection, the same volume of 10% $CaCl_2$ solution was injected for PRP activation. The control side received an injection of a placebo.

PCs: platelet concentrates, RCT: randomized clinical trial, PMs: premolars, M: molars, rpm: revolutions per minute, Ni-Ti: nickel-titanium.

Table 4. Canine retraction rates from studies in which PCs were injected

Author(s)	Year	Type of PC	PC injection route	Localization of the injections	Timing of PC injection						When was canine distalization started in reference to 1st PM extractions?	Overall retraction rate			Comments
					Immediately after 1st PM extraction	2 wk	3 wk	4 wk	6 wk	8 wk		Control side	Test side	*P*-value	
Erdur et al. [11]	2021	i-PRF	IL	Distobuccal (2 mL) and distopalatal (2 mL) of the canine	X	X					Immediately	3.89±0.34 mm	6.06±0.29 mm	0.001[a]	Mean movement increased significantly in weeks when the i-PRF was applied
Zeitounlouian et al. [12,21]	2021	i-PRF	IF through attached gingiva	Buccal (2 mL) and palatal (1 mL) equidistant from canine and 2nd PM		X		X			15 days after	22.83±6.71 mm	23.89±7.04 mm	0.655	The rates of canine retraction were only StS in the test sides vs. control sides at the 2nd mo (1.5 times greater). Greater movement was also observed on the test side at 4th (23%) and 5th mo (25%) ($P>0.05$[a]).
Çağlı Karcı and Baka [17]	2021	i-PRF	IF through attached gingiva	Buccal, palatal and distal (2.5 mL) of maxillary canine	X			X		X	Immediately	2.73±0.25 mm	3.47±0.25 mm	0.049[a]	The amount of closure in the extraction space was StS greater in test sides than in control sides in the first 2 wk and in the overall treatment time.
El-Timamy et al. [9]	2020	PRP	IL and IF	IL in the middle (0.05 mL), buccal (0.05 mL) and palatal (0.05 mL) areas of the distal surface of the canine + IF injections buccally (0.05 mL) and palatally (0.05 mL)		X	X		X		15 days after	4.53±1.12 mm	4.57±1.32 mm	0.895	An StS increase in the rate of canine retraction in test sides was only observed during the 1st mo (a 15% increase), concomitant with PRP injections). But PRP did not exhibit long-term acceleration effects.

PCs: platelet concentrates, PMs: premolars, i-PRF: injected platelet-rich fibrin, IL: intraligamentary, IF: infiltrative, UNS: unspecified by authors, StS: statistically significant difference compared to the baseline.
[a]Statistically significant difference compared to the baseline.

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significant difference between the test and control sides (P=0.020) was seen. Greater closure was observed on the control sides, with a mean value of 1.01±0.63 mm/month compared with 0.59±0.96 mm/month for the PRP sides, reflecting a deceleration in the rate of tooth movement on the intervention side following cessation of PRP injections (the movement was 40% slower in the PRP side).

In addition to investigating the effect of PRF on the canine retraction rate, the effect of piezocision was also studied in the double split-mouth RCT by Çağlı Karcı and Baka [17]. These authors observed that both test sides (i-PRF and piezocision) exhibited greater canine retraction movement than the control sides (P<0.05); however, there was no significant difference between the 2 test sides (P=0.686).

Overall treatment duration

Treatment duration was assessed by 2 groups (the same studies as above) [12,21]. The overall duration of canine retraction did not differ significantly between the experimental (3.28±1.00 months) and control (3.57±1.16 months) sides. Canine distalization and i-PRF injections were started 2 weeks after first premolar extraction.

Canine rotation/inclination

This parameter was assessed by 3 studies [9,17,21]. The differences in canine rotation were statistically non-significant between the test (PC) and control sides in all studies [9,17,21]. El-Timamy et al. [9] found that canine distal-in rotation was comparable between the test and control groups, with a mean difference of 1.036°. Çağlı Karcı and Baka [17] found that there were no statistically significant differences between the differently treated test sides (i-PRF and piezoincision) or between the test and control sides. In detail, the amount of canine rotation was 2.67°±2.84° in the i-PRF group and 3.91°±2.21° on the control side (P=0.175), while it was 2.33°±0.75° in the piezocision group and 3.68°±0.54° on the corresponding control side (P=0.065).

Anchorage loss

Anchorage loss was assessed by 2 studies [17,21]. The differences in anchorage loss were statistically insignificant between both groups [21]. El-Timamy et al. [9] did not measure this parameter, but in their study, the first molars were anchored to two mini-screws inserted in the interradicular region between the upper second premolars and first molars on each side. Çağlı Karcı and Baka [17] also anchored the first molars with miniscrews, but they recorded the amount of molar mesial movement. Statistically significant differences were not found between the experimental and control sides in both groups, or between the 2 experimental sides (P=0.562) or the 2 control sides (P=0.326) in a 12-week follow-up period. On the i-PRF side, the amount of mesial molar movement was 0.64±0.05 mm, and on the control side, it was 0.68±0.08 mm (P=0.931). On the piezocision side, the anchorage loss was 0.65±0.08 mm, while on the control side, it was 0.79±0.07 mm (P=0.126).

Postoperative morbidity

This parameter was assessed by El-Timamy et al. [9] In their study, none of the patients—regardless of whether they received PRP injections or placebo injections—reported using analgesics. An increase in pain scores evaluated with a visual analogue scale (VAS) was reported in the first, fourth, and seventh weeks following each injection in both groups.

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Buccal and palatal bone crest height

This parameter was assessed only by Zeitounlouian et al. [12]. The bone crest level was measured on the buccal and palatal aspects of the retracted canine. The differences in buccal and palatal bone crest height were not statistically significant between the experimental (i-PRF) and control sides (−0.05±0.64 mm and −0.13±0.91 mm, respectively; $P>0.05$), although the reduction in height was greater on the test side and for palatal crest height, compared with the control side (test side: buccal alveolar bone crest height [BABH] changes= −0.09±0.44 mm, and palatal alveolar bone crest height [PABH] changes= −0.25±0.89 mm; control side: BABH changes= −0.03±0.44 mm, and PABH changes= −0.12±0.52 mm).

Bone thickness

Bone thickness was evaluated by Zeitounlouian et al. [12]. Buccal and palatal bone thickness was measured perpendicular to the long axis from the root surface to the corresponding buccal and palatal alveolar bone plate at 3 and 6 mm from the CEJ. The differences in bone thickness between the test (i-PRF) and control sides at both levels were not statistically significant at 5 months. Dehiscence was more prevalent in both groups postoperatively on the buccal and palatal aspects, while fenestrations were observed only at the buccal aspect on both the experimental and the control sides.

Pocket depth, plaque index, and bleeding on probing

These periodontal assessments were evaluated pre- and post-treatment by Çağlı Karcı and Baka [17]. The authors did not observe significant differences between the experimental (i-PRF or piezocision) and control sides in either group or between the 2 experimental sides.

Risk of bias within studies

Using the methodological quality assessment for RCTs and quasi-experimental studies (non-randomized experimental studies) according to the JBI Prevalence Critical Appraisal Tool [15], we determined that all included papers were of high quality (8–13 domains [9,11,12,17,19-21] or 6–9 domains [7,16,18]) (**Tables 5** and **6**).

Table 5. JBI Critical Appraisal Checklist for randomized controlled trials [13]

Parameters	Reyes Pacheco et al. [19] (2020)	Tehranchi et al. [20] (2018)	Erdur et al. [11] (2021)	Zeitounlouian et al. [12] (2021)	Zeitounlouian et al. [21] (2021)	Çağlı Karcı and Baka [17] (2020)	El-Timamy et al. [9] (2020)
1. Was true randomization used for assignment of participants to treatment groups?	?	+	+	+	+	+	+
2. Was allocation to treatment groups concealed?	+	+	?	+	+	?	+
3. Were treatment groups similar at the baseline?	+	+	+	+	+	+	+
4. Were participants blind to treatment assignment?	−	−	+	−	−	−	+
5. Were those delivering treatment blind to treatment assignment?	−	−	−	−	−	−	−
6. Were outcomes assessors blind to treatment assignment?	?	?	?	+	+	?	?
7. Were treatment groups treated identically other than the intervention of interest?	+	+	+	+	+	+	+
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	+	+	+	+	+	+	+
9. Were participants analyzed in the groups to which they were randomized?	●	●	●	●	●	●	●
10. Were outcomes measured in the same way for treatment groups?	+	+	+	+	+	+	+
11. Were outcomes measured in a reliable way?	+	+	+	+	+	+	+
12. Was appropriate statistical analysis used?	+	+	+	+	+	+	+
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	+	+	+	+	+	+	+

+: yes, −: no, ?: unclear, ●: not applicable.

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Table 6. JBI Critical Appraisal Checklist for quasi-experimental studies (non-randomized experimental studies) [13]

Parameters	Ahmed et al. [16] (2020)	Gonen et al. [7] (2019)	Nemtoi et al. [18] (2018)
1. It is clear in the study what is the "cause" and what is the "effect" (i.e., there is no confusion about which variable comes first)?	+	+	+
2. Were the participants included in any comparison similar?	+	+	+
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	+	+	+
4. Was there a control group?	+	+	+
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	+	+	+
6. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	+	+	+
7. Were the outcomes of participants included in any comparisons measured in the same way?	+	+	+
8. Were outcomes measured in a reliable way?	+	+	?
9. Was appropriate statistical analysis used?	+	+	+

+: yes, -: no, ?: unclear.

DISCUSSION

In recent decades, the treatment of patients in several dental specialties has been improved with the discovery of PCs. With this goal, PCs have also been introduced recently in orthodontics. It has been hypothesized that the anti-inflammatory properties of PCs may reduce the rate of OTM because OTM relies on inflammation [19]. In addition, PCs contain growth factors such as transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), epidermal growth factor, insulin-like growth factor (IGF), platelet-derived endothelial cell growth factor, and vascular endothelial growth factor. Their presence may influence the balance between osteoblasts and osteoclasts, decreasing turnover and inducing bone formation [19]. TGF-β stimulates the proliferation of osteoblasts and osteoprotegerin and collagen synthesis in favor of bone formation [22,23]. Meanwhile, TGF-β decreases the action of osteoclasts and thus bone resorption, which is necessary for OTM to occur. This may explain why in some studies mentioned above, the rate of tooth movement decreased on the side where alveolar treatment with PCs was used [19]. Despite these data, the present systematic review suggests that PCs accelerate overall treatment time in canine retractions. It is not possible to assume that this result is also applicable to corticotomy, given that this has not been studied yet. Reinforcing these findings, some authors have stated that PCs increase OTM velocity [24-26]. As mentioned in PRP studies, PRF can also promote inflammatory and anti-inflammatory responses, and their precise effect could be closely related to the timing of growth factor release and the concentration and content of the growth factors [27]. Many growth factors, cytokines, and enzymes contained in PCs might demonstrate anti-inflammatory effects responsible for improved tissue healing capacity, while at the same time, many cytokines, such as tissue necrosis factors, might aggravate the inflammatory response and lead to accelerated OTM [28]. Liou [24] reported that injections of submucosal PRP accelerated OTM by stimulating the bone damage mechanism without surgical intervention and alveolar bone loss, while Güleç et al. [25] reported that the PRP injection technique might accelerate OTM by decreasing alveolar bone density.

PRP and PRGF are defined as substances containing a high concentration of autologous platelets in a small volume of plasma. They contain large amounts of platelets, growth factors, and coagulation factors [29]. In contrast, PRF has been defined as a second-generation PC that does not require the addition of any platelet-activating substances (e.g., bovine thrombin or calcium chloride), unlike PRP or PRGF [13]. In other words, glass tubes can be used without any additives. In all included studies, PRF was preferred over PRP or

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PRGF, except in 1 study where i-PRP was used [9]. The reason for this is that the growth factors contained in PRP/PRGF are released very quickly and, as a result, thrombin may exert a toxic effect on surrounding tissues. Although the growth factors contained in PRP/PRGF and PRF are similar in quantity, the growth factors contained in PRF are released more slowly [30]. Furthermore, the growth factors contained in PRF (PDGF, TGF-β, and IGF-1) enrich the blood clot formed after surgery and subsequently enhance wound healing and bone regeneration, with no inhibitory effect on the natural healing process [31,32].

PCs in canine distalization have been used as injections or placed in post-extraction sockets. In both approaches, a key factor for achieving faster OTM was to use PCs together with first premolar extraction, immediately after the start of canine distalization [11,17,18,20]. This is in line with the results obtained by Yuan et al. [31] regarding the best time to start OTM into extraction sites. They concluded that orthodontic retraction should be initiated at an early stage after tooth extraction to take optimal advantage of bone remodeling at extraction sites. Both the resorptive and the formative parameters over time were manifested by a peak at day 7 after tooth extraction.

Reyes Pacheco et al. [19] reported a statistically significant higher canine retraction rate on the control sides than on the test sides, but canine distalization started 15 days after extraction. Likewise, Zeitounlouian et al. [12,21] and El-Timamy et al. [9] reported a higher retraction rate on the test sides than on the control sides, but without statistically significant differences. A point of concordance between both studies is that canine distalization started 15 days after the first premolar extraction.

A direct association was observed between the amount of canine retraction and PC injections [9,11,12,17,21]. In this regard, *in vitro* and *in vivo* studies have shown that the release of growth and healing factors peaks at around 7 days after buccal vestibular mucosal injection in rat models [25,33]. However, this acceleratory effect is transient and seems to decrease over the next 2–3 weeks. This pattern is in accordance with Tehranchi et al. [20], who found that the total amount of tooth movement in the experimental group was significantly higher on days 14 and 28.

Çağlı Karcı and Baka [17] conducted a double split-mouth RCT evaluating the effects of local PRF injections and piezocision techniques on canine distalization and comparing these effects with each other and the control group. They found that the total amount of space closure was significantly greater on the test sides than on the control sides, but without statistically significant differences between the PRF and piezocision experimental sides. Taking these findings into account, PRF injections may be preferred over piezocision to accelerate OTM because the former is a less invasive method than piezocision. Considering this, Munoz et al. [34] performed corticotomies in 11 patients, combining a BG with 3–4 L-PRF membranes over the surgical site. All patients experienced accelerated flap healing with no signs of infection or adverse reactions. No severe pain was reported; there was no need for analgesics for more than 6 days, and inflammation was mild in 89.90% of the patients. The main limitation of that study was the absence of a control group.

In addition to the above-mentioned advantages, PC membranes supply additional stability in corticotomy and, in combination with BG, provide protection against exposure and contamination [34]. Other benefits are a significant increase in BBT when PCs are used alone.

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Gonen et al. [7] reported a significant increase in BBT in the PRF group and the BG group versus the control group, as well as between test groups, favoring BG alone. Furthermore, it has been reported that PCs and BG can be used together with optimal results [16]. The presence of a transitory matrix of PCs around particulate BG facilitates cellular migration throughout the fibrin network into the regenerative sites, as well as the development of neoangiogenesis and vascularization, promoting the healing of the site [35]. The sponge-like architecture of the PC membranes provides an ideal scaffold for free cell migration into the surgical site, while the release of growth factors for up to 28 days post-surgery provides the continuous long-term stimuli required for chemotaxis and the osteogenic differentiation of osteoblasts, periodontal ligament cells, and bone marrow mesenchymal stem cells [36]. An added advantage is that not using BG simplifies and reduces the cost of the technique.

In canine distalization, filling a post-extraction socket with PCs causes neovascularization to occur through the PC clot, leading to the development of an epithelial covering. Despite the infectious and inflammatory potential of extraction sockets, rapid healing of the wound occurs without pain, swelling, and other attending signs of inflammation and infectious processes. In addition, this technique seems to reduce alveolar ridge resorption following tooth extractions [18]. A reason for this may be that TGF-β, which is present in PCs, stimulates the proliferation of osteoblasts and osteoprotegerin and collagen synthesis, favoring bone neoformation [22,23].

This systematic review presents several strengths, such as previous registration of the protocol, an unrestricted search of the literature (including the gray literature), a clear process of searching for studies, and the fact that data extraction and risk analysis bias were performed in duplicate. The overall quality of the included studies was deemed to be high. However, a limitation may be the availability of few studies in the literature and the heterogeneity of those studies, which makes it difficult to compare them.

Further studies should specifically investigate the overall treatment time, comparing the use of PCs alone and in combination with BG in corticotomy, compared with BG + corticotomy and a control group. It may also be interesting to investigate whether PCs reduce the need for post-surgical non-steroidal anti-inflammatory drugs, the effect of combining PC injections and PC membranes in fresh extraction sockets, and the effect of repeated injections of PCs throughout the course of canine retraction to maintain a steady rate of accelerated OTM.

In conclusion, the studies included in this review were very diverse, making it difficult to draw convincing conclusions. However, a tendency was observed for OTM to be accelerated by using PCs as an adjuvant in canine distalization after premolar extraction when distalization was started in the same session. Likewise, studies seem to indicate an association between the amount of canine retraction and PC injections. However, it is not possible to affirm that the use of PCs in corticotomy shortens the overall treatment time, as this question has not been studied adequately.

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