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Long-term effectiveness of intra-articular injectables in patients with knee osteoarthritis: a systematic review and Bayesian network meta-analysis

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Abstract

Background Intra-articular injectables are proposed as a solution for pain relief and functional improvement in knee osteoarthritis (OA), however most studies involving intra-articular knee injectables are focused on short-term relief, leaving the recommendations regarding long-term management unclear. This network meta-analysis aimed to evaluate the mid- to long-term effectiveness of intra-articular knee injection of platelet-rich plasma (PRP), hyaluronic acid (HA), corticosteroids (CS), and their combinations for management of knee OA.

Methods Relevant studies were searched through PubMed, EMBASE, Scopus, and Cochrane Register of Trials databases from inception to 20th October, 2024 for randomized controlled trials (RCTs) of knee OA patients who had taken intra-articular injectable treatment with a follow-up duration of at least one year. The study included 37 RCTs involving 5089 patients. The outcomes assessed were pain relief and functional improvement of knee joint. The random effects Bayesian model was carried out for network meta-analysis. The surface under the cumulative ranking (SUCRA) curve demonstrated the rank probability of each injectable therapy for different outcomes.

Results Analysis revealed that, in terms of both knee pain relief and improvement of functional outcomes, the combined intra-articular injection of PRP and HA was ranked ahead of the isolated administration of PRP, followed by combination of HA with CS, HA alone, placebo, and CS at the end of one year.

Conclusion These findings emphasize the sustained efficacy of PRP, particularly when combined with HA, in providing superior long-term pain relief and functional improvement in knee OA compared to other intra-articular injectables, highlighting its potential as a preferred treatment modality.

Keywords Osteoarthritis, Knee, Intra-articular injections, Platelet-rich plasma, Hyaluronic acid, Corticosteroid, Bayesian analysis

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Introduction

Knee osteoarthritis (OA) is a highly prevalent and progressive joint disorder, marked by chronic pain and functional impairment [1]. It represents nearly 80% of the global burden of OA, with its prevalence rising significantly in association with aging and obesity [2]. It leads to severe morbidity and reduces physical activity to a large extent, accounting for disability in the especially in the elderly population [1, 3]. Effective management of knee OA necessitates long-term strategies focused on pain control, maintenance of physical activity, and addressing structural changes in the joint [4]. Though it is a chronic disease, most systematic reviews and studies have focused on the short-term control of knee pain and do not emphasize medium to long-term results [5, 6]. This has resulted in lack of clear guidelines on the medium to long-term management of the disease. Currently, the management of knee OA involves mainly conservative approaches and surgical intervention [7]. Due to various reasons like comorbidities, socioeconomic factors and risks associated with surgery, medical management is preferred in the majority of cases [8]. Conservative treatment includes oral medications, physical therapy and intra-articular (IA) injections [7]. While nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used, safety concerns regarding the long-term use of these drugs exist [9]. Intra-Articular injections are an alternative treatment approach to tide over the pain episodes and resume routine activities [10]. The commonly used agents for IA administration include hyaluronic acid (HA), corticosteroids (CS) and platelet-rich plasma (PRP) [10]. These agents are used in isolation or combination to improve pain relief and patient functional outcomes. According to the Osteoarthritis Research Society International (OARSI) [11] and the American College of Rheumatology (ACR) [12] guidelines, IA corticosteroids are conditionally recommended for knee OA due to their short-term pain control. However, concerns regarding their long-term safety profile limit their widespread use. Similarly, intra-articular HA injections are conditionally recommended against by the ACR guidelines due to limited evidence supporting their efficacy [12]. Nevertheless, OARSI guidelines acknowledge potential benefits of HA injections in providing pain relief beyond 12 weeks of treatment and emphasize their favorable long-term safety profile compared to repeated intra-articular CS injections [11]. Emerging therapies such as PRP and stem cell injections, while investigational, are not yet endorsed by OARSI or ACR due to the very low amount of evidence and lack of standardization in formulation and administration [11, 12].

In the past few years, numerous studies have compared intra-articular injection therapies with one another [13–15]. Sadabad et al. in their metanalysis, reported PRP's efficacy over HA [14]. However, Cole et al. found no difference between HA and PRP in pain relief in patients suffering from knee osteoarthritis [15]. Similarly, studies have reported varied results in patients treated with HA or corticosteroids [16]. Despite a large number of clinical trials that had investigated the effect of HA, CS and PRP, they had included a small subset of subjects leading to low statistical power and conflicting results. Moreover, majority of these studies and meta-analyses have focused on the short-term gains, neglecting the medium- to long-term effects of IA injections. A network meta-analysis would offer the advantage of achieving a combined and coherent analysis of data in the trials drawing evidence from both indirect and direct comparisons of HA, CS, PRP and their combined administration. Hence, the objective of the current study is to systematically search, review and quantify the mid to long-term results from the randomized trials conducted on knee OA patients receiving IA injections of either platelet-rich plasma, hyaluronic acid, corticosteroids or their combined administration.

Methods

In the current systematic review and meta-analysis, we followed a peer-reviewed protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021255932) [17]. The network meta-analysis was prepared as per the guidelines of the Preferred Reporting Items for Meta-analysis (PRISMA) statement [see Additional file 1]. [18]. The analyses were performed on the previously published data, so no patient consent or ethical approval was required.

Search strategy and data sources

Two researchers (KK, AD) developed the search strategy in collaboration with the research search team. A systematic online search was performed to check for eligible trials from PubMed, Scopus, Embase and Cochrane. Published studies from inception to 20th October 2024 were systematically searched. A national library of medicine weekly alert was set for the main search query until November 2024, but it did not yield any results relevant to the study. There were no language restrictions. The references of the material obtained were manually searched for to look out for any relevant literature. The complete search strategy has been elaborated in Supplementary Material [see Additional file 2].

Eligibility criteria

1. All randomized controlled trials (RCTs) involving patients with knee osteoarthritis.

2. Studies with Corticosteroids (CS), Hyaluronic acid (HA), and Platelet Rich Plasma (PRP) as test or control groups.
3. The studies with at least 80% patient follow-up.
4. Trails with treatment or follow-up duration of at least 1 year. The one-year duration is the minimum duration for long-term assessment of conservative modalities in knee OA [19].

We excluded the trials in the case of animal or cadaveric studies, conference papers, literature reviews, editorials, expert opinions and retrospective studies.

Study selection

Two investigators, AD and AL, independently screened the articles for the title, abstract and full text. The study was included in the review as decided by consensus; however, in case of any dispute, the opinion of a third researcher (KK) was sorted.

Outcomes assessment and data extraction

The other investigators (NG, KK, AL) independently extracted the author's information, clinical outcomes and overall risk of bias. The trials were included if they reported at least one of the outcomes to be measured: pain or function. Knee pain was chosen as the primary outcome to be measured because pain is the principal symptom that causes stress to patients with knee osteoarthritis. The other secondary outcome to be measured was the functioning of knee joint.

Different scales assessed pain or physical functioning of the knee joint in the trials, so, the prioritization method described in a previous study was used [20]. The best outcome measure was the Visual Analogue Scale (VAS) [21], followed by the pain assessment subscale of Western Ontario and McMaster University Osteoarthritis Index (WOMAC) [22]. For the physical functioning of the knee joint, total WOMAC score based on the WOMAC questionnaire [23] was considered the best outcome measure. In addition to WOMAC, International Knee Documentation Committee (IKDC) score [24] was also used as an outcome measure for physical function. The outcomes were evaluated at 6 months and 12 months.

The outcomes at baseline, 6 month-follow-up, 12-month follow-up, and change in the parameters from baseline to 12 months were extracted. The graphical data was extracted using WebPlotDigitizer software (version 5.0) [25]. Other data extracted were first author's name, year of publication, demographics and study design to check for the quality of the trial, type of injection received, sample size, mean age of participants, male to female ratio, body mass index (BMI), grade of osteoarthritis, dose and duration of the treatment, and follow-up time points. Authors of a study were contacted in cases where additional data was needed for analysis.

Methodology for quality assessment

The quality of studies was checked by researchers independently in a blinded fashion. Any disagreement was resolved through consensus. Quality assessment and risk of bias assessment of the included studies was carried out with the Cochrane Collaboration Tool [26].

Statistical analysis

Analysis was done using mean values and standard deviation (SD) of the outcome scores at follow-ups, and change in mean from baseline to 12-month follow-up and its SD. In cases where SD for the mean change in outcome scores was unavailable, the SD was calculated through Meta-Analysis Accelerator tool [27], using formula given in Cochrane handbook [28], assuming a correlation of 0.5 between pre- and post-measurements. In studies where median, interquartile ranges, and ranges were provided instead of mean and SD, the method outlined by Wan et al. [29] were employed to estimate the means and SD. Bayesian multiple network meta-analysis with random-effects model was performed with both placebo and active-controlled trials. Trails with a high risk of bias were excluded before performing main or subgroup analysis.

The statistical analysis for this network meta-analysis (NMA) was performed with a Bayesian framework using MetaInsight (version 6.2.0; National Institute for Health Research Complex Reviews Support Unit) [30], an online application that facilitates NMA and performs Bayesian statistical calculations utilizing the R package gemtc [31] and R package BUGSNET [32]. Network plots and Forest plots were generated to illustrate all comparisons derived from the studies. Surface under the cumulative ranking (SUCRA) curve with Rankogram plot were used to report summarized probability values, and Litmus Rank-O-Gram along with Radial SUCRA plots were generated [33]. The variance between all the treatment effects with consideration of location and hierarchy of treatment were recorded. The value of the worst treatment under SUCRA curve was rated as zero and 100 in case of best available option. Node splitting analysis was performed to verify consistency assumptions and homogeneity [34]. If the direct and indirect comparison results showed no statistically significant difference ($P > 0.05$), it indicated good consistency. The residual deviances from (unrelated mean effect) UME inconsistency model and NMA model were plotted to check for inconsistency [see Additional file 3] [35]. Residual deviance of less than 2 suggested a good fit. If the Gelman-Rubin convergence assessment plots had stability around one, it suggested a

good fit. The leverage plot was used to identify influential or poorly fitting studies and to check how each study was affecting the overall model fit, with leverage values below 3 suggesting a good fit [35, 36]. To evaluate the presence of publication bias, Egger's regression test was conducted using R software (version 4.4.2). A p-value of less than 0.05 suggested potential small-study effects or publication bias. Additionally, comparison-adjusted funnel plots [37] were generated using NMAStudio (version 2.0) [38], an online software for network meta-analysis, to visually inspect asymmetry and detect potential biases across different treatment comparisons.

Results

Study selection

A total of 4171 studies were screened, out of which 37 RCTs (n = 5089) met the eligibility criteria and were included in the meta-analysis [15, 39–74]. The study flow diagram outlines the selection of studies (Fig. 1).

Characteristics of included studies

Out of the included trials 34 interventions were studied for pain and 28 for physical functioning of the knee joint. The duration of the trials varied from one year to five years. Hyaluronic acid (HA) was used alone in 30 trials (1797 participants) and in combination with corticosteroid in 2 trials (51 participants). Platelet rich plasma (PRP) was used alone in 26 trials (1499 participants) and in combination with HA in 5 trials (243 participants) and corticosteroid injection was used alone in 8 trials (400 participants). Among the 37 RCTs, 14 were placebo-controlled trials. The characteristics of the trials included in the study are tabulated in Table 1. The mean age of patients included in the trials ranged from 46.2 years to 71.5 years, with more women than male participants. The duration of the disease varied between two to eleven years. The radiological grading based on Kellgren and Lawrence (KL) classification was mainly between grade 2 and 3. In all the RCTs, the intra-articular injections were administered at variable intervals.

Bias assessment

According to the Cochrane collaboration tool for assessment of the risk of bias, the studies included in the present review were of high quality and had minimal risk of bias (Fig. 2). Risk of bias assessment for each individual

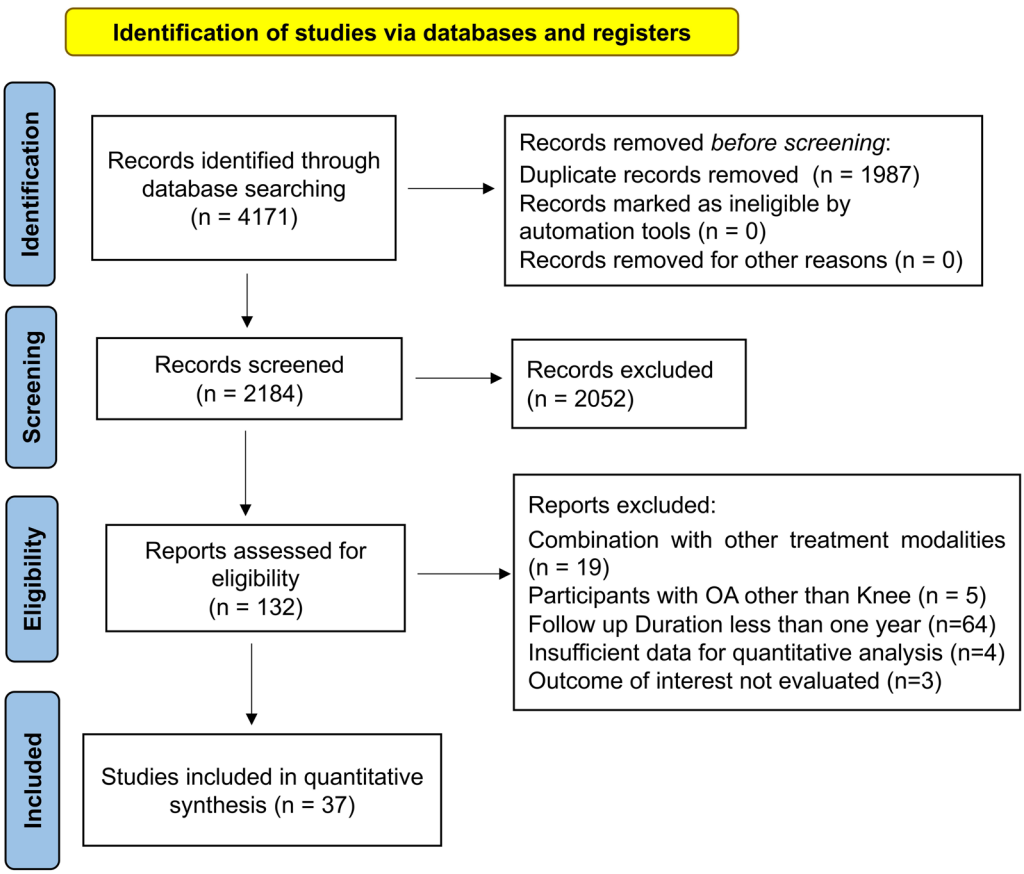

Fig. 1 Prisma flow diagram for study selection

Table 1 Characteristics of included studies

S.no	Study	Drug	Dosage	Number of injections	Dosage interval (in days)	Number of patients	Mean Age (in yrs)	Male/ Female	BMI	OA Grade	Duration of follow up (months)	Measured outcome
1	Annaniemi et al. [39]	PRP	5 ml	3	7	94	57.4	34/60	28.9	1–3	12	WOMAC, VAS, ROM
		HA	48 mg/6 ml or 75 mg/3 ml	3	7	86	65.7	36/50	29.7	1–3	12	WOMAC, VAS, ROM
2	Bansal et al. [40]	HA	88 mg/4 ml	1	NA	68	65.8	42/26	25.2	1–3	12	WOMAC, IKDC, 6MWD, MRI, X RAY
		PRP	8 ml	1	NA	64	64.4	39/25	24.8	1–3	12	WOMAC, IKDC, 6MWD, MRI, X RAY
3	Bisicchia et al. [41]	HA	24 mg/3 ml	2	7	75	71.5	22/53	NR	2–3	12	VAS pain, WOMAC, SF-36
		CS	40 mg/ml	2	7	75	68.6	25/50	NR	2–3	12	VAS pain, WOMAC, SF-36
4	Branch et al. [42]	PRP	4–5 ml	3	7	32	55.78	20/12	27.8	1–4	24	WOMAC, IKDC, KOOS
		HA + PRP	4–5 ml PRP + 3 ml HA	3	7	32	60.66	16/16	28.8	1–4	24	WOMAC, IKDC, KOOS
5	Buendía-López et al. [43]	PRP	5 ml	1	NA	33	56.15	16/17	24.9	1–2	12	WOMAC, VAS, MRI, Xray
		HA	60 mg/2 ml	1	NA	32	56.63	15/17	24.9	1–2	12	WOMAC, VAS, MRI, Xray
6	Chu et al. [44]	PRP	5 ml	3	7	308	53.9	123/185	27.5	1–3	60	VAS pain, WOMAC, IKDC
		PLACEBO	5 ml	3	7	302	54.5	127/175	27.9	1–3	60	VAS pain, WOMAC, IKDC
7	Cole et al. [15]	PRP	4 ml	3	7	49	55.9	28/21	27.4	1–3	12	VAS pain, WOMAC, IKDC
		HA	16 mg/2 ml	3	7	50	56.8	20/30	29	1–3	12	VAS pain, WOMAC, IKDC
8	Davalillo et al. [52]	HA	2.5 ml	5	7	97	62.7	38/59	28.3	2–3	12	WOMAC, VAS, MCII
		CS	5 mg/2 ml	2	28	98	62.8	41/57	26.3	2–3	12	WOMAC, VAS, MCII
9	Di Martino et al. [45]	PRP	5 ml	3	7	85	52.7	100/67	27.2	1–3	64	IKDC, EuroQol VAS and Tegner score
		HA	30 mg/2 ml	3	7	82	57.5	53/33	26.8	1–3	64	IKDC, EuroQol VAS and Tegner score
10	Dougados et al. [62]	HA	20 mg/2 ml	4	7	55	67	13/42	NR	NR	12	VAS pain during exercise
		PLACEBO	2 ml	4	7	55	69	19/36	NR	NR	12	VAS pain during exercise
11	Dulic et al. [46]	PRP	NR	1	NA	34	58.8	15/19	28.4	2–4	12	IKDC, KOOS, WOMAC
		HA	20 mg/2 ml	3	7	30	59.4	13/17	29.98	2–4	12	IKDC, KOOS, WOMAC
12	Duymus et al. [47]	PRP	3–4 ml	2	30	33	60.4	1/32	27.6	2–3	12	VAS pain, WOMAC
		HA	40 mg/2 ml	1	NA	34	60.3	1/33	28.4	2–3	12	VAS pain, WOMAC
13	Elksniņš-Finogejevs et al. [48]	PRP	8 ml	1	NA	20	66.4	17/3	28.6	2–3	12	VAS pain, KSS, IKDC
		CS	40 mg/1 ml	1	NA	20	70.2	15/5	30.5	2–3	12	VAS pain, KSS, IKDC

Table 1 (continued)

S.no	Study	Drug	Dosage	Number of injections	Dosage interval (in days)	Number of patients	Mean Age (in yrs)	Male/ Female	BMI	OA Grade	Duration of follow up (months)	Measured outcome
14	Erturk et al. [49]	HA	2.5 ml	5	7	35	61.4	9/26	30.1	2–4	12	WOMAC pain
		HA + CS	2.5 ml HA + 1 ml CS	5	7	35	62.7	8/27	30.6	2–4	12	WOMAC pain
15	Filardo et al. [50]	PRP	5 ml	3	7	94	53.32	52/37	26.6	1–3	12	IKDC, EQ-VAS, TEGNER, KOOS
		HA	30 mg/2 ml	3	7	89	57.55	60/34	26.9	1–3	12	IKDC, EQ-VAS, TEGNER, KOOS
16	Fossati et al. [51]	PRP	5 ml	3	14	55	60.59	65/108	26.0	1–3	12	WOMAC, IKDC, VAS, TEGNER, KOOS
		HA	40 mg/2 ml	3	14	56				1–3	12	WOMAC, IKDC, VAS, TEGNER, KOOS
		PRP + HA	5 ml PRP + 2 ml HA	3	14	54				1–3	12	WOMAC, IKDC, VAS, TEGNER, KOOS
17	Huang et al. [53]	PRP	4 ml	3	21	40	54.5	25/15	25.2	1–2	12	VAS pain, WOMAC
		HA	2 ml	3	7	40	54.8	19/21	24.5	1–2	12	VAS pain, WOMAC
		CS	1 ml	1	NA	40	54.3	21/19	24.5	1–2	12	VAS pain, WOMAC
18	Jorgensen et al. [54]	HA	20 mg/2 ml	5	7	167	62.6	56/111	28.8	NR	12	VAS during walking
		PLACEBO	2 ml	5	7	170	61.4	73/96	28.8	NR	12	VAS during walking
19	Jubb et al. [55]	HA	20 mg/2 ml	9	7	160	63.5	57/151	29.8	2–3	12	VAS pain, JSW
		PLACEBO	2 ml	9	7	159	65	72/128	29.8	2–3	12	VAS pain, JSW
20	Lana et al. [56]	HA	20 mg/2 ml	3	14	36	60	3/33	28.2	1–3	12	WOMAC, VAS pain
		PRP	5 ml	3	14	36	60.9	7/29	27.4	1–3	12	WOMAC, VAS pain
		HA + PRP	5 ml PRP + 2 ml HA	3	14	33	62	6/27	29.1	1–3	12	WOMAC, VAS pain
		PLACEBO	5 ml	3	7	28	60.1	12/16	29.9	1–2	12	VAS pain, KOOS, EQ-5D
21	Li et al. [57]	PRP	4 ml	3	7	34	59.53	21/46	25.5	1–3	12	VAS pain, WOMAC
		HA	20 mg/2 ml	3	7	33	58.91		25.8	1–3	12	VAS pain, WOMAC
22	Lin et al. [58]	PRP	2 ml	3	7	31	61.17	9/22	23.9	1–3	12	WOMAC, IKDC
		HA	2 ml	3	7	29	62.53	10/19	26.2	1–3	12	WOMAC, IKDC
		PLACEBO	2 ml	3	7	27	62.23	10/17	24.9	1–3	12	WOMAC, IKDC
23	Lisi et al. [59]	PRP	5 ml	3	28	30	53.5	20/10	NR	2–3	12	VAS pain, WOMAC, Lysholm, Lequesne Index
		HA	20 mg/2 ml	3	28	28	57.1	16/12	NR	2–3	12	VAS pain, WOMAC, Lysholm, Lequesne Index

Table 1 (continued)

S.no	Study	Drug	Dosage	Number of injections	Dosage interval (in days)	Number of patients	Mean Age (in yrs)	Male/ Female	BMI	OA Grade	Duration of follow up (months)	Measured outcome
24	Listrat et al. [60]	HA	20 mg/2 ml	9	7	20	60	9/11	27.5	NR	12	VAS pain, Lequesne Index
		PLACEBO	NR	9	7	19	64	4/15	26.6	NR	12	VAS pain, Lequesne Index
25	McAlindon et al. [61]	CS	40 mg/1 ml	4	84	70	59.1	33/37	30.8	2–3	24	VAS Pain, WOMAC
		PLACEBO	1 ml	4	84	70	57.2	32/38	31.7	2–3	24	VAS Pain, WOMAC
26	Nunes-Tamashiro et al. [63]	PRP	NR	1	NA	34	67.6	4/30	29.2		12	VAS pain, WOMAC
		CS	40 mg/2 ml	1	NA	33	65.8	3/30	29.5		12	VAS pain, WOMAC
		PLACEBO	2 ml	1	NA	33	68	3/30	30.2		12	VAS pain, WOMAC
27	Ozturk et al. [64]	HA	15 mg/2 ml	6	7	24	58	0/24	31.5	2–3	12	WOMAC pain
		HA + CS	2 ml HA + 1 ml CS (TA)	6	7	16	58.06	1/15	30.3	2–3	12	WOMAC pain
28	Pham et al. [65]	HA	2.5 ml	3	7	131	64.9	38/93	28.5	1–4	12	VAS pain, Lequesne Index
		PLACEBO	2.5 ml	3	7	85	64.9	33/52	29.8	1–4	12	VAS pain, Lequesne Index
29	Raeissadat et al. [66]	PRP	4–6 ml	2	28	87	56.85	8/69	28.2	1–4	12	WOMAC, SF-36
		HA	20 mg/2 ml	3	7	73	61.13	15/47	27.0	1–4	12	WOMAC, SF-36
30	Raeissadat et al. [67]	PRP	2 ml	2	21	52	56.09	13/39	27.4	2–3	12	VAS pain, WOMAC, Lequesne Index
		HA	20 mg/2 ml	3	7	49	57.91	12/37	27.4	2–3	12	VAS pain, WOMAC, Lequesne Index
31	Raynauld et al. [68]	CS	40 mg/1 ml	8	90	34	63.1	9/25	NR	2–3	24	VAS pain, WOMAC, ROM
		PLACEBO	1 ml	8	90	34	63.3	13/21	NR	2–3	24	VAS pain, WOMAC, ROM
32	Smith et al. [69]	PRP	3–8 ml	3	7	15	53.53	5/10	29.5	2–3	12	WOMAC
		PLACEBO	3–8 ml	3	7	15	46.6	6/9	27.4	2–3	12	WOMAC
33	Srikanth et al. [70]	PRP	3–4 ml	2	28	50	49.92	40/10	NR	1–4	12	VAS pain, WOMAC
		HA	20 mg/2 ml	3	7	50	54.16	41/9	NR	1–4	12	VAS pain, WOMAC
34	Su et al. [71]	PRP	6 ml	2	14	25	54.16	11/14	28.1	2–3	18	VAS pain, WOMAC
		HA	2 ml	5	7	30	53.13	12/18	28.8	2–3	18	VAS pain, WOMAC
35	Tschopp et al. [72]	PRP	3 ml	1	NA	30	62	17/13	26	1–3	12	NRS pain, WOMAC
		HA	6 ml	1	NA	30	64	19/11	25.5	1–3	12	NRS pain, WOMAC
		CS	1 ml	1	NA	30	59	14/16	27	1–3	12	NRS pain, WOMAC
		PLACEBO	1 ml	1	NA	30	58	18/12	25.1	1–3	12	NRS pain, WOMAC

Table 1 (continued)

S.no	Study	Drug	Dosage	Number of injections	Dosage interval (in days)	Number of patients	Mean Age (in yrs)	Male/ Female	BMI	OA Grade	Duration of follow up (months)	Measured outcome
36	Xu et al. [73]	PRP	4 ml	3	15	30	56.9	10/20	22.5	2–3	12	VAS pain, WOMAC, Lysholm, Lequesne Index
		HA	2 ml	3	15	20	57.1	5/15	22.8	2–3	12	VAS pain, WOMAC, Lysholm, Lequesne Index
		PRP + HA	4 ml PRP + 2 ml HA	3	15	28	57.9	8/20	21.5	2–3	12	VAS pain, WOMAC, Lysholm, Lequesne Index
37	Yu et al. [74]	PRP	2–14 ml	6	30	104	46.2	50/54	NR	1–4	13	WOMAC, Karnofsky performance
		HA	0.1–0.3 mg	6	30	88	51.5	48/40	NR	1–4	13	WOMAC, Karnofsky performance
		HA + PRP	0.2 mg HA + 8 ml PRP	6	30	96	46.5	50/46	NR	1–4	13	WOMAC, Karnofsky performance
		PLACEBO	NR	6	30	72	56.2	42/30	NR	1–4	13	WOMAC, Karnofsky performance

PRP: Platelet Rich Plasma, HA: Hyaluronic Acid, CS: Corticosteroid, NR: Not Reported, NA: Not Applicable, BMI: Body Mass Index, OA: Osteoarthritis, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, VAS: Visual Analog Scale, EQ-VAS: EuroQol Visual Analogue Scale, NRS: Numeric Rating scale, IKDC: International Knee Documentation Committee, ROM: Range of motion, 6MWD: 6-min walk distance, SF-36: Short Form 36 Health Survey Questionnaire, EQ-5D: EuroQol 5 Dimension

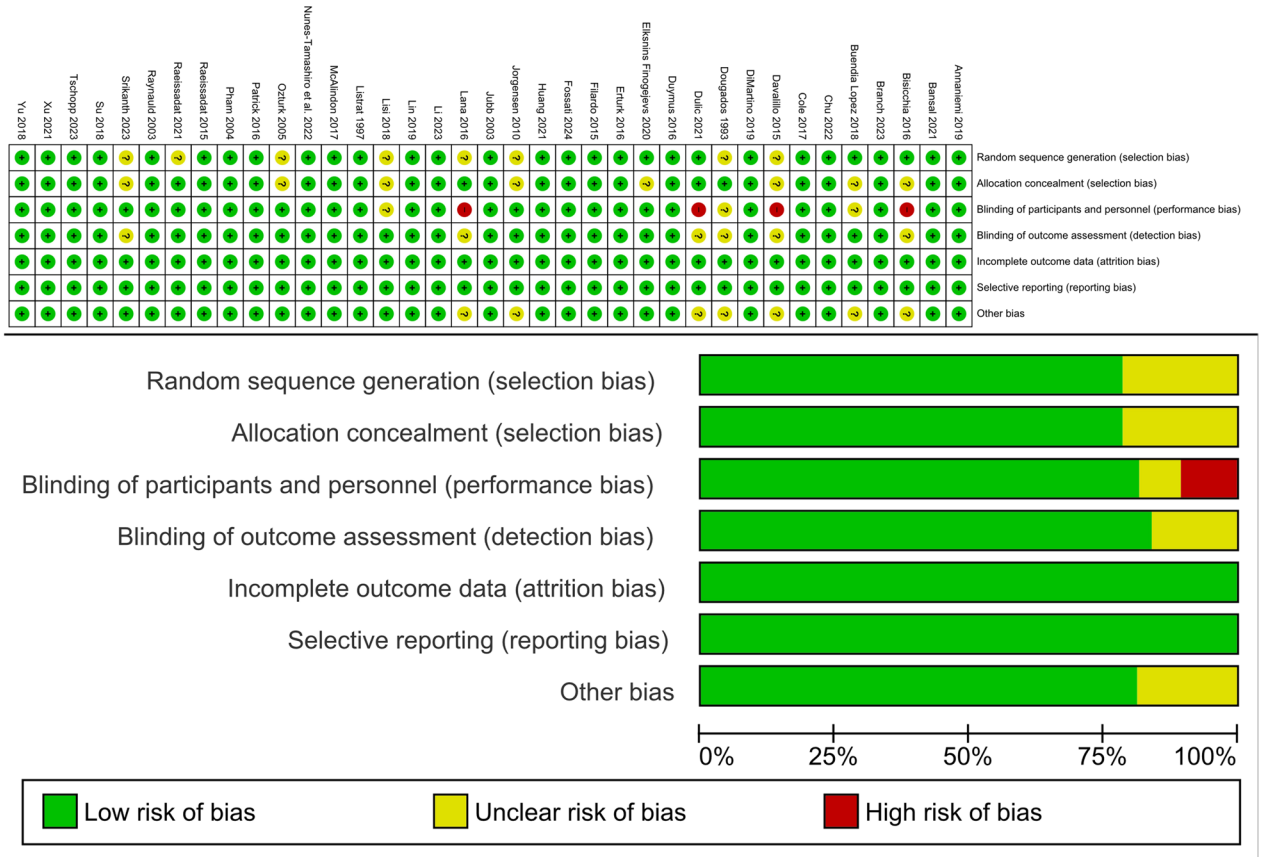

Fig. 2 Summary of risk of bias assessment of the included studies. Note: 'Patrick 2016 [69]' in this figure corresponds to the study by Smith et al., as cited in the text

study is illustrated in Fig. 3. In 25 studies (67.5%), the risk of bias was low; in 12 studies (32.4%), it was moderate; and in 4 studies (10.8%), it was high. The network meta-analysis was deemed appropriate for quantitative synthesis of the evidence in the light of inclusion and exclusion criteria, measurement of outcome, comparability in the study design and subset of the population involved. The assumptions made regarding homogeneity and consistency required for the analysis were confirmed.

Primary outcome

Among the 34 trials assessing pain, the most common outcome measured was VAS knee pain in 28 trials (82.3%), followed by WOMAC pain score in 19 trials (55.8%). The network plots for the VAS knee pain at the follow-ups are shown in Fig. 4. Network plots for WOMAC pain at the follow-ups are shown in Fig. 5.

Pain relief measured through VAS score

The combined administration of HA with PRP had the best probability, with a SUCRA value of 96.89 of pain relief at the end of the six months. It was followed by PRP (SUCRA: 80.7), the combination of HA with CS (SUCRA: 47.7) and HA (SUCRA: 47.5). The intraarticular injections of corticosteroids resulted in minimum pain relief at the end of six months with a SUCRA value of 8.62. Saline fared (SUCRA: 18.44) better than CS in pain relief at the end of six months.

The VAS score was used again to assess pain relief at the end of one year. The combination of HA with PRP had the highest probability of being the best long-term treatment, with a SUCRA value of 96.68. It was followed by the PRP alone (SUCRA: 81.8), HA (SUCRA: 44.4), HA with CS (SUCRA: 42.1), and saline (SUCRA: 17.6). CS alone had lowest SUCRA value at 17.2 at the end of one year. In pairwise comparison, the network meta-analysis revealed that the combination of HA with PRP was associated with the highest decrease in pain (MD: − 24.4; 95% CrI: − 37.2 to − 11.5) in comparison to all other treatment modalities.

The combined administration of HA with PRP had the best probability for decrease in VAS pain score from baseline to the follow-up at 12 weeks, with a SUCRA value of 95.84 and mean difference (MD) of − 25.3 (95%

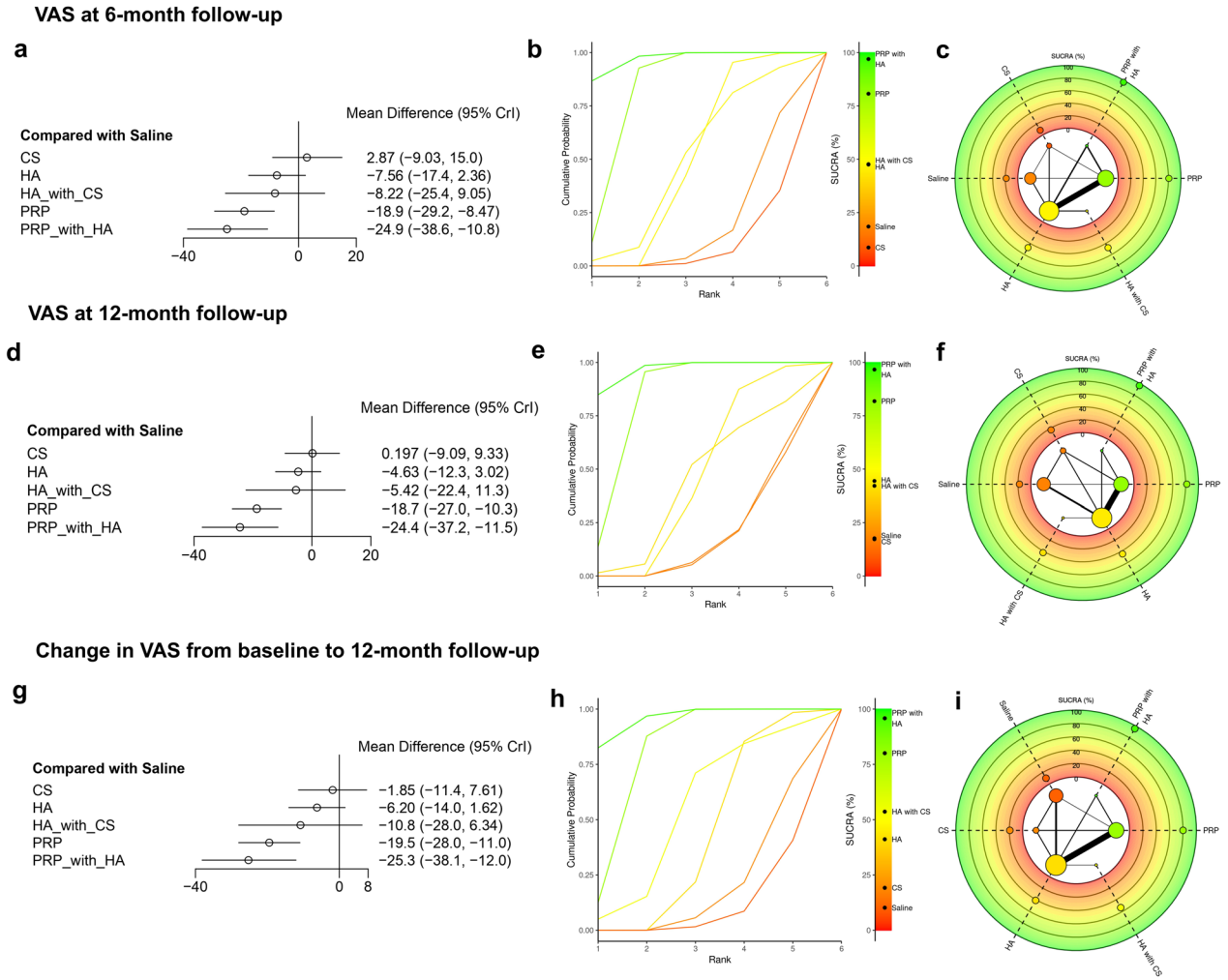

Fig. 3 Network comparisons using VAS pain score. **a**–**c** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using VAS score at 6 months. **d**–**f** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using VAS score at 6 months. **g**–**i**: Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using change in VAS score from baseline to 12-month follow-up

CrI: − 38.1 to 12). It was followed by PRP with a SUCRA value of 80.06 (MD: − 19.5; CrI: − 28 to − 11), combination of HA and CS with a SUCRA value of 53.62 (MD: − 10.8; CrI: − 28 to 6.34), HA alone with a SUCRA value of 41.14 (MD: − 6.2; CrI: − 14 to 1.62), and CS with a SUCRA value of 19.17 (MD: − 1.85; CrI: − 11.4 to 7.61). Each treatment had better probability than saline (SUCRA value: 10.18).

The node splitting model demonstrated no significant inconsistency ($p > 0.05$) between direct and indirect comparisons of any interventions, except for the comparison of HA vs saline at 6 months ($p = 0.038$) and the comparison of CS vs PRP at 12 months ($p = 0.027$). The residual deviances from UME inconsistency model and NMA model were plotted. The residual deviance was less than two in all the studies, and leverage values were below three, suggesting a good fit. The Gelman-Rubin convergence assessment plots for all the treatment arms reached stability around one, which is suggestive of a good fit of the Bayesian network metanalysis.

Pain relief measured through WOMAC pain score

PRP alone had the best probability for pain relief as assessed through WOMAC pain score at the end of the six months, with a SUCRA value of 78.57. It was followed by combination of HA with PRP (SUCRA: 77.17), the combination of HA with CS (SUCRA: 71.43) and HA (SUCRA: 51.53). The intra-articular injections of CS resulted in minimum pain relief at the end of six months with a SUCRA value of 5.9. Saline (SUCRA: 15.3) fared better than CS in pain relief at the end of 6 months.

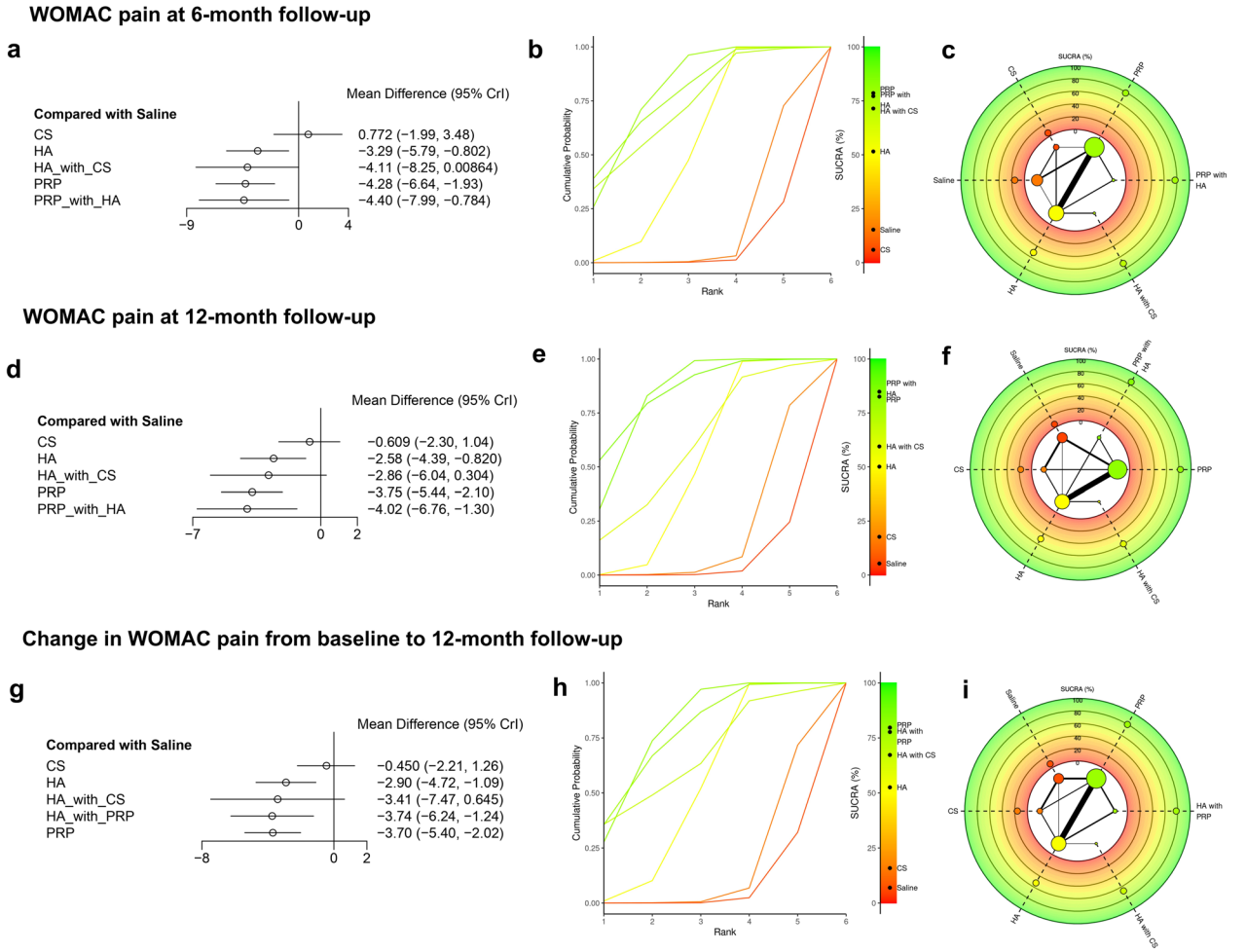

Fig. 4 Network comparisons using WOMAC pain score. **a**–**c** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using WOMAC pain score at 6 months. **d**–**f** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using WOMAC pain score at 6 months. **g**–**i** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using change in WOMAC pain score from baseline to 12-month follow-up

The WOMAC pain score was used again to assess pain relief at the end of one year. The combination of HA with PRP had the highest probability of being the best for long-term pain relief, with a SUCRA value of 84.84. It was followed by the PRP alone (SUCRA: 82.54), HA with CS (SUCRA: 59.46), HA (SUCRA: 50.09), and CS (SUCRA: 17.7). Each treatment had better probability than saline (SUCRA value: 5.33). In pairwise comparison, the network meta-analysis revealed that the combination of HA with PRP was associated with the highest decrease in pain (MD: − 4.02 CrI: − 6.76 to − 1.3) in comparison to all other treatment modalities.

For decrease in WOMAC pain score from baseline to the follow-up at 12 weeks, the combined administration of PRP had the best probability, with a SUCRA value of 79.69 and mean difference (MD) of − 3.70 (95% CrI: − 5.4 to − 2.02). It was followed by HA with PRP with a SUCRA value of 77.68 (MD: − 3.74; CrI: − 6.24 to − 1.24), combination of HA and CS with a SUCRA value of 67.25 (MD: − 3.41; CrI: − 7.47 to 0.645), HA alone with a SUCRA value of 52.55 (MD: − 2.9; CrI: − 4.72 to − 1.09), and CS with a SUCRA value of 15.86 (MD: − 0.45; CrI: − 2.21 to 1.26). Each treatment had better probability than saline (SUCRA value: 6.94).

There was an evidence of inconsistency between the comparison of CS vs PRP ($p = 0.004$), CS vs saline ($p = 0.048$) at 6 months, CS vs PRP ($p = 0.006$), HA vs saline ($p = 0.04$) at 12 months, and CS vs PRP ($p = 0.004$), HA vs saline ($p = 0.04$) for change from baseline to 12-month follow-up as per node splitting analysis. The residual deviances from NMA and UME model reported good fit. The Gelman-Rubin convergence assessment plots had also reported stability around one. The leverage plot also indicated a good fit.

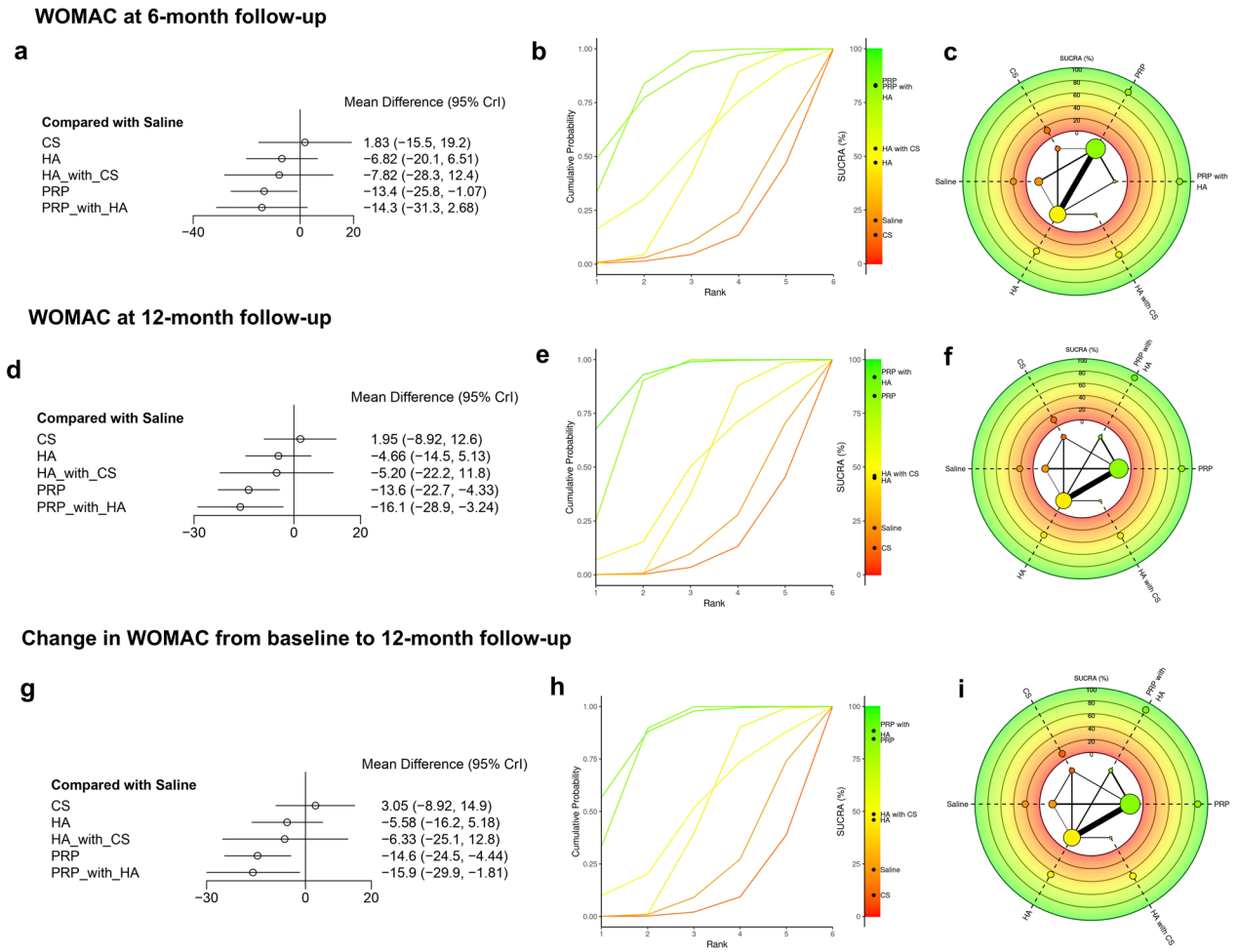

Fig. 5 Network comparisons using WOMAC score. **a**–**c** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using WOMAC score at 6 months. **d**–**f** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using WOMAC score at 6 months. **g**–**i** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using change in WOMAC score from baseline to 12-month follow-up

Secondary outcome

Among the 28 trials assessing physical function of knee joint, the most common outcome measured was total WOMAC score in 24 trials (85.7%), followed by IKDC score in 10 trials (35.7%). The network plots for total WOMAC score at the follow-ups are shown in Fig. 5. Network plots for IKDC scores at the follow-ups are shown in Fig. 6.

Functional improvement assessed through WOMAC scores

WOMAC score was used to assess the functional improvement at 6 months. PRP was ranked highest among the ranking of the interventions (SUCRA: 83.11), followed by combination of HA with PRP (SUCRA: 82.7), combination of HA with CS (SUCRA: 53.58), HA (SUCRA: 47.04), saline (SUCRA: 20.18) and CS (SUCRA: 13.36). All medications had reported significantly better WOMAC scores vis-a-vis saline except CS.

At the end of one year, the combination of HA with PRP fared well over treatment modalities in terms of long-term functional improvement, with a SUCRA value of 91.86 (MD: − 16.1; CrI: − 28.9 to − 3.24). It was followed by the PRP alone (SUCRA: 83.12), HA with CS (SUCRA: 45.9), HA (SUCRA: 44.8), and saline (SUCRA: 21.7). CS alone had lowest SUCRA value of 12.4 at the end of one year.

The combined administration of HA with PRP had the best probability for decrease in total WOMAC score from baseline to the follow-up at 12 weeks, with a SUCRA value of 88.36 and mean difference (MD) of − 15.9 (95% CrI: − 29.9 to − 1.81). It was followed by PRP with a SUCRA value of 84.54 (MD: − 14.6; CrI: − 24.5 to − 4.44), combination of HA and CS with a SUCRA

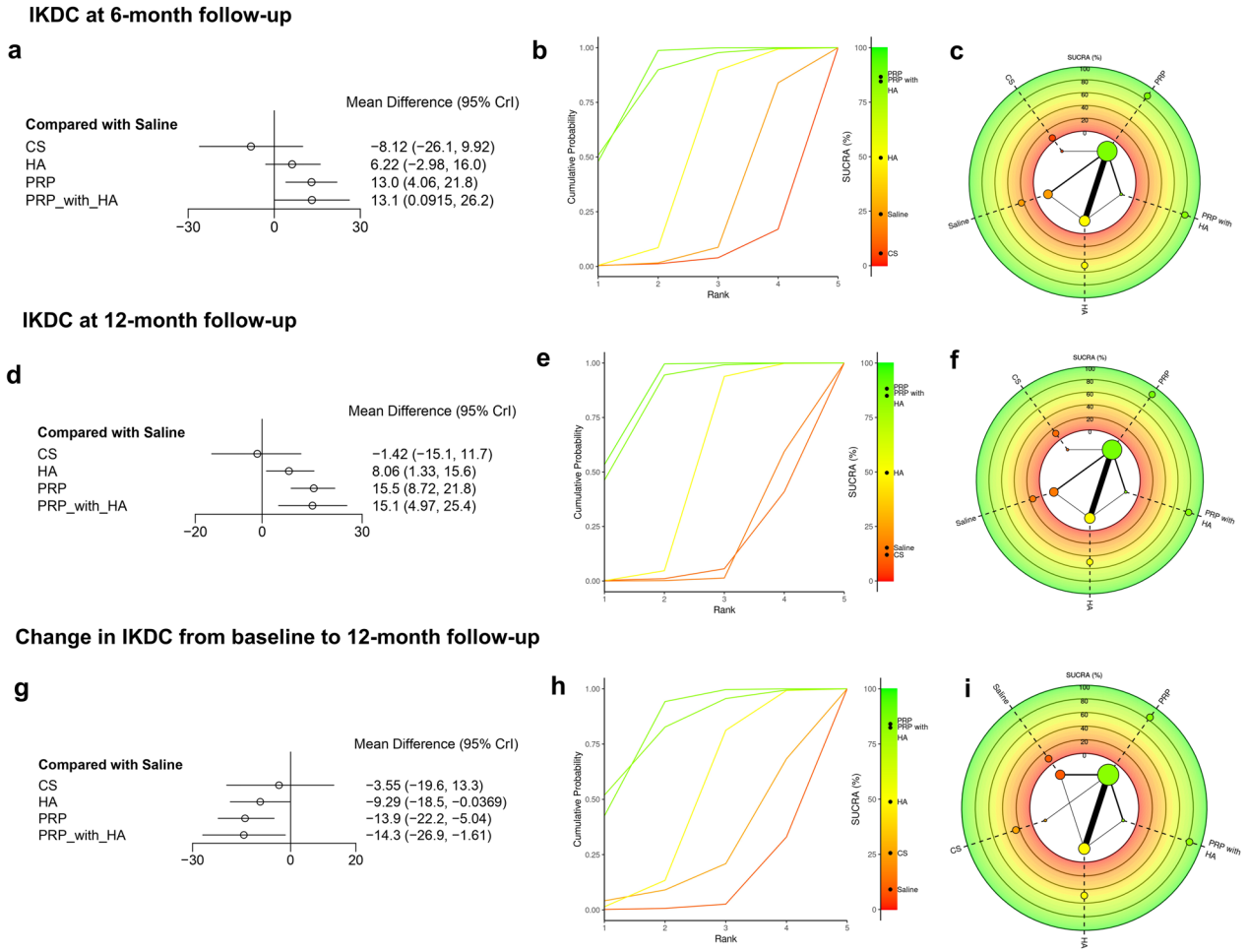

Fig. 6 Network comparisons using IKDC score. **a**–**c** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using IKDC score at 6 months. **d**–**f** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using IKDC score at 6 months. **g**–**i** Forest plot of Bayesian analysis, Litmus Rank-O-Gram and Radial SUCRA plot for studies using change in IKDC score from baseline to 12-month follow-up

value of 48.69 (MD: − 6.33; CrI: − 25.1 to 12.8), HA alone with a SUCRA value of 46 (MD: − 5.58; CrI: − 16.2 to 5.18), and CS with a SUCRA value of 10.12 (MD: 3.05; CrI: − 8.92 to 14.9). Saline (SUCRA value: 22.29) fared better than CS in terms of decrease in WOMAC from baseline to follow-up.

The residual deviances from NMA and UME model reported good fit, except for one arm of a study (Lin et al. 2019) which had deviance of 2.46 from NMA model. The Gelman-Rubin convergence assessment plots had reported stability around one, suggesting a good fit. There was no evidence of inconsistency between the comparison groups as per node splitting analysis.

Functional improvement assessed through IKDC scores

IKDC score was also used to assess functional improvement at 6 months. PRP was ranked highest among the ranking of the interventions (SUCRA: 86.64), followed by combination of HA with PRP (SUCRA: 84.52), HA (SUCRA: 49.51), saline (SUCRA: 23.65) and CS (SUCRA: 5.66). All treatments reported significantly better WOMAC scores vis-a-vis saline except CS.

At the end of one year, PRP fared well over treatment modalities in terms of long-term functional improvement, with a SUCRA value of 88.22 (MD: 15.5; CrI: 8.72 to 21.8). It was followed by the combination of HA with PRP (SUCRA: 84.95), HA (SUCRA: 49.61), and saline (SUCRA: 15.22). CS alone had lowest SUCRA value of 11.97 at the end of one year.

PRP had the best probability for increase in IKDC score from baseline to the follow-up at 12 weeks, with a SUCRA value of 84.08 and mean difference (MD) of − 13.9 (95% CrI: − 22.22 to − 5.04). It was followed by combined administration of HA with PRP with a SUCRA

value of 82.41 (MD: − 14.3; CrI: − 26.9 to − 1.61), HA with a SUCRA value of 48.41(MD: − 9.29; CrI: − 18.5 to − 0.036), and CS with a SUCRA value of 25.59 (MD: − 3.55; CrI: − 19.6 to 13.3). Each treatment had better probability than saline (SUCRA value: 9.1).

The residual deviances from NMA and UME model reported good fit. The Gelman-Rubin convergence assessment plots had also reported stability around one. There was no evidence of inconsistency between the comparison groups as per node splitting analysis.

Publication bias

Egger's test was done and comparison-adjusted funnel plots were generated for both the WOMAC and VAS outcomes at 12 months to assess for potential publication bias. For the WOMAC outcome at 12 months, Egger's test did not indicate significant publication bias with an intercept of 4.2921 (95% CI: − 0.3335 to 8.9177), and a p-value of 0.0683. Similarly, for the VAS outcome at 12 months, Egger's test yielded a p-value of 0.2920 with an intercept of − 3.8982 (95% CI: − 11.2346 to 3.4382), further supporting the absence of significant publication bias. The comparison-adjusted funnel plots [see Additional File 4] visually confirmed these findings, showing no clear asymmetry. Overall, the results suggest absence of substantial small-study effects or publication bias.

Discussion

The present systemic review and network meta-analysis (NMA) provides a comprehensive evaluation of the mid- to long-term effectiveness of IA injections of HA, CS, and PRP for managing knee OA. By synthesizing evidence from 37 high-quality RCTs, this NMA aimed to address a critical gap in the literature regarding the long-term effects of these commonly employed IA interventions. The analysis revealed that the intraarticular administration of a combination of HA with PRP results in better pain relief and functional outcomes in comparison to other combinations or individual drug administration in the medium to long term. PRP alone emerged as the second most effective intervention, outperforming HA and CS in all analyses. CS, while providing some short-term benefits, were found to be least effective for long-term pain relief and functional outcomes, often faring worse than saline.

Various studies have demonstrated the effectiveness and superiority of PRP as a treatment option for knee OA and other arthritic conditions [13, 75–77]. Migliorini et al. reported PRP to be more effective than corticosteroids, HA, and placebo [78]. A recent meta-analysis reported significant improvements in pain and function when PRP was compared with HA, over an average follow-up of 11.1 months [13]. However, a meta-analysis by Jevsevar et al. found no significant difference in pain and function between PRP and IA placebo at 42 days [79], suggesting that PRP's full therapeutic effects may require longer follow-up to manifest. Another meta-analysis by Shen et al. highlighted that PRP significantly reduced pain and improved function from 3 to 12 months, with the strongest effect on WOMAC pain scores at 6 months compared to placebo [75]. Similarly, a meta-analysis by Dai et al., also suggested a time-dependent relationship in PRP efficacy, showing no significant advantage over HA at 6 months but marked improvement in WOMAC, IKDC, and Lequesne scores by 12 months [80]. To address the limitations of isolated PRP administration, there has been a growing focus on combination therapies. For instance, PRP combined with HA has demonstrated enhanced efficacy, as this synergy appears to leverage the regenerative properties of PRP and the chondroprotective effects of HA [81]. This combination also appears to improve the bioactivity of key signaling molecules, including inflammatory cytokines, catabolic enzymes, and growth factors [56, 82]. Zhao et al. reported that this combination yields superior pain relief and functional improvement compared to PRP alone [83].

A network meta-analysis by Qiao et al. found PRP to be superior in enhancing joint function when compared to PRP combined with HA, HA alone, corticosteroids, and placebo [84]. Similar results were echoed in analyses by Singh et al. [85] and Jawanda et al. [86], with PRP consistently demonstrating improved outcomes in pain relief and functional scores compared to alternatives. Interestingly, Qiao et al. also noted that PRP combined with HA was more effective than PRP alone in reducing pain [84]. The present study differs from these analyses by incorporating only studies with a minimum follow-up duration of 1 year, providing a more comprehensive assessment of long-term outcomes. Additionally, by incorporating a broader range of studies, larger sample size and employing stricter inclusion criteria, the current study improves reliability, reduces variability, and enhances statistical power and generalizability of the results.

Corticosteroids are effective for short-term pain relief but have limited mid- to long-term benefits. A meta-analysis by Jevsevar et al. indicated better short-term results for CS compared to HA, PRP, or saline [79]. This may be attributed to differences in follow-up durations, with shorter studies possibly overestimating CS's short-term benefits. Intra-articular CS has been shown to reduce pain more effectively than HA in the first month following injection, but HA provides superior analgesic effects over the long term, particularly beyond 6 months [16, 87]. For instance, Najm et al. found that while CS offered early pain relief, it did not result in better clinical outcomes than HA at later follow-ups

[88]. Furthermore, some studies suggest worse outcomes with CS compared to saline in terms of pain and function, as observed in the present study. This aligns with findings from Godwin et al., who noted no significant differences between CS and saline, questioning the long-term efficacy of CS [89]. Additionally, Wernecke et al. reported potential adverse effects of CS on knee cartilage volume, raising concerns about their safety with prolonged use [90]. Combining HA with CS, has demonstrated moderately improved mid- to long-term outcomes compared to HA or CS alone [49, 64], as also observed in the present study, making this combination potentially beneficial for acute exacerbations of knee pain.

Overall, our findings confirm the superiority of PRP over HA, both in pairwise comparisons and NMAs, corroborating prior meta-analyses. The sustained efficacy of PRP, particularly in combination with HA, underscores its potential as a preferred treatment modality. However, the variability in study designs and follow-up durations contributes to significant statistical heterogeneity in intra-articular injection studies. To address this heterogeneity, a random-effects model was employed in this NMA. Fortunately, the consistency between the comparisons was good and the model of the present study fit well. With application of strict selection criteria and regression analysis, the impact of different characteristics of studies included was lowered, thus providing reliable results.

The present study had a few limitations. Firstly, though there were 37 RCTs with approximately 5089 patients but there were few trials with direct comparisons. Second 40% studies had less than 100 participants in the study which could result in bias due to small study effect. Third, 10% studies had features of high risk of bias and low quality of methodology. Fourth, the safety of the IA injection among various injectable was not studied as an outcome measure. Fifth, physical therapy is usually prescribed after administration of intra-articular knee injections or otherwise which may have effect on the final outcome of the study. Sixth, in this NMA, heterogeneity may arise from the differences in study designs, patients characteristics, PRP preparation protocols, HA formulations, CS dosing regimens and outcome measures across included studies introduces potential biases. It might affect generalizability, as certain interventions could have different effects in different subpopulations or in varying clinical settings. Lastly, inconsistencies were noted in a few comparisons though overall model fit was acceptable. Future research should focus on standardizing PRP and HA preparation protocols to reduce variability and conducting long-term RCTs to assess outcomes beyond 12 months (more than 2 to 5 years).

Conclusion

This network meta-analysis highlights the superior efficacy of intra-articular injection of PRP combined with HA, in providing sustained pain relief and functional improvement for knee OA over a follow-up of one year, compared to individual PRP injections, combined HA and CS injections, or individual injections of HA, CS, or saline/ placebo. The sustained efficacy of PRP, particularly in combination with HA, underscores its potential as a preferred treatment modality. There is need for comparison between different IA injectables and other nonoperative management methods individually and in combination to understand the effectiveness of these treatment modalities in long-term management of knee OA. Future research should focus on longer follow-up periods and efforts to standardize treatment protocols to further validate and optimize these therapeutic approaches.

Abbreviations

ACR	American College of Rheumatology
CrI	Credible intervals
CS	Corticosteroid
HA	Hyaluronic acid
IA	Intra-articular
IKDC	International Knee Documentation Committee
MD	Mean difference
NMA	Network meta-analysis
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PRP	Platelet rich plasma
RCT	Randomized control trial
SD	Standard deviation
SUCRA	Surface Under the Cumulative RAnking curve
UME	Unrelated mean effect
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-025-05574-w.

Additional file 1: PRISMA 2020 checklist.

Additional file 2: Search Strategy for PubMed, Scopus, Embase and Cochrane Central Register of Controlled Trails.

Additional file 3: Additional Results: Contains tables for Treatment effects for all studies (comparison of all treatment pairs), inconsistency tests with node splitting model for all studies, deviance report for all studies and sensitivity analysis, Leverage plots for all analyses, Gelman convergence assessment plots of all analyses.

Additional file 4.

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Author contributions

Kavin Khatri and Anshul Dahuja conceptualized and designed the study. Kavin Khatri, Anshul Dahuja and Amit Lakhani developed the search strategy and did the literature search. Nikhil Gupta, Kavin Khatri and Amit Lakhani, collected the data and performed all the analysis. Nikhil Gupta and Kavin Khatri wrote the manuscript. Amandeep Randhawa and Kapil Bansal thoroughly

reviewed the manuscript and suggested necessary changes. Vivek Bansal and Amandeep Randhawa did revisions and proof-reading of the manuscript. All the authors have reviewed and approved the final version of the manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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