

Review

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Review

Protocol Heterogeneity in Platelet-Rich Plasma Treatment for Knee Osteoarthritis: A Scoping Review of Preparation, Delivery, and Outcomes

Qing Zhao Ruan ¹, Woojin Lee ¹, Jung Mi Haisman ¹, Vahid Grami ², Kasra Amirdelfan ³, Dawood Sayed ⁴, Christopher M. Lam ⁴, Cyrus Yazdi ⁵, Ronald J. Kulich ^{6,7}, Claire Yuan ⁸, Steven M. Falowski ⁹, Jamal J. Hasoon ¹⁰ and Christopher L. Robinson ^{2,*}

- ¹ Warren Alpert Medical School, Brown University, Providence, RI, USA
- ² Division of Pain Medicine, Department of Anesthesiology and Critical Care, The Johns Hopkins University School of Medicine, Johns Hopkins School of Medicine, Department of Anesthesiology and Critical Care Medicine, 1800 Orleans Street, Baltimore, MD 21287, USA
- ³ Boomerang Healthcare, Walnut Creek, CA
- ⁴ Department of Anesthesiology, The University of Kansas School of Medicine, Kansas City, Kansas, USA
- ⁵ Department of Anesthesiology, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA
- ⁶ Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA
- ⁷ Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
- ⁸ Department of History and Philosophy of Science, Christ's College, University of Cambridge, Cambridge, UK
- ⁹ Neurosurgical Associates of Lancaster, Lancaster, PA, USA
- ¹⁰ Department of Anesthesia, Critical Care, and Pain Medicine, UTHealth, McGovern Medical School, Houston, TX, USA
- * Correspondence: crobi151@jh.edu

Abstract

Platelet-rich plasma (PRP) is a commonly used intra-articular therapy for knee osteoarthritis (OA), yet substantial heterogeneity in PRP preparation and delivery limits comparability across trials and complicates clinical translation. We conducted a scoping review in accordance with PRISMA and PRISMA-ScR guidance. MEDLINE and Embase were searched from inception to 15 November 2025 for English-language randomized controlled trials comparing PRP with non-regenerative comparators (e.g., hyaluronic acid, corticosteroids, radiofrequency ablation, or saline placebo) in adults with knee OA. Data were charted on study characteristics, OA severity, injection guidance, centrifugation protocols, injected PRP volume and platelet concentration, dosing regimens, follow-up, adverse events, and overall conclusions (superior/non-inferior/inferior). Twenty-one studies (2012–2025) were included, spanning multiple regions and enrolling 21–288 participants per study with follow-up from 12 weeks to 60 months. PRP protocols varied widely, including single- versus double-spin centrifugation, spin rates and durations, injected volumes (approximately 1.4–8 mL), and platelet enrichment (approximately 1.15x to 9.85x baseline when reported). The most common regimen was three injections, typically weekly. Across studies, major adverse events were not reported, and post-injection pain or transient synovitis/effusion were the most frequent events. PRP for knee OA is generally safe and frequently demonstrates comparable or improved outcomes versus standard injectables, but marked protocol heterogeneity persists. Standardized reporting and consensus parameters for PRP preparation and administration are needed to improve reproducibility and guide evidence-based practice.

Keywords: platelet-rich plasma; knee osteoarthritis; heterogeneity

1. Introduction

The role of platelets in the therapeutic and healing process has been thought to be secondary to the vast array of growth factors released in the context of tissue injury. The acquisition of platelet-rich plasma (PRP) furthers the concept of growth factor and cytokines action delivered at supraphysiologic concentrations to directly impact the site of injury, stimulating recovery and regeneration.[1] Its effects have been extensively investigated in the pathology of knee osteoarthritis (OA), with the latter driven by cartilage loss and concurrent synovial inflammation, altering the structural and functional balance of the joint.[2–5] In the intra-articular environment, PRP has been demonstrated to possess anti-inflammatory and immunomodulatory properties, promoting anabolic activities that mitigate the deterioration of the knee joint.[6] This has been attributed to the platelet alpha-granules releasing an abundance of growth factors, cytokines, and other bioactive molecules.[7] Given the prevalence of knee OA and the excess morbidity associated with the disease across the globe, the minimally invasive technique of intra-articular PRP delivery serves to be an attractive and relevant therapy in the management of this condition.[8–10]

At present, several commercially available devices are available to produce the appropriate quality and volume of PRP for clinical application. However, there is significant variation in the manner of preparation and delivery, including the time and speed of centrifugation, the final volume of PRP derived, platelet concentration achieved, the technique of injection, and the frequency of PRP delivery.[11,12] Our scoping review seeks to delineate the most commonly adopted parameters in the production and delivery of PRP knee injections associated with positive therapeutic outcomes without significant adverse events.

2. Methods

The scoping review was conducted in accordance with criteria defined by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Databases queried included MEDLINE and Embase and the query was performed on 15 November 2025 with time frame of article search set from database inception to 15 November 2025. The definition of search strategy was determined by two authors (QR and CR) and discussed and approved by all authors with necessary amendments made. Article screening and inclusion in the subsequent review were collectively performed by authors QR and CR and, in the event of disagreement, a third author was consulted for opinion. Data charting and summary were then completed in unison on calibrated templates determined prior to article selection. The data points collected included article publication year, country of study completion, patient number, study population age, gender ratio, Kellgren-Lawrence (KL) grade, injection guidance modality, PRP concentration injected, PRP volume injected, injection frequency, centrifuge setting, follow-up durations, complications, and study conclusions. Study conclusions are specifically categorized as superior when PRP outperformed therapeutic alternatives such as corticosteroids, hyaluronic acid (HA), or radiofrequency ablation; non-inferior when PRP was demonstrated to be equivalent in efficacy to alternative therapies; or inferior when PRP was demonstrated to be inferior to alternative therapeutic alternatives or equivalent to research placebos, most commonly saline. Critical appraisal and detailed statistical analyses were not performed in keeping with the delineated checklist published in PRISMA Extension for Scoping Reviews (PRISMA-ScR).[13] No funding was acquired for the study.

2.1. Search Strategy and Selection Criteria

A comprehensive search of PubMed was performed on 15 November 2025 adopting the following strategy: (“platelet rich plasma” OR “autologous conditioned plasma”) AND (“knee”)

AND (“osteoarthritis” OR “degeneration” OR “gonarthrosis”). An identical strategy was carried out via query on Embase and the results are displayed in Figure 1.

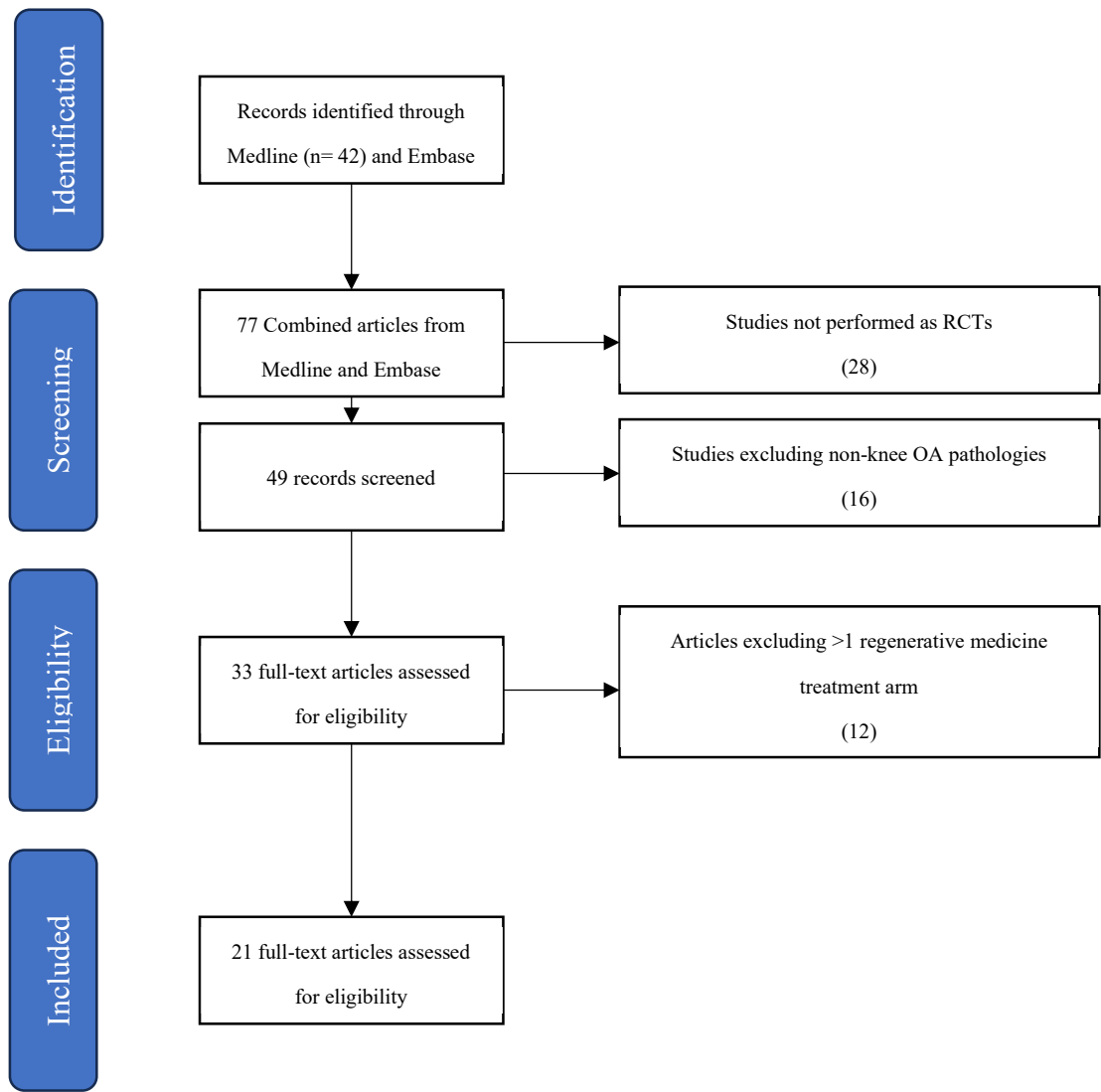


Figure 1. PRISMA Flowchart overview of scoping review analysis.

2.2. Inclusion Criteria

The following inclusion criteria were selected: (1) studies with titles, articles, and abstracts written in the English language; (2) peer-reviewed randomized controlled trials (RCTs) comparing PRP against non-regenerative medicine alternatives; (3) studies including patients ≥ 18 years of age; and (4) studies exclusively investigating PRP effects on knee osteoarthritis.

2.3. Exclusion Criteria

The following exclusion criteria were adopted: (1) articles not written in English; (2) non-human studies; (3) individuals ≤ 18 years of age; (4) studies with multiple regenerative medicine modalities, in addition to PRP, in its treatment arms; (5) review articles, systematic analyses, or meta-analyses; (6) studies investigating pathologies other than knee osteoarthritis.

3. Results

A total of 21 independent articles were identified and incorporated into our review using the databases previously defined (Figure 1).[14–34] The articles selected were published between 2012 and 2025, with studies performed across North America, South America, Europe, and Asia. The total number of patients in each study ranged from 21 to 288, with follow-up durations ranging from 12 weeks to 60 months. Hyaluronic acid was used as the alternative injectate in close to half of the studies (n=10/21),[17,22–27,30,32,33] with the remaining being corticosteroid [15,21,28,33], radiofrequency ablation,[14,20] and saline placebo.[16,29,31,34] Captured patient population knee osteoarthritis severity ranged widely from Kellgren-Lawrence grades 0 to IV, and all articles reported at least one measurable clinical end point indicating degree of pain control or physical functionality. Twelve studies described the injection modalities adopted for their respective PRP therapies.[14,16,17,19–21,27–30,33,34] Ultrasound [16,19–21,30] and the landmark technique [17,27–29,34] were utilized in 5 studies each while fluoroscopy [14,33] was engaged in the remaining 2 studies. Article demographics and injection methodologies are summarized and presented in Tables 1 and 2.

Table 1. Study demographics, osteoarthritis severity and therapy injection modalities. AB: Ahlback; KL: Kellgren-Lawrence; OA: osteoarthritis; PRP: platelet-rich plasma; SD: standard deviation; Tx: treatment.

Author/ Year	Study Country	Total Patients (n)	Age (PRP vs Alternative)	PRP Gender Ratio (M:F)	Alternative Tx Gender Ratio (M:F)	OA Severity Grade	PRP Injection Modality
Anwar et al., 2025	Pakistan	200	56 ± 5.90 vs 55.63 ± 6.21	33:67	42:58	KL II–III	Fluoroscopy
Bains et al., 2025	USA	52	52 ± 15.6 vs 48 ± 15.6	5:21	7:19	KL II–III	Undefined
Bennell et al., 2021	Australia	288	62.2 ± 6.3 vs 61.6 ± 6.6	59:85	60:84	KL II–III	Ultrasound
Cerza et al., 2012	Italy	120	66.5 ± 11.3 vs 66.2 ± 10.2	23:35	28:32	KL I–III	Landmark
Chu et al., 2022	China	610	53.91 ± 5.0 vs 54.51 ± 5.1	41:59	-	Undefined	Undefined
Dorio et al., 2021	Brazil	62	66.4 ± 5.6 vs 66.1 ± 7.5 vs 62.5 ± 8.1	1:19	2:19 vs 2:19	KL II–III	Ultrasound
Elawamy et al., 2021	Egypt	200	48.45 ± 7.7 vs 47.78 ± 6.9	50:50	49:51	KL III–IV	Ultrasound
Elksniņš-Finogejevs 2020	Latvia	40	66.4 ± 8.4 vs 70.2 ± 9.2	17:3	15:5	KL II–III	Ultrasound
Filardo 2012	Italy	109	55 vs 58	37:17	31:24	KL 0–III	Undefined
Filardo 2015	Italy	192	53.32 ± 13.2 vs 57.55 ± 11.8	60:34	52:37	KL 0–III	Undefined
Fossati 2024	Italy	173	60.37 ± 12.91 vs 60.66 ± 11.19	23:34	19:39	KL III and under	Undefined
Ghorbani 2024	Iran	90	60.24 ± 1.97 vs 61.90 ± 2.06	15:26	18:26	KL I–III	Undefined
Gormeli 2017	Turkey	162	53.7 ± 13.1 vs 53.8 ± 13.4 vs 53.5 ± 14 vs 52.8 ± 12.8	16:23; 19:25	17:22; 20:20	KL 0–IV	Undefined
Montañez-Heredia 2016	Spain	53	66.3 ± 8.3 vs 61.5 ± 8.6	12:15	9:17	KL I–III	Landmark

Nunes-Tamashiro 2022	Brazil	100	67.6 ± 7.4 vs 65.8 ± 6.1 vs 68 ± 6.2	4:30	3:30; 3:30	KL II–III	Landmark
Patel 2013	India	156	53.11 ± 11.55 vs 51.64 ± 9.22 vs 53.65 ± 8.17	11:16; 5:20	6:17	AB I-II	Landmark
Paterson 2016	Canada	21	49.91 ± 13.72 vs 52.70 ± 10.30	8:3	7:3	KL II-III	Ultrasound
Smith 2016	USA	30	53.53 ± 8.22 vs 46.60 ± 9.37	5:10	6:9	KL II-III	Undefined
Spaková 2012	Slovakia	120	52.80 ± 12.43 vs 53.20 ± 14.53	33:27	31:29	KL I–III	Undefined
Tschopp 2023	Switzerland	120	62.00 (56.00, 68.00) vs 64.00 (54.75, 72.00) vs 59.00 (49.00, 65.00) vs 58.00 (54.00, 61.00)	13:17	11:19; 16:14; 12:18	KL I–III	Fluoroscopy
Yoshioka 2024	Japan	30	65.9 ± 6 8.0 vs 67.9 ± 6 10.7	3:12	6:9	KL II–III	Landmark

Table 2. Study PRP preparation protocols, conclusions and complications. F/U: follow-up; HA: Hyaluronic acid; PRP: platelet-rich plasma; RPM: revolutions per minute.

Author/Year	Mean PRP Concentration	PRP Volume Injected	PRP Injection Regimen	Centrifuge Setting	Comparative Tx Modality	Longest f/u Duration	Study Conclusion	Conclusion Grading	Complications
Anwar et al., 2025	Undefined	Undefined	Single, x1	1000g for 10 mins	RFA	24 months	PRP superior long-term to GNRFA	Superior	None observed
Bains et al., 2025	Undefined	3 mL	Single, x1	Undefined	Steroid: Triamcinolone 1mL + 1% Lidocaine 4mL	3 months	CS better short-term at 6 weeks; Both improved pain from baseline at 3 months without significant difference in magnitude	Non-inferior	None observed
Bennell et al., 2021	1.6 - 5x baseline	5 mL	Weekly, x3	1500g 5 mins	Saline placebo	12 months	Intra-articular injection of PRP, compared with injection of saline placebo, did not result in a significant difference in symptoms or joint structure at 12 months	Inferior	More in the PRP group reported pain, swelling, and stiffness after injections but none severe.
Cerza et al., 2012	Undefined	5.5 mL	Weekly, x4	Undefined	HA	24 weeks	PRP superior to HA at 6 mo with improved WOMAC score	Superior	Not reported
Chu et al., 2022	4.3x baseline	5 mL	Weekly, x3	3200 rpm 5 mins, 3300 rpm 3 mins	Saline placebo	60 months	PRP superior to saline up to 5 yrs	Non-inferior	In 3 PRP cases, mild pain was present during the first 1 or 2 days. One case of severe pain spontaneousl

									y resolved after 1 week.
									Adverse effects twice as frequent in PRP group with the most frequent reported being mild to moderate knee pain with a mean duration of 2 days.
Dorio et al., 2021	3x baseline	1.4 - 5 mL	Bi-weekly, x2	1500 rpm 12 mins, 2300 rpm 10 mins with 10 mins interval	Plasma and saline	24 weeks	The primary outcome, VAS for overall pain at 24 weeks, demonstrated significant improvement in the 3 groups, without statistical difference between them	Inferior	
Elawamy et al., 2021	>3x baseline	5-6 mL	Single, x1	3500 rpm 10 mins, 4000 rpm 7 mins	RFA	12 months	Pulsed RF can offer more sustained pain relief and hence better patient satisfaction when compared to intraarticular injection of PRP	Inferior	2 ablation patients experienced pain that resolved in a week, one patient in the PRP group had joint effusion which resolved with conservative management
Elksniņš-Finoģejevs 2020	Undefined	8 mL	Single, x1	1800 rpm 8 mins	Steroid: Triamcinolone 40mg	12 months	PRP superior to CS by 15 wks	Superior	15 patients (75%) in the PRP group within the first week after treatment which resolved spontaneously
Filardo et al., 2012	5x baseline	Undefined	Weekly, x3	1480 rpm 6 mins, 3400 rpm 15 mins	HA	12 months	No significant difference between PRP vs HA	Non-inferior	Significantly higher post-injective pain reaction in PRP group but none major
Filardo et al., 2015	4.6 ± 1.4x baseline	Undefined	Weekly, x3	1480 rpm 6 mins, 3400 rpm 15 mins	HA	12 months	No superiority of either modality; both improved	Non-inferior	None observed
Fossati et al., 2024	1.8x baseline	Undefined	Bi-weekly, x3	3500 rpm 5 mins	HA	12 months	No difference among PRP+HA, PRP, HA	Non-inferior	Sixty-four patients reported at least one adverse event, which in 92.3% of cases consisted of increased knee pain or knee swelling. Nonetheless,

									no significant differences among the three groups were encountered in the adverse events characteristics : throughout the whole duration of the study. No serious adverse events related to any intraarticular injection regimen were reported (Table S13—supplementary materials)
Ghorbani et al., 2024	Undefined	5 mL	x3 in 1 month	1600 rpm 15 mins, 2800 rpm 7 mins	HA	5 months	PRP better than HA in pain control and function	Superior	None observed
Gormeli et al., 2017	5.2 - 5.2x baseline	5 mL	Weekly, x1-3	1500 rpm 6 mins, 3500 rpm 12 mins	HA	6 months	For patients with early OA, multiple (3) PRP injections are useful in achieving better clinical results. For patients with advanced OA, multiple injections are unnecessary and do not significantly affect patient knee scores.	Superior	Not reported
Montañez-Heredia et al., 2016	1.15 - 9.80x baseline	Undefined	q15 days, x3	Double centrifugation, spin rpm undefined	HA	6 months	PRP injections proved to be effective in reducing pain and improving patient functionality with an effectiveness pattern comparable to the control treatment (HA)	Non-inferior	Pain related to infiltration in nine of 27 PRP injections and in four of 26 for HA, but only one patient (in PRP group) had transitory swelling that resolved itself
Nunes-Tamashiro et al., 2022	2.5 - 5x baseline	Undefined	Single, 1x	1200 rpm 10 mins	Steroid: Triamcinolone; saline	6 months	The effectiveness of the intra-articular knee injection with Triamcinolone Hexacetonide, Platelet-Rich Plasma or Saline was similar to pain, range of motion, quality of life, and functional tests at 52 weeks of follow-up.	Non-inferior	None observed
Patel et al., 2013	2–3× baseline	8 mL	Single vs q3 wkly x2	1500 rpm 15 mins	Saline placebo	6 months	short-term effectiveness of PRP injection over a	Non-inferior	Significantly more adverse effects in PRP

								placebo for relieving pain and stiffness and improving knee functions in early knee OA. There are more benefits in early OA, and in our experience, a single dose of PRP is as effective as a double dose.		groups with symptoms of syncope, dizziness, headache, nausea, gastritis, sweating, tachycardia, pain and stiffness
Paterson et al., 2016	Undefined	3 mL	Weekly, x3	2000 rpm for 5 mins, 3000 rpm for 3 mins	HA	12 weeks		PA-PRP improves self-reported pain, subscales of the KOOS and KQoL-26, and tests of lower extremity functional ability in knee OA patients, but not more so than HA	Non-inferior	2 from the PRP group experienced minor pain and swelling which resolved in a week
Smith et al., 2016	Undefined	4 - 7.1 mL	Weekly, x3	1500 rpm 5 mins	Saline placebo	12 months		ACP is safe and provides quantifiable benefits for pain relief and functional improvement with regard to knee OA.	Non-inferior	1 patient in the placebo group felt pain in the target leg
Spaková et al., 2012	4.5x baseline	3 mL	Weekly, x3	3200 rpm 15 mins, 1500rpm 10 mins, 3200 rpm for 10 mins	HA	6 months	PRP superior to HA	Superior		Temporary mild worsening of pain after PRP in six cases, which was spontaneously resolved after 2 days
Tschopp et al., 2023	~500 x 10^3/μL	3mL	Single, x1	1500 rpm 5 mins	HA; Steroid; Saline placebo	24 months		The post hoc contrasts for the effect model showed no significant differences between the effects of placebo or glucocorticoid and the other drugs within the first 6 months after injection	Inferior	One patient experienced facial redness and palpitations immediately after glucocorticoid injection and presented with knee joint swelling with effusion at 3 months, but no signs of infection. The other patient experienced nausea and vomiting immediately after receiving the glucocorticoid.
Yoshioka et al., 2024	475.4 ± 106.7 x 10^3 /μL	6 mL	Weekly, x3	2100rpm 8 mins	Saline placebo	24 weeks		PRP superior; BMLs reduced	Non-inferior	Not reported

3.1. PRP Centrifugation Regimen

Eighteen studies defined centrifugation settings to attain the desired concentrations of PRP injectate (Table 2). Nine studies [14,16,21,24,28,29,31,33,34] performed a single spin, and the remaining 9 studies [18–20,22,23,25,26,30,32] performed a double spin. The lowest rates of the first and second spins were both 1500 revolutions per minute (rpm), while the longest were 3500 and 4000 rpm, respectively.[19,20,29,31] The shortest spin duration was a 5-minute single spin demonstrated in studies performed by Smith et al. [31] and Tschopp et al. [33], and the longest was performed by Dorio et al.[19] for a total of 22 minutes, split into a first spin of 12 minutes and a second spin of 10 minutes. [19]Smith et al.’s short-spin duration protocol achieved improvement in WOMAC score for the PRP group from 2 weeks following injection until study completion at 12 months ($p < 0.001$), which was statistically significantly superior to the saline group.[31] The long-spin duration protocol adopted by Dorio et al. yielded no difference in overall VAS pain scores between groups which received PRP, plasma, and saline ($p = 0.499$).[19] This was no different for all secondary measures involving WOMAC, QoL, PGA, ADL and TUGT scores.

3.2. PRP Injection Concentration

A total of 14 studies analyzed published, defined platelet concentrations in their injectates (Table 2). Concentration of platelets utilized for intra-articular injection ranged from a value close to patient’s baseline at 1.15 times of platelet enrichment to 9.85 times of platelet enrichment, demonstrated via the same study.[27] Out of the remaining 26 patients, platelet enrichment was achieved through at least 3.31 times of baseline concentration, and the study revealed equivalent efficacy between injectates containing PRP and HA after the third infiltration ($p = 1.0$), at 3 months ($p = 0.227$), and at 6 months ($p = 1$). Fossati et al. prepared platelets at a much lower concentration at approximately 1.8 times of baseline values for 116 patients, which is at the low end of the platelet concentration spectrum across all analyzed studies.[24] The study similarly demonstrated little difference between treatment groups PRP, HA, and PRP with HA measured via WOMAC ($p = 0.45$, 0.64), IKDC ($p = 0.12$, 1), KOOS ($p = 0.15$, 0.44), and VAS ($p = 0.40$, 0.65) at 6 and 12 months, respectively. Other included studies described platelet enrichment at magnitudes ranging from 2 to 5 times of patients’ baselines (Table 2).

3.3. PRP Injection Volume

Fifteen studies defined the volume of PRP injected during each treatment with volumes ranging from 1.4 mL to 8 mL (Table 2). Dorio et al. prepared PRP injectate concentrations at 1×10^6 platelets/mm³, attaining PRP volumes ranging from 1.4 mL to 5 mL for each injection. The team compared efficacy of PRP against plasma and saline injections and were unable to elicit statistically significant advantage of PRP over the 2 alternatives, as measured using VAS and WOMAC.[19] The PRP group did demonstrate higher incidence of adverse events ($p = 0.025$) described as pain of mild or moderate intensity with a mean duration of 2.1 days. Elksniņš-Finogejevs et al. prepared higher volumes of PRP injectate at 8 mL per treatment, evaluating its efficacy against 40 mg triamcinolone acetone and 5 mL of 2% lidocaine.[21] VAS score at 1 year demonstrated a significantly greater reduction in pain in the PRP group compared to the corticosteroid group (-3.1 ± 2.0 vs -0.8 ± 1.8 , $p = 0.0002$). Functional improvement of the joints was similar between the 2 groups ($p > 0.05$). It was noted that 15 patients in the PRP group developed a mild synovitis, which self-resolved without adverse events. Patel et al. similarly performed intra-articular injections with higher PRP volume of 8 mL.[29] The study evaluated efficacy of a single PRP injection versus 2 sequential injections and a third group of placebo saline injection. At every timepoint of follow-up, defined as 6 weeks, 3 months, and 6 months, pain, stiffness, and physical function were all superior in the first 2 groups using PRP injections compared to placebo ($p < 0.001$ for all categories). Out of the remaining articles, 6 and 4 papers described PRP injection volumes of 5 mL and 3 mL respectively, making them the most frequently injected volumes in our study selection (Table 2).

3.4. PRP Injection Frequency

The most popular therapeutic regimen was 3 PRP injections, with one performed each week (Table 2). Nine articles described this defined regimen, with 3 additional articles reporting 3 injections within the duration of one month and 3 injections spaced 2 weeks and 15 days apart, respectively.[24,25,27] In total, 12 articles described 3 consecutive doses of PRP as part of their therapeutic regimen. Eleven articles demonstrated superiority to saline injection and at least equivalent, if not improved, efficacy in pain control and function compared to alternative therapies, defined as either corticosteroids or HA. Only Bennell et al. failed to demonstrate superiority of PRP injections compared to saline, revealing no difference in pain or measured tibial cartilage volume as part of the primary outcome.[16]

The next most frequent injection regimen was a one-off single PRP injection to the joint described in 7 of the 21 articles. Out of the studies adopting low frequency single PRP injections, 2 failed to demonstrate PRP superiority compared to alternative therapy. Elawamy et al. showed that at 6 ($p = 0.01$) and 12 months ($p = 0.04$) that VAS and ISK were both superior in the pulsed radiofrequency ablation group.[20] Similarly Tschopp et al. did not find significant determination of pain and function being attributed to the content of the injectate, whether it is corticosteroid, HA, or PRP.[33]

Patel et al. included 2 groups, with the first being a single injection and the second being 2 injections of PRP spaced 3 weeks apart, incorporating both low frequency and intermediate frequency injection groups.[29] The team subsequently revealed no significant difference in pain score ($p = 0.410$) during follow-up at 6 months. Cerza et al. adopted the highest frequency of PRP injections, performing weekly injections for a total of 4 times.[17] At 4, 12, and 24 weeks, WOMAC scores were significantly lower in the PRP group compared to the HA group ($p < 0.001$ for each period).

3.5. Adverse Events

Significant major adverse events were not reported in any of the studies, and the most comprehensive capture of complications were carried out by Patel et al. where the group recorded in detail the incidence of syncope, dizziness, nausea, gastritis, sweating, tachycardia, pain, and stiffness.[29] Many of these were transient, lasting merely 30 minutes, and none led to any clinically-relevant consequences. The study further delineated correlation between total platelet injected and the incidence of event occurrence, noting a positive relationship ($p = 0.02$). Multiple other studies similarly demonstrated more minor events occurring in groups with PRP intervention, which self-resolved without long-term complications.[16,18,19,21,23,27,30,32]

4. Study Results

Seventeen of the 21 studies demonstrated at least equivalence in efficacy comparing PRP against alternative non-placebo therapy, defined as saline or a sham procedure with no intended therapeutic relevance aside from the placebo effect. Six of the 17 clearly demonstrated a significant therapeutic benefit and are therefore classified as superior (Table 2). In the superior group, Anwar et al. ran the study with the largest group of participants ($n = 200$), comparing a single PRP injection to genicular nerve ablation under fluoroscopic guidance.[14] Both groups showed a steady decrease in VAS from 2 weeks to 6 months following therapies. However, at 12 and 24 months, the recurrence of pain was significantly quicker in the RFA group, attaining VAS of 4.73 ± 2.63 and 6.06 ± 2.01 compared to PRP's 2.99 ± 1.78 and 4.05 ± 1.82 , respectively, over the same period, both with p values < 0.05 . [14]

Eleven studies were considered non-inferior when pitted against alternative therapies of corticosteroids, HA, radiofrequency ablation, and local anesthetic. Chu et al. analyzed a total of 630 participants with 308 in the PRP group and 322 in the sham saline group.[18] The respective injectates were applied for a total of 3 times spaced 1 week apart. Although WOMAC scores were improved in both groups at 3 months, only the PRP group demonstrated sustained benefits at 48 months ($p < 0.001$). This result was similar when the authors looked at IKDC scores where the improvement

remained significantly robust only in the PRP group up to 60 months ($p < 0.001$). The study also picked up on objective measurables such as TNF-alpha and IL-1B levels in synovial fluid and tibiofemoral cartilage volumes, with both demonstrating superiority in the PRP group (both $p < 0.001$).[18]

Of the remaining 4 studies considered therapeutically inferior, 3 demonstrated equivalent efficacy to saline while 1 was seen to be inferior to radiofrequency ablation (Table 2). The RESTORE trial randomized a total of 288 subjects to receive either PRP or saline injections for a total of 3 times spaced 1 week apart. At 12 months, despite pain score improvement favoring the PRP group, the difference failed to achieve statistical significance (-2.1 , SD 2.7 PRP vs -1.8 , SD 2.5 saline).[16] There was also no demonstrable difference between tibial cartilage volume change between the groups. The authors further delineated 12 secondary end points, including but not limited to knee effusion measures, areas of cartilage thinning, meniscus morphology, cartilage defect, and perceived global change. Only perceived global change at 2 ($p = 0.02$) and 12 months ($p = 0.05$) statistically favored the PRP group.

5. Discussion

Our scoping review showed the extensive variability present in the preparation and conduction of PRP injections in the management of knee osteoarthritis, ranging from centrifuge settings, PRP injectate volume and concentration, therapeutic frequency of injection, and the image-guidance modality, when adopted, during injection. This trend is perceived despite our extensive efforts in attempting to standardize the articles selected, excluding papers that compared multiple regenerative medicine treatment modalities to acquire discernable clinical outcomes when PRP was pitted against current standards of treatment or placebo. This review is therefore timely in delineating basic practice standards for PRP injection of the knee in attaining therapeutic efficacy while avoiding clinically significant complications.

Therapeutic efficacy of intra-articular knee injections while adopting various image-guidance techniques were explored in multiple studies. Lundstrom et al. explored ultrasound-guided intra-articular knee injection of HA compared to the traditional landmark technique (mostly suprapatellar bursa approach), measuring efficacy via subsequent arthroplasty rates and repeat HA and corticosteroid injections.[35] The authors revealed that knee arthroplasty rates were significantly reduced in the US-guided cohort compared to the pure landmark technique (33.2% vs 45.8%; $p < 0.001$). Furthermore, significantly fewer patients in the US-guided cohort received subsequent corticosteroid injection compared to the landmark-guided cohort (27.4% vs 34.0%; $p < 0.002$), suggesting greater accuracy in needle placement when US is adopted for injections.[35] This was corroborated in other studies where image-guidance, defined as US, fluoroscopy, or arthrography, substantially improved injection accuracy (98% accuracy) compared to landmark approaches using superolateral patellar and superomedial patellar techniques (87% and 82%, respectively).[36–38] Given repeated demonstration of superiority in efficacy of image-guidance in intra-articular knee injections, it would be prudent to adopt a suitable mode of image-guidance in PRP injections of the knee.

Given that conceptually, the clinical benefits of PRP are derived from growth factors, cytokines, and bioactive platelet molecules stored in platelet alpha granules, one would extrapolate that the concentration of platelets in the injectate would be determinant of therapeutic efficacy.[39] In vitro, it had been postulated that PRP concentration is directly associated with proliferation of certain mesenchymal cell lines, including mesenchymal stem cells, chondrocytes, osteoblasts, and fibroblasts.[40–45] Given that the normal human range of platelet concentration is between 150,000 to 450,000 platelets/ μL , it was previously suggested that a 4-fold increase of platelets from this baseline could yield more predictable benefits.[46] Bensa et al. performed a sub analysis on platelet concentrations in their meta-analysis, defining low PRP concentration as $< 800,000$ platelets/ μL and high concentration as $1 \times 10^6 \pm 2 \times 10^5$ platelets/ μL . [47] The authors found that when compared against placebo in osteoarthritic knee injections, the high platelet concentration articles demonstrated

statistical superiority in both VAS and WOMAC scores at 6 and 12 months. Bansal et al. seemingly corroborated this suggestion of high platelet count in their therapeutic injectate, their protocol attaining a mean platelet concentration of $14.38 \pm 1.76 \times 10^5$ platelets/ μL . The authors further recommended an injection volume of 8 mL, suggesting that this regimen was crucial in achieving sustained chondroprotective effects up to 12 months out from initial treatment. Despite the definitions of concentration cut-offs being arbitrary, there may be value in attempting to achieve a higher platelet count in preparation of PRP injectates.

The frequencies of intra-articular PRP injections adopted in our selection of studies have been highly variable. Tao et al. determined in their meta-analysis that a triple-dose regimen of PRP injections is superior to a single dose in the treatment of osteoarthritic knee pain.[48] This was seen in a significantly lower VAS at 12 months ($p < 0.0001$) in studies with triple-dose regimens, and the frequency of adverse events registered were not significantly higher in the triple-dose regimen studies ($p = 0.23$). On the contrary, comparing double and single-dose regimens, neither the VAS ($p = 0.50$) nor the rate of adverse events ($p = 0.28$) were different between the single and double-dose regimens. Functionality was also shown to be improved measured using WOMAC and IKDC scores when adopting a multiple-injection regimen ($p < 0.01$).[49] Interestingly, the same study did not demonstrate an improvement in VAS between the single and multiple dosing groups ($p = 0.48$). Clinical practice guideline published by American Academy of Orthopedic Surgeons hinted at three intra-articular PRP injection being the standard that appeared to achieve more favorable clinical results.[50]

The safety profile of PRP knee injections has been relatively consistent in our review, with the most frequent complaint being a transient self-limiting localized inflammatory reaction (Table 2). A major clinical concern of intra-articular interventions is the deterioration of cartilage volume with successive therapy over the long run, while PRP in relation to current mainstream treatments of corticosteroids and HA appeared to be protective with respect to morphological cartilage parameters measured via quantitative MRI.[51] Overall, safety attributes of PRP given its autologous nature would continue to be one of its most reassuring features.

6. Limitations

Our study is constrained by its very nature of being a scoping review, and therefore no in-depth statistical analysis was performed. In addition, the immense variability in the manners in which the RCTs were performed made it exceptionally challenging to derive measured recommendations that could be standardized across the board. The individual RCT conclusions drawn, describing clinical outcomes of PRP against placebo, could not be interpreted meaningfully against that of a current standard of care, such as a corticosteroid injectate. These further compounds the difficulty making recommendations that could be implemented across guidelines.

7. Conclusions

PRP as a therapeutic modality in the treatment of knee osteoarthritis has proven itself to be safe and largely efficacious when compared against current standards of treatment involving corticosteroids and HA. While much more work in the future is needed to statistically ascertain the parameters for PRP delivery, a strategy of platelet concentration to 4 times of baseline followed by a total injection frequency of 3 sessions performed under reliable image-guidance would be a prudent one to adopt in the treatment of knee osteoarthritis.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1: title; Table S1: title; Video S1: title.

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Abbreviations

- ACP — autologous conditioned plasma
- ADL — activities of daily living
- BMLs — bone marrow lesions
- CS — corticosteroids
- GNRFA — genicular nerve radiofrequency ablation
- HA — hyaluronic acid
- IKDC — International Knee Documentation Committee
- IL-1B — interleukin 1 beta
- ISK — Insall–Salvati knee score
- KL — Kellgren–Lawrence
- KOOS — Knee injury and Osteoarthritis Outcome Score
- KQoL-26 — Knee Quality of Life (26-item)
- OA — osteoarthritis
- PA-PRP — photo-activated platelet-rich plasma
- PGA — patient global assessment
- PRISMA — Preferred Reporting Items for Systematic Reviews and Meta-Analysis
- PRISMA-ScR — PRISMA Extension for Scoping Reviews
- PRP — platelet-rich plasma
- QoL — quality of life
- RCT — randomized controlled trial
- RFA — radiofrequency ablation
- rpm — revolutions per minute
- TUGT — Timed Up and Go Test
- TNF-alpha — tumor necrosis factor alpha
- Tx — treatment
- US — ultrasound
- VAS — visual analog scale
- WOMAC — Western Ontario and McMaster Universities Osteoarthritis Index

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