Is platelet-rich plasma better than hyaluronic acid in the treatment of knee osteoarthritis? A meta-analysis of randomized controlled trials

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Abstract

Introduction: Due to the complicated surgical procedure of knee arthroplasty and low effectivity of hyaluronic acid (HA) in the treatment of knee osteoarthritis, various studies highly recommend the use of platelet-rich plasma (PRP). However, some studies also reported lower efficacy and limited use of PRP.
Aim: To analyze systematically the different randomized controlled trials (RCTs) comparing the effectiveness of HA vs. PRP for the treatment of knee osteoarthritis.
Material and methods: A systematic literature review was conducted using Medline and Central databases for RCTs about the comparison of HA vs. PRP for the treatment of knee osteoarthritis. Studies were included as per the PICOS criteria and relevant event data were extracted. Risk of bias was analyzed and a random-effects model was used to calculate the pooled odds ratio and risk ratio using RevMan software.
Results: A total of 14 studies were included in the meta-analysis from year 2000 to 2021 including 613 patients. The current meta-analysis has a low risk of publication bias and we obtained the pooled odds ratio (OR) of 2.55 (95% CI: 1.35–4.84) with a τ^2 value of 1.01, χ^2 value of 52.79, I^2 value of 77%, Z value of 2.87 and p-value < 0.00001. The pooled risk ratio was 1.34 (95% CI: 1.09–1.65) with a τ^2 value of 0.09, χ^2 value of 73.48, I^2 value of 84%, Z value of 2.80 and p-value < 0.00001.
Conclusions: The current meta-analysis highly recommends the use of PRP for the treatment of knee osteoarthritis.

Key words: knee osteoarthritis, hyaluronic acid, platelet-rich plasma, meta-analysis, randomized controlled trials.

Introduction

Knee osteoarthritis (KOA) is a common disorder characterized by cartilage deterioration and joint space shortening [1]. Patients commonly get a variety of therapies to halt or stop the progression of KOA; however, no medication has been proven to do so. The present treatment focuses primarily on symptom remission, with the prime objective of pain relief and function improvement. Nonsurgical illnesses are treated with both nonpharmacological and pharmacological therapy [2]. Non-pharmacological therapy such as diet and exercise are frequently recommended; however, they are not always followed [3]. The most prevalent pharmacological therapy for KOA is oral glucosamine, chondroitin, acetamino-

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phen, celecoxib, and chondroitin. However, non-steroid anti-inflammatory drugs (NSAIDs) and analgesics are usually associated with side effects [4]. Total knee arthroplasty can be one of the treatment options, but it has a complicated surgical procedure. The American College of Rheumatology (ACR) authorized intra-articular hyaluronic acid (HA) injections in the therapy of patients with KOA in 2012 [5], but owing to its low effectivity, various studies [6–10] highly recommend the use of platelet-rich plasma (PRP). PRP is an autologous product made from a patient's blood using a gradient density centrifugation procedure. PRP contains a variety of growth factors and other bioactive compounds that have been shown to help control abnormal inflammatory processes, rebuild tissue structures, and promote tissue repair. Autologous PRP has a low risk of immunological responses and infectious disease transmission, and it has been routinely utilized to treat rotator cuff tendinopathy. For example, Lin *et al.* found that intra-articular injections of leukocyte-poor PRP can give a clinically meaningful functional improvement in patients with mild-to-moderate osteoarthritis of the knee for at least 1 year. However, some studies also reported less efficacy and limited use of PRP.

Aim

Therefore, the present meta-analysis aimed to systematically analyze the different randomized controlled trials (RCTs) comparing the effectiveness of HA vs. PRP for the treatment of knee osteoarthritis and see how effective and safe intra-articular PRP is for KOA patients.

Material and methods

Search strategy

This meta-analysis is based on an extensive literature search conducted using Medline (PubMed), Cinahl (Ebsco), Scopus, Web of Sciences, and Cochrane Register of Controlled Trials (CENTRAL) databases from the year 2000 to 2021. The following search words were used: knee osteoarthritis, HA, PRP, meta-analysis, and RCTs.

Study selection or inclusion/exclusion criteria

Studies were selected randomly irrespective of their language, publication status, or study type, and those having potentially relevant titles and abstracts were scanned, and their full-text versions were read. Included RCTs [6–19] with sufficient event data were selected as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (registration number CH#/IRB/2021/555). Studies with insufficient data, non-randomized studies, quasi-experimental studies, retrospective and cohort studies, and related studies published before 2000 were excluded.

Data extraction and quality assessment

After identifying relevant articles that met the desired inclusion criteria, event data were extracted using a predefined data extraction form, and the demographic summary is presented in Table I. It includes the following items: author of the study, publication year, study type, duration of the study, and number of patients included, their age, sex ratio, and dose of drugs used for both intervention (PRP) treated patients and control (HA) treated patients, a parameter to assess positive outcome and statistical significance of results in terms of the *p*-value. In order to assess the methodological quality of the included studies, the Cochrane Collaboration's risk of bias tool was used, including the criteria of randomization, allocation concealment, blinding, and completeness of follow-up as the significant assessment parameters. The risk of bias for each item was graded as high, low, or unclear risk.

Sources of heterogeneity

The investigated heterogeneity sources were full-text publications versus abstracts, randomized controlled trials of patients of various age groups, different numbers of patients, variable duration of treatment, different scales of analysis, and comparison of PRP with different control medicines.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine (CH#/IRB/2021/555) and informed consent was not required.

Quantitative data synthesis

In order to assess the comparative efficiency of HA and PRP in the treatment of knee osteoarthritis, patients of different age groups were treated with ei-

Table I. Demographic summary of the included studies

Study ID and year	Type of study	Duration of treatment	PRP (platelet rich plasma) treated group					Hyaluronic acid treated group					Detection method	P-value
			Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome	Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome		
Cerza et al. 2012	Randomized controlled trial	24 weeks	4 intra-articular injections of PRP (specifically, autologous conditioned plasma (ACP), 5.5 ml)	60	66.5	25/35	31/60	4 intra-articular injections of HA (20 mg/2 ml)	60	66.2	28/32	10/60	Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index	< 0.001
Filardo et al. 2012	Randomized controlled trial	12 months	3 autologous PRP intra-articular injections	54	55	37/17	50/54	h 3 HA (> 1500 kDa; Hyalubrix W, Fidia, Abano Terme (PD), Italy) injections	55	58	31/24	47/55	IKDC, KOOS, EQVAS for general health status, and Tegner scores	0.039
Vaquerizo et al. 2013	Randomized controlled trial	5 months	3 injections of PRGF-Endoret (BTI Biotechnology Institute, Vitoria, Spain)	48	62.4	16/32	40/48	One single intra-articular injection of Durolane hyaluronic acid (HA) (Q-MED AB, Uppsala, Sweden)	48	64.8	22/26	7/48	30% reduction in Western Ontario and McMaster Universities Arthritis Index (WOMAC) score	< 0.001
Raeissadat et al. 2014	Randomized controlled trial	12 months	Liquid PRP was injected in a sterile condition using a 22G needle through the classic approach for intra-articular injection	87	56.85	8/69	77/87	HA with Hyalgan® was injected (Fidia Farmaceutici S.p.A, Abano Terme, Italy), with high molecular weight (500,000–730,000 Da) fraction of purified natural sodium hyaluronate	73	61.13	15/47	62/73	reduction in Western Ontario and McMaster Universities Arthritis Index (WOMAC) score	< 0.001

Table I. Cont.

Study ID and year	Type of study	Duration of treatment	PRP (platelet rich plasma) treated group					Hyaluronic acid treated group					Detection method	P-value
			Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome	Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome		
Gormeli et al. 2015	Randomized controlled trial	6 months	3 IA PRP injections (1 ml of CaCl$_2$ was added to activate the platelets)	44	53.8	19/25	40/44	3 HA injections (HA preparation (30 mg/2 ml, Orthovisc (Anika Therapeutics Inc, Woburn, Massachusetts, USA))	39	53.5	17/22	34/39	EuroQol visual analogue scale (EQ-VAS) and International Knee Documentation Committee (IKDC) subjective scores	0.001
Paterson et al. 2016	Randomized controlled trial	3 months	3 ml of PA-PRP injected under ultrasound guidance (Logic i, GE Healthcare)	12	49.91	8/4	10/12	HA (Synvisc® Hylan G-F 20, Genzyme Biosurgery, Ridgefield, NJ, USA)	11	52.70	7/3	9/11	Knee Injury and Osteoarthritis Outcome Score (KOOS)	< 0.01
Lana JFSD et al. 2016	Randomized controlled trial	12 months	5 ml of platelet rich plasma (white blood cells (WBC) rich, red blood cells (RBC) poor, activated with serum	36	60.9	7/29	23/36	2.0 ml (20 mg of HA) of high molecular weight (2.4–3.6 million daltons) non-cross-linked hyaluronic acid extracted from bacteria cells (Eufflexa-Ferring 10 mg/ml HA)	36	60	3/33	16/36	Western Ontario and McMaster Universities Arthritis Index (WOMAC) score and Visual Analogue Scale (VAS) score	< 0.0001

Table I. Cont.

Study ID and year	Type of study	Duration of treatment	PRP (platelet rich plasma) treated group					Hyaluronic acid treated group					Detection method	P-value
			Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome	Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome		
Heredia et al. 2016	Randomized controlled trial	6 months	PRP injections (Magellan-PRPTM (Global Orthobiologic, Miami, Florida, USA)	27	66.3	12/15	25/27	HA in the form of sodium hyaluronate (Adant®, Manufactured by Tedec-Meiji Farma, Alcalá de Henares, Madrid, Spain, Molecular Weight: 799.638329 g/mol)	26	61.5	9/17	17/26	Visual Analogue Scale (VAS); the Knee and Osteoarthritis Outcome System (KOOS) scale and the European Quality of Life scale (EURO-QOL)	0.13
Doria et al. 2017	Randomized controlled trial	12 months	Three weekly intra-articular injections of autologous PRP preparation (consisted of a 150-ml venous blood sample)	40	67.3	-	7/40	Three weekly intra-articular injections of hyaluronic acid (Hyalubrix 15 mg/ml, Fidia; Abano Terme, Italy)	40	68	-	9/40	WOMAC score,11 Harris Hip Score,12 and pain VAS score	< 0.05
Lisi et al. 2017	Randomized controlled trial	6 months	Three autologous platelet-rich plasma plus calcium gluconate (as activator) intra-articular injections at four-week intervals	28	53.5	20/10	14/28	Three intra-articular hyaluronic acid (20 mg/2 ml; Hyalgan; Fidia, Abano Terme, Italy) injections	22	57.1	16/12	2/22	Magnetic resonance imaging (MRI)	< 0.003

Table I. Cont.

Study ID and year	Type of study	Duration of treatment	PRP (platelet rich plasma) treated group					Hyaluronic acid treated group					Detection method	P-value
			Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome	Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome		
Tavassoli et al. 2019	Randomized controlled trial	12 weeks	Intra-articular injection of PRP; injected using a 22-gauge needle with classic inter-articular approach	28	66.04	6/22	28/28	Three injections of Hyalgan brand hyaluronic acid (high molecular weight 500–730 kilodalton fraction of purified sodium hyaluronate (30 mg/2 ml)	27	63.80	8/19	0	30% reduction in Western Ontario and McMaster Universities Arthritis Index (WOMAC) score	< 0.001
Buendía López et al. 2019	Randomized controlled trial	52 weeks	A total 5 ml of an LP-PRP preparation (activated by 1 ml of calcium chloride)	33	56.15	16/17	16/33	A single high molecular weight preparation (60 mg/2 ml, Durolane©)	32	56.63	15/17	7/32	Western Ontario and McMaster Universities Arthritis Index (WOMAC) score and Visual Analogue Scale (VAS) score	< 0.001
Lin et al. 2019	Randomized controlled trial	12 months	PRP (RegenKit-THT; Regen Lab, Le Mont-sur-Lausanne, Switzerland)	31	61.17	9/22	20/31	HA (Hyruan Plus, 20 mg/2 ml; molecular weight > 2,500 kDa; LG Chem, Seoul, Republic of Korea)	29	62.53	10/19	14/29	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score and International Knee Documentation Committee (IKDC) subjective score	< 0.05

Table I. Cont.

Study ID and year	Type of study	Duration of treatment	PRP (platelet rich plasma) treated group					Hyaluronic acid treated group					Detection method	P-value
			Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome	Dosage	Total number of patients	Mean age	Gender M/F	Positive outcome		
Martino et al. 2019	Randomized controlled trial	12 months	Intra-articular PRP injection, activated by adding 10% calcium chloride	85	52.7	53/32	45/85	Intra-articular injections of HA (Hyalubrix 30 mg/2 ml, molecular weight: 1500 kDa; Fidia SpA)	82	57.5	47/35	53/82	International Knee Documentation Committee (IKDC) subjective (main outcome), EuroQol visual analog scale, and Tegner scores	0.014

ther HA or PRP. Their positive outcomes were reported in terms of either MRI findings, EuroQol visual analog scale (EQ-VAS), International Knee Documentation Committee (IKDC) subjective scores, Knee Injury and Osteoarthritis Outcome Score (KOOS), or Western Ontario and McMaster Universities Arthritis Index (WOMAC) score. Meta-analysis was performed using this extracted data, and statistical parameters such as diagnostic odds ratios and relative risk with a 95% confidence interval were calculated by the Mantel-Haenszel method with random bivariate effects using RevMan software (Review Manager, RevMan, Version 5. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. 2020) along with their respective forest plots. Meta-analyses were done using a random-effects model (Mantel-Haenszel method), and heterogeneity in the included studies was evaluated using the τ^2 value, χ^2 value, I^2 value, and Z value. A p-value < 0.00001 was considered statistically significant. Publication bias of the included studies was summarized in Table II and assessed via funnel plot in which the log risk ratio of each study was plotted against its standard error.

Results

Literature search results

We found a total of 1397 studies through electronic scans from different databases. We excluded 335 studies by reading their titles and abstracts, and 1062 records were screened among these studies. Further, due to invalid references and duplicity, we excluded 704 studies and included only 358 studies for final screening. Out of these 358 studies, 317 were excluded based on the inclusion criteria, and the eligibility of the remaining 41 studies was assessed further. The critical reasons for omission were inadequate evidence and inappropriate comparison criteria to create 2x2 tables for review. Finally, for the meta-analysis, 14 studies that fulfill the inclusion criteria, i.e., use of HA vs. PRP, were used (Figure 1).

Bias assessment

The outcome of risk of bias evaluation via RevMan software is shown in Figure 2. Overall, there was a moderate to high risk of bias due to risk related to randomization, blinding, and selective reporting domains. As shown in Figure 3, the funnel plot was symmetrical and indicated a low possibility of publication bias.

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Table II. Risk assessment for included studies

Variable	Cerza et al. 2012	Filardo et al. 2012	Va-querizo et al. 2013	Raeis-sadat et al. 2014	Gorme-li et al. 2015	Pat-erson et al. 2016	Lana JFSD et al. 2016	Heredia et al. 2016	Doria et al. 2017	Lisi et al. 2017	Tav-assoli et al. 2019	Buendía López et al. 2019	Lin et al. 2019	Mar-tino et al. 2019
Was a consecutive or random sample of patients enrolled?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did the study avoid inappropriate exclusions	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did all patients receive the same reference standard	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were all patients included in the analysis	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Was the sample frame appropriate to address the target population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were study participants sampled in an appropriate way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were valid methods used for the identification of the condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the condition measured in a standard, reliable way for all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was there appropriate statistical analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
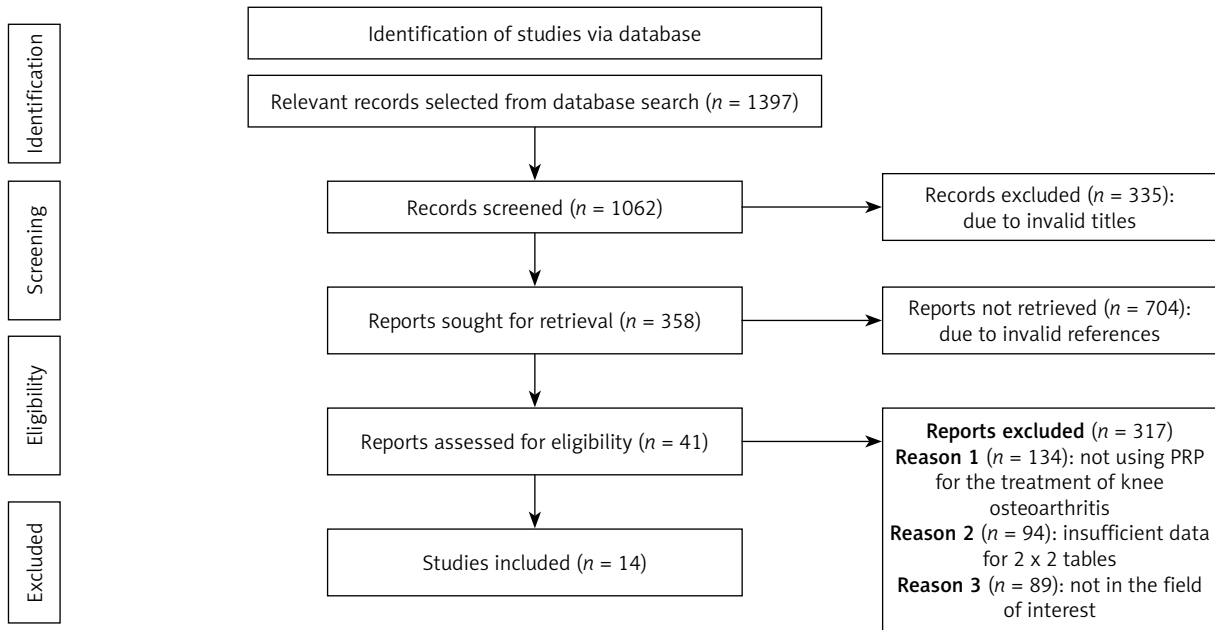
Figure 1. Flow chart for the inclusion and exclusion of studies according to PRISMA guidelines

Figure 2. Risk of bias summary of the studies included in the meta-analysis ($n = 14$)
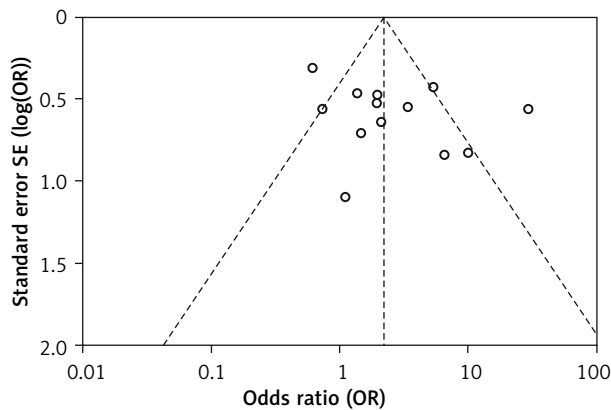
Figure 3. Funnel plot for publication bias

Meta-analysis results

The diagnostic odds ratio was calculated using RevMan software, and a forest plot was constructed, as shown in Figure 4. We obtained the pooled odds ratio (OR) value of 2.55 with 95% CI ranging from 1.35 to 4.84. Data were heterogeneous with a τ^2 value of 1.01, χ^2 value of 52.79, I^2 value of 77%, Z value of 2.87 and p-value < 0.00001. In the forest plot, an odds ratio value greater than 1 designates that the condition or event is more likely to occur. Since we also obtained an odds ratio value greater than 1, i.e., 2.25, it indicates that PRP is more effective for the treatment of knee osteoarthritis as compared to hyaluronic acid.

Relative risk was also calculated using RevMan software, and a forest plot was constructed, as shown in Figure 5. The pooled risk ratio was 1.34, with 95% CI ranging from 1.09 to 1.65. The risk ratio value of more than 1 suggests random sampling of data, use of categorical study variables with high performance, selection, and attrition bias. Since we also obtained a risk ratio value greater than 1, i.e., 1.34, it proves that PRP is safe and reduces the clinical symptoms and EQ-VAS score, IKDC subjective scores, KOOS, and WOMAC score of patients with fewer side effects. Heterogeneity was evaluated as a τ^2 value of 0.09, χ^2 value of 73.48, I^2 value of 84%, Z value of 2.80 and p-value < 0.00001. The I^2 value above 75% suggests that the PRP's use in the treatment of knee osteoarthritis should be highly preferred. Similarly, a p-value less than 0.00001 means that all these results are highly statistically significant and favor the use of PRP for the treatment of knee osteoarthritis.

Combining all of these meta-analysis results, it is clear that PRP is a better alternative than hyaluronic acid and thus highly recommended for the treatment of knee osteoarthritis.

Discussion

Knee osteoarthritis (KOA) is a frequently reported musculoskeletal disorder among middle- and old-aged persons, characterized by deterioration and shortening of joint spaces and cartilage. Due to

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, random, 95% CI	Odds ratio M-H, random, 95% CI
Buendia Lopez *et al.* 2019 [17]	16	33	7	32	8.1	3.36 (1.14, 9.91)	
Cerza *et al.* 2012 [6]	31	60	10	60	8.9	5.34 (2.29, 12.47)	
Doria *et al.* 2017 [14]	7	40	9	40	8.0	0.73 (0.24, 2.20)	
Filardo *et al.* 2012 [7]	50	54	47	55	7.5	2.13 (0.60 7.54)	
Gormeli *et al.* 2015 [10]	40	44	34	39	7.0	1.47 (0.37, 5.92)	
Heredia *et al.* 2016 [13]	25	27	17	26	6.2	6.62 (1.27, 34.51)	
Lana JFSD, *et al.* 2016 [12]	23	36	17	36	8.6	1.98 (0.77, 5.08)	
Lin *et al.* 2019 [18]	20	31	14	29	8.3	1.95 (0.69, 5.49)	
Lisi *et al.* 2017 [15]	14	28	2	22	6.3	10.00 (1.96, 51.11)	
Martino *et al.* 2019 [19]	45	85	53	82	9.6	0.62 (0.33, 1.15)	
Paterson *et al.* 2016 [11]	10	12	9	11	4.8	1.11 (0.13, 9.61)	
Raeissadat *el al.* 2014 [9]	77	87	62	73	8.7	1.37 (0.54, 3.43)	
Tavassoli *et al.* 2019 [16]	28	28	0	0		Not estimable	
Vaquerizo *et al.* 2013 [8]	40	48	7	48	8.0	29.29 (9.71, 88.33)	
Total (95% CI)		613		553	100.0	2.55 (1.35, 4.84)	
Total events	426		288				

Heterogeneity $\tau^2 = 1.01$; $\chi^2 = 52.79$, d$f = 12$ (p < 0.00001); $I^2 = 77\%$
Test for overall effect $Z = 2.87$ ($p = 0.004$)

Figure 4. Forest plot for odds ratio

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, random, 95% CI	Odds ratio M-H, random, 95% CI
Buendia Lopez *et al.* 2019 [17]	16	33	7	32	4.7	2.22 [1.05, 4.66]	
Cerza *et al.* 2012 [6]	31	60	10	60	5.8	3.10 [1.67, 5.74]	
Doria *et al.* 2017 [14]	7	40	9	40	3.8	0.78 [0.32, 1.88]	
Filardo *et al.* 2012 [7]	50	54	47	55	11.5	1.08 [0.95, 1.24]	
Gormeli *et al.* 2015 [10]	40	44	34	39	11.3	1.04 [0.90, 1.21]	
Heredia *et al.* 2016 [13]	25	27	17	26	9.7	1.42 [1.05, 1.91]	
Lana JFSD, *et al.* 2016 [12]	23	36	17	36	8.0	1.35 [0.89, 2.07]	
Lin *et al.* 2019 [18]	20	31	14	29	7.6	1.34 [0.85, 2.11]	
Lisi *et al.* 2017 [15]	14	28	2	22	1.9	5.50 [1.39, 21.70]	
Martino *et al.* 2019 [19]	45	85	53	82	10.2	0.82 [0.63, 1.06]	
Paterson *et al.* 2016 [11]	10	12	9	11	8.6	1.02 [0.70, 1.48]	
Raeissadat *et al.* 2014 [9]	77	87	62	73	11.6	1.04 [0.92, 1.18]	
Tavassoli *et al.* 2019 [16]	28	28	0	0		Not estimable	
Vaquerizo *et al.* 2013 [8]	40	48	7	48	5.1	5.71 [2.85, 11.46]	
Total (95% CI)		613		553	100.0	1.34 [1.09, 1.65]	
Total events	426		288				

Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 73.48$, $df = 12$ ($p < 0.00001$); $I^2 = 84\%$
Test for overall effect $Z = 2.80$ ($p = 0.005$)

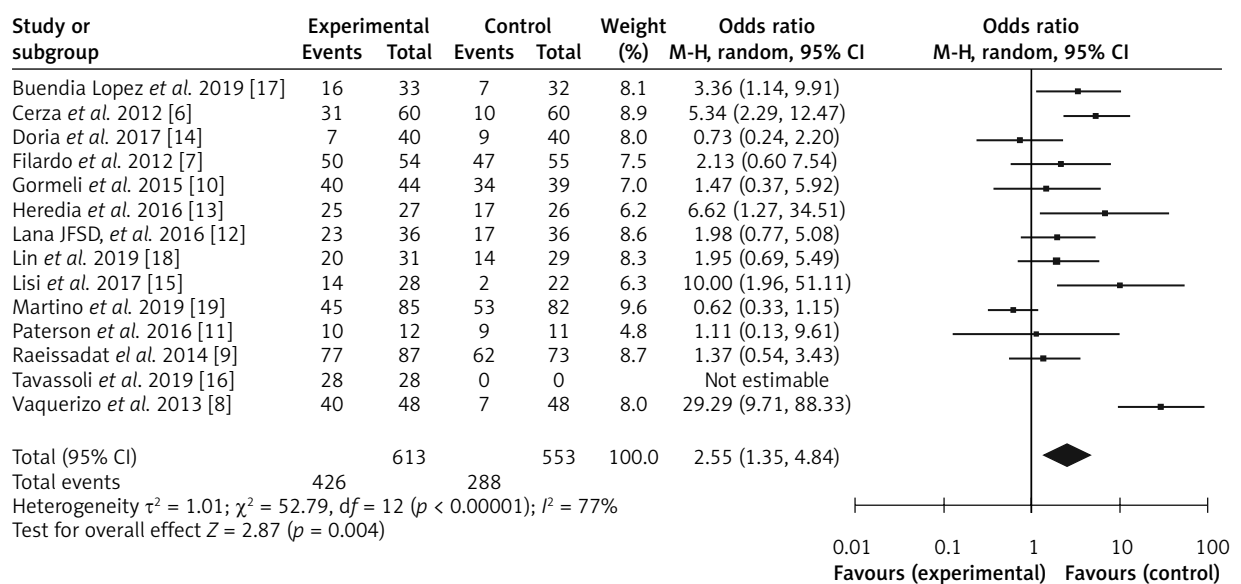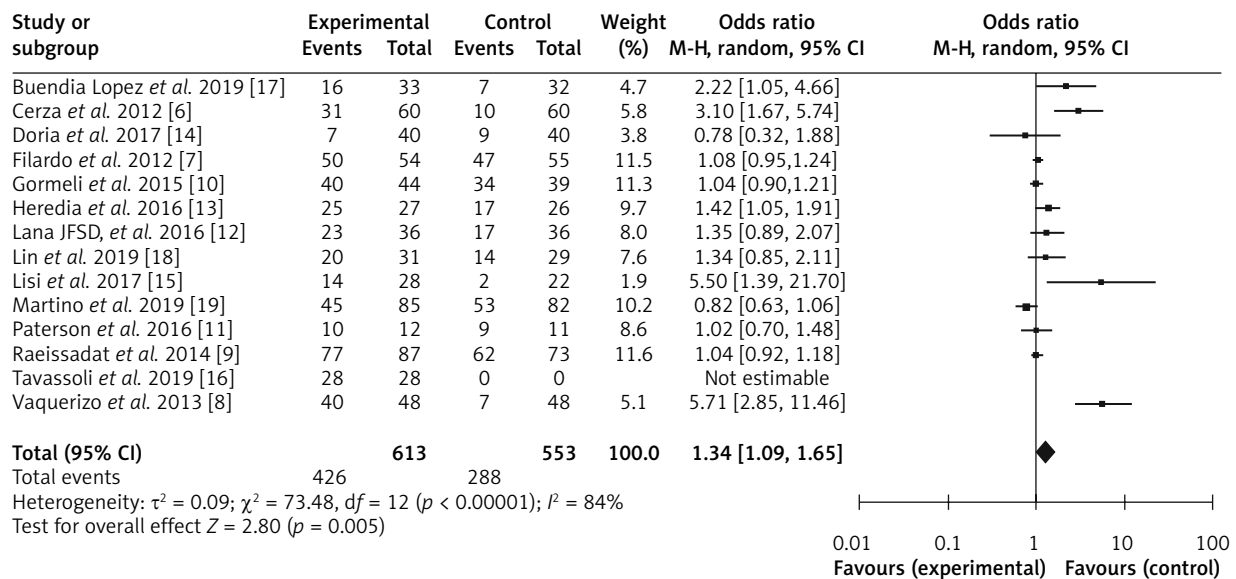**Figure 5.** Forest plot for risk ratio

these deteriorations, patients have issues such as difficulty walking, limited motion, and less flexible movements. Diet control, rest, medication therapies, and knee arthroplasty are common treatment strategies. These strategies are aimed to either halt or stop the progression of knee osteoarthritis; however, no medication has been proven to do so completely. The existing treatment provides relief from pain, symptom remission, and function improvement. The commonly used medicines are oral glucosamine, chondroitin, acetaminophen, celecoxib, and chondroitin, but these drugs are usually associated with side effects, specifically liver issues. Arthroplasty can be a good substitute; still, it is not generally preferred due to its complicated surgical procedure.

Due to the shortcomings of the existing treatment procedure, various studies focus on applying PRP as an effective substitute and highly recommend its use. Since PRP is an autologous product made from a patient's blood, it is entirely safe with no chance of graft rejection or any adverse inflammatory or allergic response. Furthermore, PRP consists of many growth factors and biologically active components; it promotes cell division fast and heals the deteriorated tissue.

For example, Cerza *et al.* in 2012 [6], Dai *et al.* in 2016, and di Martino *et al.* in 2019 [19], based on randomized controlled trials conducted by them, reported that in comparison to HA and saline, intra-articular injection of PRP is more beneficial for pain relief and functional improvement for osteoarthritis

patients. Furthermore, in the meta-analysis conducted by Chen *et al.* in 2020 [20], and Karasavvidis *et al.* in 2020 [21], they also concluded that the use of PRP alone or in combination with hyaluronic acid is the safest and the best strategy for the treatment of knee osteoarthritis in patients of all age groups. Kon *et al.* (2020) also concluded that PRP may be superior to other supplements for pain reduction and functional recovery of knee osteoarthritis. However, in contrast to these results, some studies, e.g. Khosbin *et al.* in 2013 [22] and Han *et al.* in 2020 [23], reported no change in the patient's clinical symptoms using the PRP treatment strategy and reported that lower efficacy limited use of PRP.

In the current meta-analysis, similar to the PRP supported studies, we also obtained the pooled odds ratio (OR) value of 2.55 with a 95% CI range of 1.35–4.84 with the τ^2 value of 1.01, χ^2 value of 52.79, I^2 value of 77%, the Z value of 2.87 and p-value < 0.00001. The high odds ratio proved that PRP is a safe and effective strategy to reduce clinical symptoms with minimal side effects. The pooled risk ratio obtained was 1.34 to 95% CI ranging from 1.09 to 1.65 with a τ^2 value of 0.09, χ^2 value of 73.48, I^2 value of 84%, the Z value of 2.80 and p-value < 0.00001. These values reflect the possibility of random sampling and high performance, selection, and attrition bias. However, a high I^2 value above 75% highly supports the use of PRP for the treatment of knee osteoarthritis. The p-value of less than 0.00001 indicates statistically significant results and favors

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the use of PRP for the treatment of knee osteoarthritis.

Therefore, after a thorough systematic review and statistically significant meta-analysis results of the included randomized controlled trials (RCTs), the present meta-analysis highly favors PRP for the treatment of knee osteoarthritis.

The limitation of the present study is that the variability of control drugs used for the treatment of knee osteoarthritis in comparison to PRP skews the results. Similarly, considering different scores such as KOOS and WOMAC, and assessing clinical symptoms by different analytical tests performed by different persons have also influenced the risk of false-negative results. Furthermore, many studies have not reported the comparative efficiency of PRP with conventionally used HA, affecting the data to some extent. Data from other relevant studies showing the efficacy of PRP compared to hyaluronic acid can also include more results to suggest its use more precisely. Taking into account the variability, detailed data on the patient's case history, physical examination, and pathological tests can provide further grounds for a recommendation of platelet-rich plasma as an effective treatment option for knee osteoarthritis.

In conclusion, although hyaluronic acid is widely used to treat knee osteoarthritis with a significant ability to lower the clinical symptoms, KOOS and WOMAC scores of patients, still, due to its strong and adverse side effects, it is not recommended. Instead, use of PRP (platelet-rich plasma) is preferred, proving to be an efficient and safe treatment strategy for patients with minimal side effects. Therefore, based on the current meta-analysis and statistically significant results ($p < 0.00001$), the use of PRP for the treatment of knee osteoarthritis in adults is highly recommended.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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