Systematic Review

Three Doses of Platelet-Rich Plasma Therapy Are More Effective Than One Dose of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-analysis

Xinyu Tao, M.B.B.S., Angeline Ai Ling Aw, M.B.B.S., Jun Jie Leeu, M.B.B.S., and Hamid Rahmatullah Bin Abd Razak, M.B.B.S., M.Med.(Orth), F.R.C.S.Ed.(Orth)

Purpose: To compare the efficacy of a single dose of platelet-rich plasma (PRP) with multiple doses of PRP therapy in the treatment of knee osteoarthritis (KOA). **Methods:** The PubMed, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Scopus, and Cochrane Library databases were searched from database inception to May 2022; in addition, the gray literature and bibliographic references were searched. Only randomized controlled trials comparing the effect of a single dose versus multiple doses of PRP for KOA were included. Literature retrieval and data extraction were conducted by 3 independent reviewers. The inclusion and exclusion criteria were based on type of study, research subjects, intervention, outcome, language, and availability of data. Pooled analyses of visual analog scale (VAS) scores, Western Ontario and McMaster Universities Arthritis Index scores, and adverse events were conducted. **Results:** Seven studies (all randomized controlled trials) of high methodologic quality involving 575 patients were included. The ages of the patients included in this study ranged from 20 to 80 years, and the sex ratio was balanced. Triple-dose PRP therapy resulted in significantly better VAS scores compared with single-dose PRP therapy at 12 months ($P < .0001$), with no significant change in VAS scores between double-dose PRP and single-dose PRP at 12 months. Regarding adverse events, double-dose ($P = .28$) and triple-dose ($P = .24$) therapy showed no significant differences in safety from single-dose therapy. **Conclusions:** Although there is a paucity of large high-quality Level I studies, current best evidence suggests that 3 doses of PRP for KOA are more effective than 1 dose of PRP at providing pain relief up to 1 year after administration. **Level of Evidence:** Level II, systematic review of Level II studies.

The treatment of knee osteoarthritis (KOA) in its early stages to prevent any further progression is the mainstay of management. Many clinicians have adopted the use of intra-articular injections of platelet-rich plasma (PRP) to treat KOA in its early stages. PRP, also known as "autologous plasma," with a higher concentration of platelets compared with peripheral blood, is obtained by centrifugation of autologous blood.[1] The growth factors and cytokines released from platelet degranulation are hypothesized to reduce inflammation and promote regeneration, leading to its widespread application in other orthopaedic conditions.[2] Systematic reviews have concluded that the use of PRP has resulted in improved clinical outcomes by alleviating pain and slowing the progression of KOA.[3,4]

Although the existing literature suggests that outcomes in terms of both knee function and pain significantly improved with the introduction of intra-articular PRP injections, there has yet to be a consensus regarding the number of doses of PRP to be injected for optimal results. A single dose of PRP is commonly given to patients, but some clinicians have

From Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore (X.T., A.A.L.A., J.J.L.); Department of Orthopaedic Surgery, Sengkang General Hospital, Singapore, Singapore (H.R.B.A.R.); and SingHealth Duke-NUS Musculoskeletal Sciences Academic Clinical Programme, Singapore, Singapore (H.R.B.A.R.).

The authors report no conflicts of interest in the authorship and publication of this article. Full ICMJE author disclosure forms are available for this article online, as supplementary material.

Received June 21, 2022; accepted May 8, 2023.

Address correspondence to Hamid Rahmatullah Bin Abd Razak, M.B.B.S., M.Med.(Orth), F.R.C.S.Ed.(Orth), Department of Orthopaedic Surgery, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886. E-mail: hamidrazak@gmail.com

0749-8063/22776/$36.00

https://doi.org/10.1016/j.arthro.2023.05.018

postulated that multiple doses may be more effective when given some time after the initial dose to boost the effects of PRP after its initial effects begin to wean off.[5]

With KOA placing an increased burden on our population, there have been studies on the efficacy of a single dose versus multiple doses of PRP. Some studies have found that a single injection of PRP was as effective as multiple doses in terms of pain control but multiple injections seemed to be more effective in improving knee functionality compared with a single injection.[6] However, there is little evidence in existing systematic reviews evaluating the optimal number of doses of PRP, as well as the effects over a specific period. This study aimed to compare the efficacy of a single dose of PRP with multiple doses of PRP therapy in the treatment of KOA. We hypothesized that multiple doses of PRP therapy would be more effective than a single dose in the treatment of KOA.

Methods

We conducted this systematic review and meta-analysis in accordance with relevant requirements of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Literature Search Strategy

To retrieve relevant literature to review the efficacy of single-dose PRP compared with multiple doses, different databases—MEDLINE (PubMed), Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane Library, and Scopus—were searched; in addition, the gray literature (conference proceedings, industry white papers, and Google Scholar) and bibliographic references were hand-searched to identify relevant studies. Of the relevant studies, only randomized controlled trials (RCTs) were selected. The retrieval period spanned

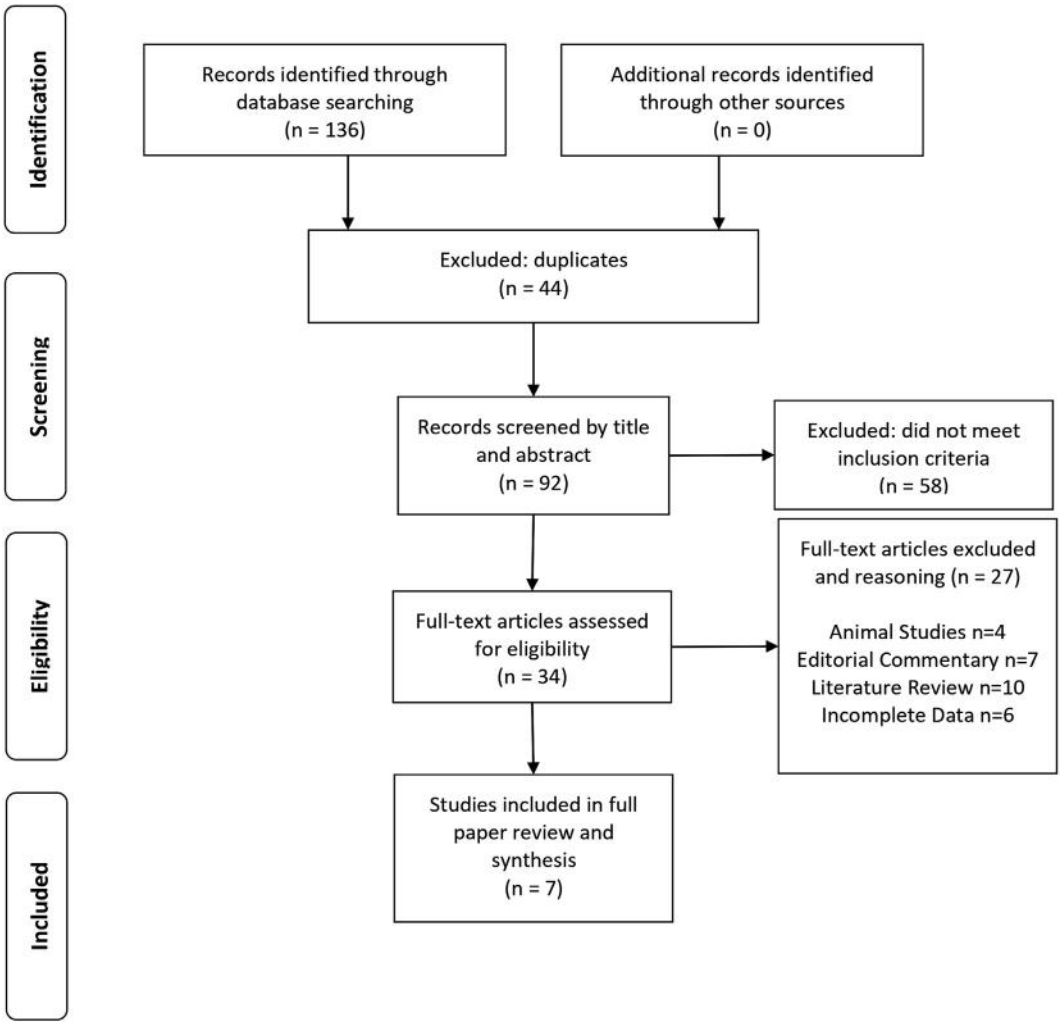


Fig 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart of study search process.

Table 1. Characteristics of Included Studies

Authors, Year	Study Design	Language	Total No. of Patients	No. of Patients			Age, yr			Sex: M:F, n			Kellgren-Lawrence Score: 1:2:3:4			Follow-up Period, mo	Outcomes Reported	LOE
				Single-Dose PRP	Double-Dose PRP	Triple-Dose PRP	Single-Dose PRP (mean ± standard deviation)	Double-Dose PRP (mean ± standard deviation)	Triple-Dose PRP (mean ± standard deviation)	Single-Dose PRP	Double-Dose PRP	Triple-Dose PRP	Single-Dose PRP	Double-Dose PRP	Triple-Dose PRP			
Vilchez Cavazos,[7] 2015	RCT	English	30	15	—	15	—	—	—	—	—	—	—	—	—	—	VAS score, WOMAC score	II
Güvendi et al.,[8] 2018	RCT	English	33	19	—	14	62.3 ± 1.6	—	60.4 ± 1.7	1:18	—	1:13	0:0:19:0	—	0:0:14:0	6	VAS score, WOMAC score	II
Subramanyam et al.,[9] 2021	RCT	English	90	30	30	30	48.4 ± 7.8	46.7 ± 6.7	47.6 ± 8	7:23	10:20	5:25	—	—	—	12	VAS score, IKDC score, KOOS	II
Simental-Mendía et al.,[10] 2019	RCT	English	35	18	—	17	54.6 ± 11.6	—	60.1 ± 10.6	1:17	—	5:12	1:17:0:0	—	1:16:0:0	12	VAS score, WOMAC score	II
Patel et al.,[11] 2013	RCT	English	52	27	25	—	53.11 ± 11.55	51.64 ± 9.22	—	11:16	5:20	—	—	—	—	6	VAS score, WOMAC score	II
Yurtbay et al.,[12] 2022	RCT	English	237	62	—	63	53.29 ± 12.9	—	57.38 ± 8.7	41:21	—	54:9	7:43:12:0		2:38:23:0	24	VAS score, KOOS	II
Kavadar et al.,[13] 2015	RCT	English	98	33	32	33	53.6 ± 6.7	54.9 ± 5.4	55.2 ± 5.7	—	—	—	0:0:33:0	0:0:32:0	0:0:33:0	6	VAS score, WOMAC score	II

F, female; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; LOE, level of evidence; M, male; PRP, platelet-rich plasma; RCT, randomized controlled trial; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

from establishment of each database to May 2022. Three researchers (A.A.L.A., J.J.L. and X.T.) cross-referenced information on the Covidence platform (Melbourne, Australia) to reduce data extraction errors. The search terms used are presented in Appendix Table 1.

Inclusion and Exclusion Criteria

The inclusion criteria for this study included the following: (1) The type of study consisted of published RCTs. (2) The research subjects comprised individuals with a diagnosis of KOA, regardless of age, sex, or nationality. (3) The intervention consisted of multiple injections of PRP used as the test group and a single injection of PRP used as the control group. (4) Regarding outcomes, at least one of the following outcome indicators was cited: Western Ontario and McMaster Universities Arthritis Index (WOMAC) score, International Knee Documentation Committee (IKDC) score, or visual analog scale (VAS) score. (5) Studies were written in English. The exclusion criteria for this study included the following: (1) retrospective studies, reviews, case reports, or case series; (2) study subjects comprising patients with non-knee osteoarthritis, animal subjects, or cadavers; (3) studies in which the intervention did not include multiple injections of PRP used as the test group and a single injection of PRP used as the control group; (4) studies detailing the mechanism of PRP in terms of outcomes; (5) studies not written in English; (6) studies with data that were unable to be extracted; and (7) studies in which data were not reported as mean and standard deviation.

Study Selection and Data Extraction

The literature retrieval was conducted under the guidelines of established inclusion and exclusion criteria. Two reviewers (A.A.L.A. and J.J.L.) performed data extraction independently before compilation and cross-referencing on the Covidence platform. A third reviewer (X.T.) assisted in the cross-referencing process independently to minimize judgment errors. All 3 reviewers are medical doctors with prior experience in publishing systematic reviews. The quantitative data extracted in this study included first author, publication year, sample size, intervention measures, ethical approval, sex, age, body mass index, follow-up period, Kellgren-Lawrence radiographic classification, relevant items for risk-of-bias evaluation, WOMAC score, VAS score, and adverse events (AEs).

Quality Assessment of Included Studies

The Cochrane risk-of-bias tool was used for quality evaluation of the included RCTs. The tool includes evaluation in 7 domains: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and

Table 2. Composition of PRP of Included Studies

Authors, Year	Study Type	PRP Composition	Injection Interval, wk
Patel et al,[11] 2013	RCT	Collected blood mixed with CPD-A1 was centrifuged for 15 min at 1,500 rpm on a table-top centrifuge, and the blood was separated into PRP and residual red blood cells with the buffy coat. The PRP was then extracted through a pipette and transferred to a test tube, and a leukocyte filter was used to filter off the leukocytes. The final PRP was assessed for platelet count and was supplied for injection in a 10-mL syringe (approximately 8 mL per knee).	3
Vilchez Cavazos,[7] 2015	RCT	NS	2
Kavadar et al.,[13] 2015	RCT	Approximately 1 mL of whole blood was separated for a complete blood count; the blood with anticoagulant was centrifuged twice: first at 1,800 rpm for 15 minutes to separate erythrocytes; then at 3,500 rpm for 5 minutes to concentrate platelets. Approximately 0.5 mL of PRP was collected for platelet counting. 0.0425 mL of 10% calcium chloride per 1 mL of PRP was added to the final product to activate the platelets.	2
Güvendi et al.,[8] 2018	RCT	Collected blood mixed with 2 mL of citrate dextrose was centrifuged for 5 min at 3.600 rpm. Before centrifugation, the platelet count was 245×10^9 L and the WBC count was 7.45×10^9 L. After centrifugation, the platelet count was 875×10^9 L and the WBC count was 8.67×10^9 L.	1
Simental-Mendía et al.,[10] 2019	RCT	Not stated/specified	2
Subramanyam et al.,[9] 2021	RCT	A total of 8 mL of blood with 2.7 mL of Acid Citrate Dextrose - Solution A anticoagulant was centrifuged for 5 min at 1,500*g* centrifugal force and 3,500 revolutions/min. This yielded 4 mL of PRP.	2
Yurtbay et al.,[12] 2022	RCT	A total of 32 mL of peripheral venous blood was mixed with 3.2% sodium citrate as an anticoagulant. The mixture was centrifuged once for 10 min at 1800 rpm. After the centrifugation process, there was approximately 4 mL of blood—with 2 mL of plasma at the top, 0.2 mL of buffy coat in the middle, and a 1.8-mL erythrocyte layer at the bottom. In each patient, the entire middle layer (0.2 mL) and 0.8 mL of the first layer, rich in platelets, just above the middle layer were collected. The 1.2-mL portion of plasma remaining at the top and the 1.8-mL erythrocyte layer were removed and discarded. The remaining 0.8 mL of plasma and 0.2 mL of buffy coat were transferred to a separate sterile tube. A total of 8 mL of PRP was collected.	4

CPD-A1, citrate phosphate dextrose and adenine; PRP, platelet-rich plasma; RCT, randomized controlled trial; WBC, white blood cell.

personnel (performance bias), (4) blinding of outcome (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other sources of bias. The risk of bias in each domain is judged to be low, high, or unclear. Quality assessment of the studies was performed independently by 3 reviewers (A.A.L.A., J.J.L., and X.T.), and any differences were resolved by consensus.

Statistical Analysis

To evaluate our main outcome of comparing the efficacy of multiple doses of PRP with a single dose of PRP, a random-effects model was used for the meta-analysis. The mean difference was used to evaluate the effects of continuous variables comparing the 2 different outcomes (WOMAC and VAS scores), with calculation of the 95% confidence interval (CI) of the mean difference. Review Manager software (RevMan, version 5.4.1; The Cochrane Collaboration, Oxford, England) was used to calculate the efficacy and safety indicators and their 95% CIs. A random-effects model was used to pool quantitative data from the primary outcomes. $P < .05$ was considered statistically significant.

Results

Literature Screening Process and Results

A preliminary examination of titles and abstracts yielded a total of 92 relevant studies after the removal of duplicates. Following the guidelines of our strict inclusion and exclusion criteria, the final sample size of ethically approved studies was narrowed down to 7 studies, each being an RCT. These studies comprised a total patient sample size of 575. Five studies were 2-arm studies, whereas two were 3-arm studies. The literature screening process and results are presented in Figure 1. The age of the patients included in this study ranged from 20 to 80 years, the KOA score per the Kellgren-Lawrence radiographic grading scale ranged from 1 to 3, and the follow-up period spanned 2 to 12 months (Table 1). Baseline demographic data, such as age, sex, and body mass index, and the sample sizes of the patients included in the 7 studies were comparable (P = not significant [NS]). Duration of treatment was not specified in most studies, but the interval between injections ranged from 1 to 4 weeks (Table 2).

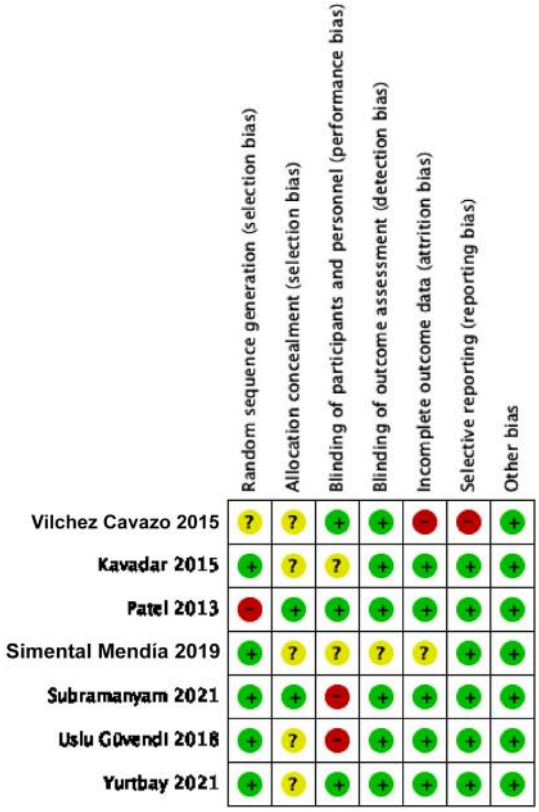


Fig 2. Quality assessment of 7 randomized controlled trials using Cochrane risk-of-bias tool. Green indicates low risk; yellow, unclear risk; and red, high risk.

Quality Assessment of Included Literature

The overall methodologic quality of the included studies is summarized in Figure 2. For random sequence generation, 6 studies (86%) were at low risk of bias whereas 1 study (14%) showed an unclear risk. For allocation concealment, 2 studies (29%) were at low risk of bias whereas 5 studies (71%) showed an unclear risk. A high risk of performance bias was observed in 2 studies (29%) (Subramanyam et al.,[9] 2021, and Güvendi et al.,[8] 2018) because the injector and patients were not blinded in the study (Fig 2). Regarding performance bias, 2 studies (29%) showed an unclear risk and 3 studies (42%) were at low risk. For detection bias, 6 studies (86%) were at low risk of bias whereas 1 study (14%) showed an unclear risk. For attrition bias, 1 study (14%) showed an unclear risk and 5 studies (71%) were at low risk. Moreover, 1 study (14%) (Vilchez Cavazos,[7] 2015) was at high risk of attrition bias because half the participants did not complete the study and most were lost to follow-up. For reporting bias, 6 studies (86%) were at low risk of bias. In contrast, 1 study (14%) (Vilchez Cavazos) was at high risk of reporting bias because not all the outcome measures for all the time frames specified were published. All the studies had a low risk of other bias. Three studies (Subramanyam et al.; Güvendi et al.; and Yurtbay et al.,[12] 2022) reported their sources of funding, whereas 3 studies (Subramanyam et al., Güvendi et al., and Yurtbay et al.) reported on any potential sources of conflict of interest.

Meta-analysis

On statistical analysis, considerable levels of statistical heterogeneity were noted for some WOMAC and VAS scores. The WOMAC score includes tasks in its function subscale that may not be performed regularly by all patients, which may result in missing data, hence increasing the statistical heterogeneity of the results. The considerable heterogeneity translates into high variability in interventional outcomes. As such, WOMAC scores have been excluded from further analysis. However, they have been included in Appendix Figure 2 for completion in coverage of extracted data. VAS scores with high heterogeneity are discussed further in Appendix Figure 1, whereas WOMAC scores with high heterogeneity are explored in Appendix Figure 2.

Visual Analog Scale. A total of 6 studies reported VAS scores at baseline. There were no significant differences

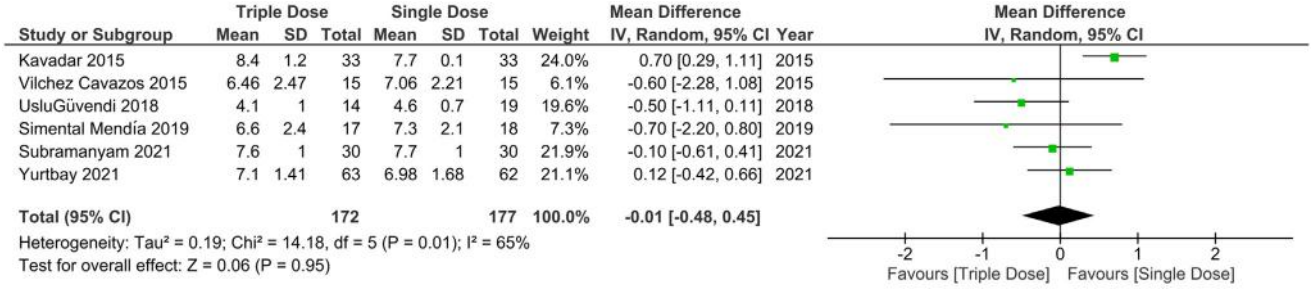


Fig 3. Forest plot comparing visual analog scale (VAS) scores at baseline between triple-dose platelet-rich plasma (PRP) and single-dose PRP. (CI, confidence interval; SD, standard deviation; IV, inverse variance.)

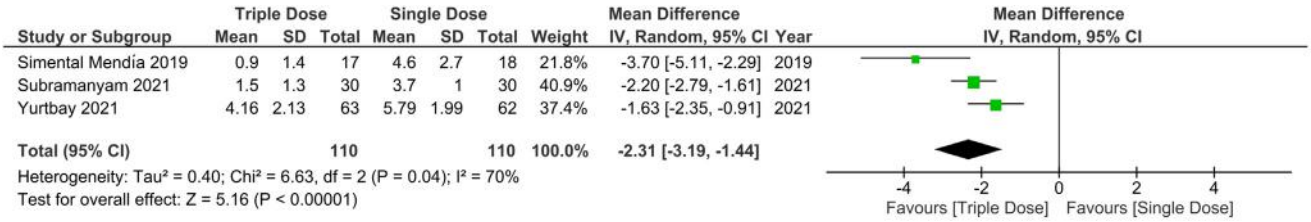


Fig 4. Forest plot comparing visual analog scale (VAS) scores at 12 months between triple-dose platelet-rich plasma (PRP) and single-dose PRP. (CI, confidence interval; SD, standard deviation; IV, inverse variance.)

in the baseline VAS scores between the single- and triple-dose groups (standardized mean difference [SMD], −0.01; 95% CI, −0.48 to 0.45; $P = .95$ [NS]) (Fig 3). A total of 3 studies reported VAS scores at 12 months after treatment. The results showed that at 12 months, patients who received triple-dose PRP had significantly better VAS scores than patients who received single-dose PRP (SMD, −2.3; 95% CI, −3.19 to −1.44; $P < .00001$) (Fig 4). For double-dose therapy, 3 studies reported baseline VAS scores. There were no significant differences in the baseline VAS scores between the single- and double-dose groups (SMD, −0.01; 95% CI, −0.24 to 0.22; $P = .93$ [NS]) (Fig 5). Comparison of the change in VAS scores from baseline to last recorded follow-up between double-dose PRP and single-dose PRP showed an insignificant mean deterioration of 0.24 points (95% CI, 0.46 to 0.94; $P = .50$ [NS]) (Fig 6).

Adverse Events. Out of the seven included studies, 3 studies did not report the occurrence of AEs. The remaining four studies reported that no major AEs such as infection occurred. However, the four studies did report on the comparison of mild AEs of double- or triple-dose PRP and single-dose PRP in KOA patients. The main types of adverse reactions were erythema, pain, and swelling. The results showed that there was an insignificant difference in the general safety of double-dose PRP compared with single-dose PRP (SMD, 1.53; 95% CI, 0.71 to 3.28, $P = .28$ [NS]) (Fig 7A) and that of triple-dose PRP compared with single-dose PRP (SMD, 1.46; 95% CI, 0.79 to 2.72, $P = .23$ [NS]) (Fig 7B).

Discussion

The main finding of this study is that triple doses of PRP are more effective at providing pain relief for KOA than a single dose of PRP. KOA has a variety of causative factors such as trauma, inflammation, biochemical reactions, and metabolic derangements.[14] Pain in KOA can be a result of changes to the non-cartilaginous components of the joint such as the synovium, subchondral bone, and periarticular muscles.[15] As the disease progresses, structural changes become more evident: synovial effusion, osteophyte formation, and weakening of the periarticular muscles.[16] Current treatment modalities are geared toward symptomatic control unless the degree of severity warrants surgical intervention.[17] PRP is one of the modalities to reduce pain and improve function in KOA. PRP is constituted from centrifuged whole blood, which comprises growth factors and proteins that enhance cartilage regeneration, hence promoting recovery of the joint.[4] PRP therapy uses its anti-inflammatory properties for stimulation of growth factors that encourage cartilage matrix synthesis and inhibition of innate immune response cytokines linked to cartilage erosion to halt the progression of osteoarthritis (OA).[18,19] Additionally, PRP reverses the process of chondrocyte senescence, restoring the regeneration ability of cartilage.[20]

Despite the cost and vulnerability to adverse effects, some studies have proved that multiple-dose therapy has improved effects in promoting cartilage regeneration and reducing inflammation in OA.[21] However, this has not been extensively studied, and some authors argue that the effects of multiple-dose therapy,

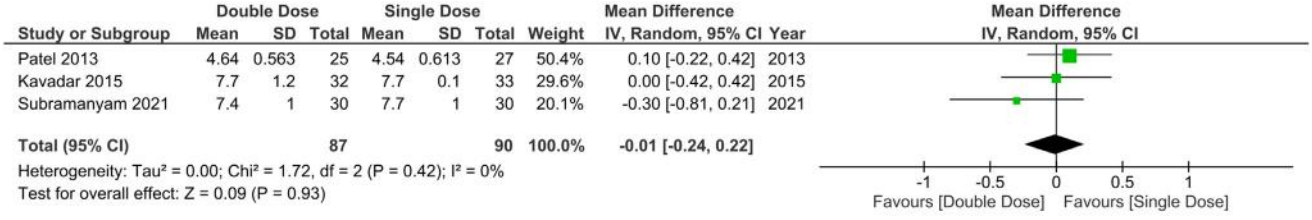


Fig 5. Forest plot comparing visual analog scale (VAS) scores at baseline between double-dose platelet-rich plasma (PRP) and single-dose PRP. (CI, confidence interval; SD, standard deviation; IV, inverse variance.)

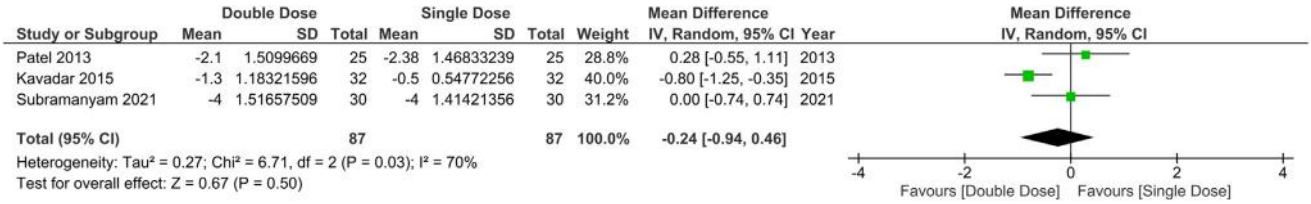


Fig 6. Forest plot comparing change in visual analog scale (VAS) scores from baseline to last follow-up between double-dose platelet-rich plasma (PRP) and single-dose PRP. (CI, confidence interval; SD, standard deviation; IV, inverse variance.)

considering the extra costs required, are not significantly different from those of single-dose PRP.[9,12,22]

Our study found that patients who received triple-dose PRP therapy had significantly better VAS scores at 12 months compared with patients who received single-dose therapy. However, there was no significant change between the double- and single-dose groups at final follow-up. This may suggest that treatment effect starts to wear off at 12 months for a double dose of PRP while there is sustained improvement at 12 months for patients receiving the triple dose of PRP, indicating continued effects of PRP and cellular regeneration in tissue.

Our study also found that the multiple-dose PRP group had a similar incidence of AEs to the single-dose PRP group. Most of the AEs reported are milder side effects such as pain and swelling. This could be explained by the presence of proinflammatory factors in PRP causing post-injection flare, regardless of the number of doses administered.[13] Alternatively, Patel et al. postulated that this might be caused by a somewhat higher quantity of platelets injected or the calcium chloride that was used as an activating agent, but the adverse effects will eventually subside within 30 minutes when the participants are under observation.[11]

Most of the studies also examined the effect of multiple doses of PRP compared with a single dose of PRP in terms of knee function.[8,7,11] Although our study attempted to perform a meta-analysis on the results, a definitive conclusion could not be reached owing to the high heterogeneity ($I^2 > 90\%$) of the included studies (Appendix Fig 2).

There is considerable heterogeneity in the studies for the VAS score. This is likely attributed to the studies including patients with differing levels of severity of KOA as evidenced by the Kellgren-Lawrence score, as well as differences in the composition of PRP between studies (Table 1). Subgroup analysis to reduce the effects of high heterogeneity was unable to be undertaken because of insufficient published data on patient characteristics in the studies and the small sample size of each included study.

There is large variation in the composition, preparation, and administration of PRP doses across the various

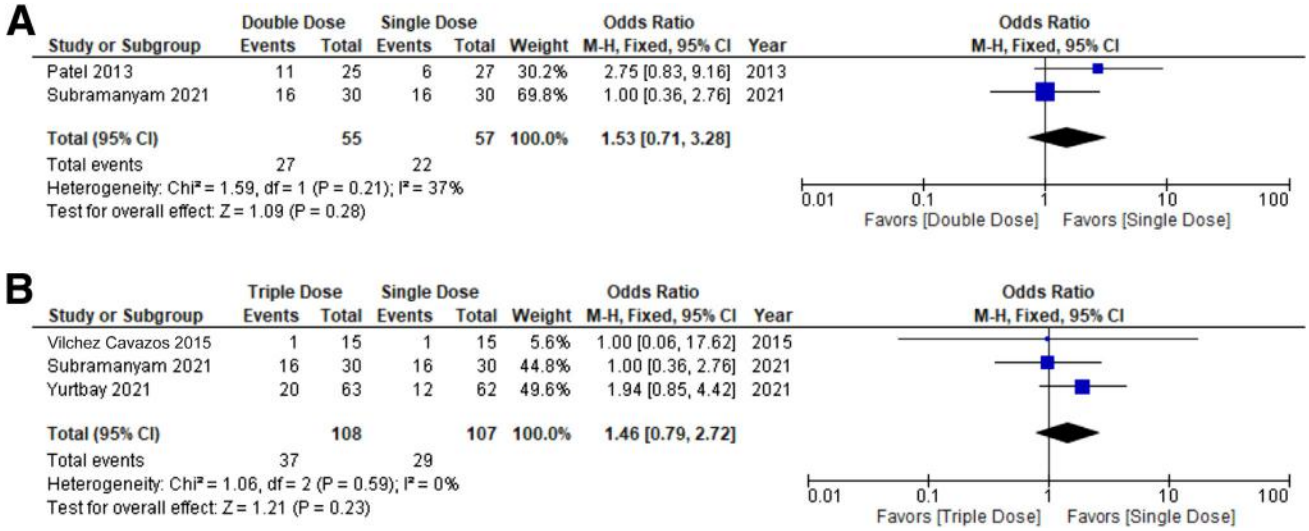


Fig 7. Forest plot comparing incidence of adverse events between double-dose platelet-rich plasma (PRP) and single-dose PRP (A) and between triple-dose PRP and single-dose PRP (B). (CI, confidence interval; SD, standard deviation; M-H, Mantel-Haenszel.)

studies included, which could limit the clinical applicability of PRP research. The dearth of and inconsistency in details reported pose a challenge to data aggregation and comparison between different studies and increase heterogeneity.[23,24] With an increasing number of studies evaluating injectable treatments in KOA, standardization of PRP preparation and reporting of the protocol are important in objectively analyzing whether multiple-dose PRP therapy has good clinical applicability.

The findings of this study are not corroborated by a systematic review by Vilchez-Cavazos et al.,[6] who did not find a compelling reason to administer multiple-dose therapy over single-dose therapy. It postulated that single-dose PRP was as effective as multiple-dose PRP in terms of pain improvement, granted that treatment with multiple injections provides greater joint functionality. Meanwhile, our study included all the studies comparing multiple-dose PRP therapy with single-dose PRP from the aforementioned study and included more recent studies by Subramanyam et al.[9] (2021) and Yurtbay et al.[12] (2022) to allow for a better-informed comparison. Additionally, it is to be noted that there was high heterogeneity ($I^2 > 90\%$) between the studies included in the systematic review by Vilchez-Cavazos et al., which could be important.

This study is one of few studies to have performed a systematic review and meta-analysis comparing multiple-dose PRP therapy and single-dose PRP therapy, given that most studies have compared the efficacy of PRP versus placebo[25] or PRP versus hyaluronic acid.[26-28] In addition, the quality of the evidence in this study is good because all the studies included were of low to moderate risk of bias.

Limitations

Several study limitations should be mentioned. First, the small number of studies (N = 8) weakens the power of conclusions drawn from the study. Moreover, as mentioned earlier, there is a high level of heterogeneity in the studies. Second, a funnel plot could not be used to assess publication bias owing to the small number of studies. Third, the PRP concentrations and preparation methods used in the literature vary across studies, which may have had an impact on the efficacy of treating KOA. Fourth, the included studies examined different outcomes at different time points while omitting other data. This resulted in a small number of studies examining a certain outcome at a certain time point, restricting our ability to draw significant conclusions at specific times. Fifth, there was little overlap in the articles discussing double- and triple-dose therapy. Although our study aimed to compare single-dose therapy against multiple-dose therapy, detailed examination of the effects of the number of doses used to achieve maximal efficacy would still strengthen the conclusions drawn. Finally, there was a lack of exploration of the varying concentrations of PRP, which could provide a more holistic perspective on KOA treatment.

Conclusions

Although there is a paucity of large high-quality Level I studies, current best evidence suggests that 3 doses of PRP for KOA may be more effective than 1 dose of PRP at providing pain relief up to 1 year after administration.

References

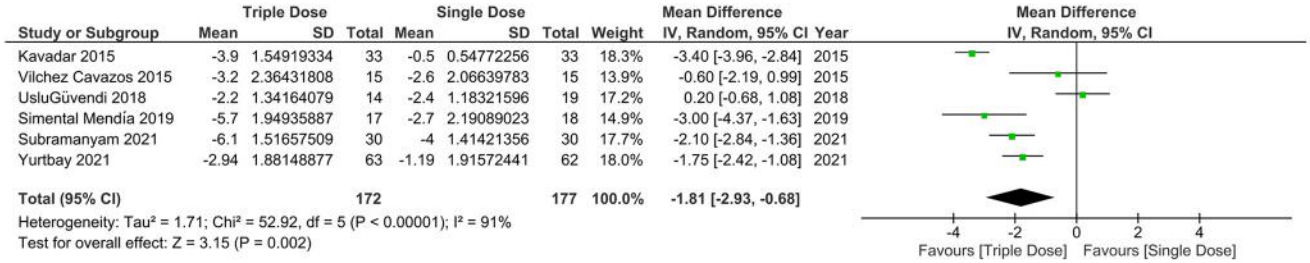
1. Alves R, Grimalt R. A review of platelet-rich plasma: History, biology, mechanism of action, and classification. *Skin Appendage Disord* 2017;4:18-24.
2. Dhurat R, Sukesh M. Principles and methods of preparation of platelet-rich plasma: A review and author's perspective. *J Cutan Aesthet Surg* 2014;7:189-191.
3. Campbell K, Saltzman B, Mascarenhas R, et al. Does intra-articular platelet-rich plasma injection provide clinically superior outcomes compared with other therapies in the treatment of knee osteoarthritis? A systematic review of overlapping meta-analyses. *Arthroscopy* 2015;31:2213-2221.
4. Hermans J, Bierma-Zeinstra S, Bos P, Niesten D, Verhaar J, Reijman M. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: A randomised controlled trial. *BMC Musculoskelet Disord* 2019;20:196.
5. Görmeli G, Görmeli C, Ataoglu B, Çolak C, Aslantürk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: A randomized, double-blind, placebo-controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2015;25:958-965.
6. Vilchez-Cavazos F, Millán-Alanís J, Blázquez-Saldaña J, et al. Comparison of the clinical effectiveness of single versus multiple injections of platelet-rich plasma in the treatment of knee osteoarthritis: A systematic review and meta-analysis. *Orthop J Sports Med* 2019;7:232596711988711.
7. Vilchez Cavazos F. Intra-articular injections of platelet-rich plasma in knee osteoarthritis: Unique application versus triple application. ClinicalTrials.gov identifier NCT02370420. https://clinicaltrials.gov/ct2/show/study/NCT02370420. Published February 25, 2015. Updated February 19, 2018. Accessed January 30, 2023.
8. Güvendi EU, Askin A, Güvendi G, Kocyigit H. Comparison of efficiency between corticosteroid and platelet rich plasma injection therapies in patients with knee osteoarthritis. *Arch Rheumatol* 2018;33:273-281.
9. Subramanyam K, Alguvelly R, Mundargi A, Khanchandani P. Single versus multi-dose intra-articular injection of platelet rich plasma in early stages of osteoarthritis of the knee: A single-blind, randomized, superiority trial. *Arch Rheumatol* 2021;36:326-334.
10. Simental-Mendía M, Acosta-Olivo CA, Hernández-Rodríguez AN, et al. Intraarticular injection of platelet-rich plasma in knee osteoarthritis: single versus triple

application approach. Pilot study. *Acta Reumatol Port* 2019;44:138-144.
11. Patel S, Dhillon M, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis. *Am J Sports Med* 2013: 41356364.
12. Yurtbay A, Say F, Çinka H, Ersoy A. Multiple platelet-rich plasma injections are superior to single PRP injections or saline in osteoarthritis of the knee: The 2-year results of a randomized, double-blind, placebo-controlled clinical trial. *Arch Orthop Trauma Surg* 2022;142:2755-2768.
13. Kavadar G, Demircioglu DT, Celik MY, Emre TY. Effectiveness of platelet-rich plasma in the treatment of moderate knee osteoarthritis: A randomized prospective study. *J Phys Ther Sci* 2015;27:3863-3867.
14. Ayhan E. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. *World J Orthop* 2014;5:351.
15. Sharma V, Anuvat K, John L, Davis M. *Arthritis of the knee. DeckerMed Pain Manage* 2017;38:189-193.
16. Dulay GS, Cooper C, Dennison EM. Knee pain, knee injury, knee osteoarthritis & work. *Best Pract Res Clin Rheumatol* 2015;29:454-461.
17. Robinson W, Lepus C, Wang Q, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2016;12:580-592.
18. Daheshia M, Yao J. The interleukin 1β pathway in the pathogenesis of osteoarthritis. *J Rheumatol* 2008;35: 2306-2312.
19. Sowers M, Karvonen-Gutierrez C. The evolving role of obesity in knee osteoarthritis. *Curr Opin Rheumatol* 2010;22:533-537.
20. Sun S, Lin G, Hsu C, Lin H, Liou I, Wu S. Comparing efficacy of intraarticular single crosslinked hyaluronan (HYAJOINT Plus) and platelet-rich plasma (PRP) versus PRP alone for treating knee osteoarthritis. *Sci Rep* 2021;11: 140.
21. Chen W, Lo W, Hsu W, et al. Synergistic anabolic actions of hyaluronic acid and platelet-rich plasma on cartilage regeneration in osteoarthritis therapy. *Biomaterials* 2014;35:9599-9607.
22. Ngarmukos S, Tanavalee C, Amarase C, et al. Two or four injections of platelet-rich plasma for osteoarthritic knee did not change synovial biomarkers but similarly improved clinical outcomes. *Sci Rep* 2021;11:23603.
23. Rodeo S. The need for minimum reporting standards for studies of "biologics" in sports medicine. *Am J Sports Med* 2019:4725312532.
24. Fadadu P, Mazzola A, Hunter C, Davis T. Review of concentration yields in commercially available platelet-rich plasma (PRP) systems: A call for PRP standardization. *Reg Anesth Pain Med* 2019:44652659.
25. Smith P. Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis. *Am J Sports Med* 2016:44884891.
26. Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012:2810701078.
27. Vaquerizo V, Plasencia M, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: A randomized controlled trial. *Arthroscopy* 2013: 2916351643.
28. Filardo G, Kon E, Di Martino A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: Study design and preliminary results of a randomized controlled trial. *BMC Musculoskelet Disord* 2012:1318.

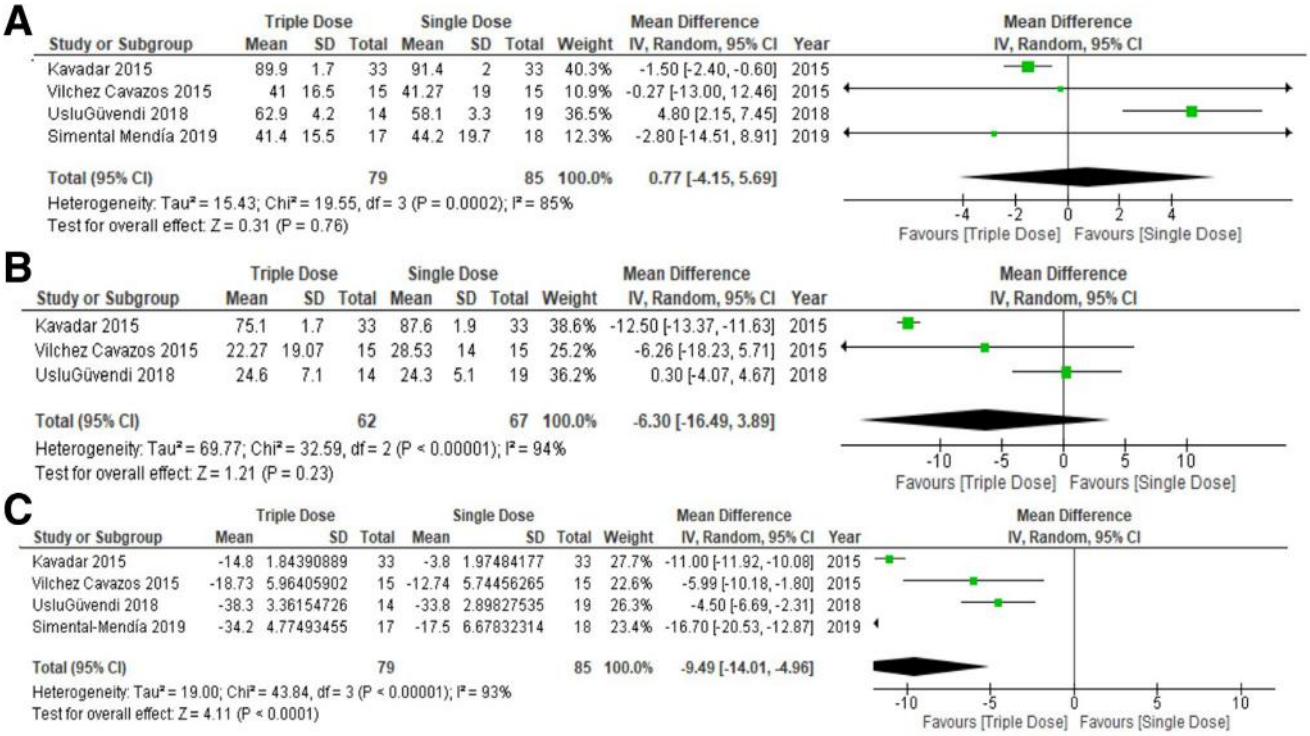
Appendix Table 1. Search Terms Used for Each Database

Database	Search Terms
MEDLINE (PubMed)	(Platelet-rich Plasma OR Platelet-derived Growth Factors OR Platelet-Rich Fibrin OR L-PRF) AND Knee AND (Osteoarthritis OR Degenerative OR Arthroses OR Arthrosis OR Osteoarthrosis OR Osteoarthrosis Deformans) AND (Multiple infiltrations OR Multiple injections OR Unique infiltration OR Unique injection OR Number of injections) AND (Single infiltration OR Single injection OR One injection)
Embase	
CINAHL	
Cochrane Library	
Scopus	(platelet-rich AND plasma) AND knee AND (osteoarthritis) AND (multiple AND injections) AND (single AND injection)

CINAHL, Cumulative Index to Nursing and Allied Health Literature.



Appendix Fig 1. Forest plot comparing change in visual analog scale (VAS) scores from baseline to last follow-up between triple-dose platelet-rich plasma (PRP) and single-dose PRP. A significant mean improvement of −1.81 points was observed (95% confidence interval [CI], −2.93 to −0.68; $P = .002$). (SD, standard deviation; IV, inverse variance.)



Appendix Fig 2. Forest plot comparing Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores at baseline (A), WOMAC scores at 6 months (B), and change in WOMAC scores from baseline to last follow-up (C) between triple-dose platelet-rich plasma (PRP) and single-dose PRP. (A) A total of 4 studies reported the WOMAC function score at baseline. There were no significant differences in the baseline WOMAC scores between the single- and triple-dose groups (standardized mean difference, 0.77; 95% confidence interval [CI], −4.15 to 5.69; $P = .76$ [not significant]). (B) A total of 3 studies reported the WOMAC function score at 6 months after treatment. At 6 months after treatment, the WOMAC function score in the triple-dose group was 6.30 points lower (better) than that in the single-dose group (standardized mean difference, −6.30; 95% CI, −16.49 to 3.89; $P = .23$ [not significant]). (C) Comparison of the change in WOMAC function scores from baseline to last recorded follow-up between triple-dose PRP and single-dose PRP showed a significant mean improvement of −9.49 points (95% CI, −14.01 to −4.96; $P < .0001$). (IV, inverse variance.)