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Comparison between intra-articular infiltrations of placebo, steroids, hyaluronic and PRP for knee osteoarthritis: a Bayesian network meta-analysis

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Abstract

Introduction Regarding the efficacy of intra-articular injections of platelet-rich plasma, hyaluronic acid and corticosteroids, current evidence is controversial. The superiority of one technique over another is questioned and debates are ongoing. The purpose of the present study was to compare and investigate the efficacy of these intra-articular infiltrations in patients with knee osteoarthritis (OA). A Bayesian network meta-analysis of randomized clinical trials (RCTs) was conducted comparing patient outcomes at 3, 6 and 12-months of follow-up.

Materials and methods This Bayesian network meta-analysis was conducted according to the PRISMA extension statement for reporting systematic reviews incorporating network meta-analyses of health care interventions. All the RCTs comparing the outcomes of two or more intra-articular infiltrations of interest for knee OA were considered for inclusion. The outcomes of interest were the WOMAC and VAS scores. The network meta-analyses were performed using the STATA routine for Bayesian hierarchical random-effects models.

Results Data from 30 RCTs (3463 patients) were collected. At 3-months follow-up, PRP showed the best WOMAC scores, followed by the Placebo, CCS and HA. At 6-months follow-up, PRP showed the best WOMAC scores, followed by HA, CCS and Placebo. At 12-months follow-up, PRP showed the best WOMAC scores, followed by the Placebo, HA and CCS. At 3-months follow-up, the PRP showed the best VAS scores, followed by CCS, HA and Placebo. At 6-months follow-up, PRP showed the best VAS scores, followed by CCS, Placebo and HA. At 12-months follow-up, the PRP showed the best VAS scores, followed by CCS, Placebo and HA.

Conclusion Intra-articular injections of PRP demonstrated the best overall outcome compared to steroids, hyaluronic acid and placebo for patients with knee osteoarthrosis at 3, 6 and 12-months follow-up. Among CCS, hyaluronic acid and placebo, no discrepancies were detected.

Level of evidence I, Bayesian network meta-analysis of RCTs.

Keywords Knee · Osteoarthritis · Infiltration · PRP · Hyaluronic acid · Steroids

Introduction

Knee osteoarthritis (OA) is a common musculoskeletal disorder [1]. OA mainly affects the elderly and incidence is expected to increase in the coming decades [2]. Knee OA considerably reduces quality of life, due to decreased mobility and independence among affected individuals [3, 4]. Symptomatic knee OA presents a considerable economic burden on global healthcare systems [5]. First-line treatment for symptomatic knee OA usually consists of systemic non-steroidal anti-inflammatory drugs (NSAID). Given the low rates of intracapsular infiltration, along with the high risk of side effects related to the chronic intake of NSAIDs, intra-articular injections of alternative substances have been promoted. So far, corticosteroids (CCS) and hyaluronic acid (HA) are the most commonly used agents for intra-articular treatments [6]. Injectable CCSs aim to modulate the

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inflammatory response directly on the osteoarthritic surface and are among the recommendations given in the guidelines of the Osteoarthritis Research Society International in 2014 and the American College of Rheumatology (ACR) in 2012 [7, 8]. However, their benefits are of very short duration [9]. Intra-articular visco-supplementation with HA has been extensively and successfully used since receiving approval in Italy in 1988 [10]. However, its comparative efficacy remains controversial [11]. More recently, there has been widespread interest in growth factors as a third alternative. Platelet rich plasma (PRP), a multifunctional autologous platelet concentration, is a simple and economic method for obtaining autologous growth factors [12–14]. So far, PRP has demonstrated regenerative potential along with inflammatory modulation [15–17], but its superiority over the others substances has not been established. The goal of the present study was to compare the efficacy of intra-articular injections of the aforementioned three substances for patients with knee OA. A Bayesian network meta-analysis of randomized clinical trials (RCTs) with follow-up at 3, 6 and 12-months was conducted. Outcomes of interest were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [18] and the visual analogic scale (VAS).

Materials and methods

Search strategy

This Bayesian network meta-analysis was conducted according to the PRISMA extension statement for reporting systematic reviews incorporating network meta-analyses of health care interventions [19]. To guide the search, the following PICO protocol was drafted:

- P (population): degenerative knee OA;
- I (intervention): intra-articular infiltrations;
- C (comparison): corticosteroids, platelet-rich plasma, hyaluronic acid, placebo;
- O (outcomes): WOMAC, VAS.

Literature search

Two independent reviewers (FM; NS) performed the literature search in December 2019. The following online databases were accessed: Pubmed, EMABSE, Scopus, Google Scholar. The following keywords were used in combination: knee, osteoarthritis, degeneration, disease, pain, therapy, treatment, infiltration, injection, corticosteroids, steroids, platelet rich plasma, PRP, hyaluronic acid, placebo, WOMAC, visual analogic scale, VAS. All articles resulting from the search were evaluated and, if of interest, full-texts were accessed. Disagreements between the reviewers were solved by a third author (JE).

Eligibility criteria

All randomized clinical trials comparing the outcomes of two or more intra-articular infiltrations of interest for knee OA were then considered. According to the authors' language capabilities, only articles in English, French, Italian, Spanish and German were examined. Following guidelines from the Oxford Centre for Evidenced-Based Medicine (CEBM) [20], only RCTs with level I evidence were considered suitable for inclusion. Editorials, posters, expert opinions, cohort and observational studies, cadaveric and biomechanics studies, and studies with animals were excluded. Studies comparing mesenchymal stem cells (MSCs) or infiltrations with other, more committed, cellular components were excluded. Studies performing infiltrations with growth factors, extracellular matrices (ECM) or other solutions, studies using additive substances along with HA, CCS or PRP, studies using mixed infiltration (e.g., HA + CCS) and studies comparing different types of HA or CCS were also excluded. Likewise, studies of intra-articular infiltrations in knees involving recent and/or imminent surgery and in knees with prosthetic implants were considered unsuitable. Only studies reporting quantitative data directly comparing the interventions of interest with follow-up at 3, 6 and/or 12-months were included in the present Bayesian network meta-analysis.

Outcomes of interest

Data extraction was performed by two independent reviewers (FM, NS). Generalities of the included papers (author, year) along with the demographic baselines of related patients (mean age and BMI, gender,) were recorded. Inclusion and exclusion criteria and treatment protocol were also recorded. Outcomes of interest were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [18] and the visual analogic scale (VAS).

Methodological quality assessment

The methodological quality assessment was performed by two independent reviewers (FM, NS). Disagreements between the reviewers were resolved by a third author (JE). Referring to the risk of bias summary of Review Manager Software (The Nordic Cochrane Collaboration, Copenhagen), the following bias were analysed: selection, detection, attrition, reporting and unknown source of potential bias.

Statistical analysis

The statistical analysis was performed by the main author (FM). For the analyses of baseline comparability among the patients, the analysis of variance (ANOVA) test was performed through the IBM SPSS Software version 25, with p values > 0.5 considered satisfactory. The network meta-analyses were performed using STATA/MP 14.1 (StataCorp, College Station, TX), through the routine for Bayesian hierarchical random-effects model. The reference values were set as follow: VAS 0/100 points and WOMAC 0/96 points. All the continuous data were analysed using inverse-variance weighting with standardized mean difference (SMD) effect measure. For each comparison, the network edge plot was performed to report amounts, connections and direct estimates. For the overall evaluation, related effect and ranking, the interval plot was performed. Both confidence (CI) and percentile (PrI) intervals were set at 95%. To evaluate the risk of publication bias, the funnel plot of each comparison was performed. The overall transitivity, consistency, heterogeneity, and within-study variance of the effect size for the treatments of interest were then evaluated. Within-loop heterogeneities have been estimated using method of moments estimation. Inconsistency was analysed through the equation for global linearity via the Wald test. Values of $p < 0.05$ detected statistically significant inconsistency, and the assumptions could not be accepted at the overall level of each treatment.

Results

Search result

The initial search resulted in 855 papers. Of them, 220 were duplicates and, thus, excluded. Only 128 were RCTs. 70 of these were excluded because they did not match the topic or did not report quantitative data according to our outcomes of interest. A further 28 focused on variables beyond the constraints of our investigation: total knee arthroplasty ($N = 7$), patients with previous or planned surgery ($N = 11$), the presence of additives or adjuvant substances ($N = 9$), poor or uncertain results ($N = 1$). This left 30 RCTs. The flow chart of the literature search is shown in Fig. 1.

Methodological quality assessment

The risk of bias summary evidenced some point of strength of the present study. First, the high-quality inherent to the type of studies included. Further, the 87% of the included studies took advantage from a blinding method. In addition, the risk of attrition, reporting and unknown biases resulted low. Concluding, the methodological assessment was affected by overall low risk of bias, providing very good quality. The methodological quality assessment is shown in Fig. 2.

Patient demographic

Data from 3463 patients were collected. In the CCS group, a total of 542 procedures were analysed. The mean age of the patients was 59.52 ± 4.9 years, the mean BMI was 28.32 ± 2.4 kg/m^2, and 61% were female. In the HA group, a total of 1292 procedures were analysed. The mean age of the patients was 58.74 ± 6.1 years, the mean BMI was 27.93 ± 1.9 kg/m^2, and 57% were female. In the PRP group, a total of 1214 procedures were analysed. The mean age of the patients was 57.04 ± 5.2 years, the mean BMI was 28.05 ± 2.2 kg/m^2, and 59% were female. In the Placebo group, a total of 374 procedures were analysed. The mean age of the patients was 60.6 ± 6.3 years, the mean BMI was 28.53 ± 2.3 kg/m^2, and 58% were female. Good baseline comparability was found among age ($p = 0.8$), BMI ($p = 0.9$) and gender ($p = 0.8$). Patient demographics are shown in Table 1.

Outcome of interest: WOMAC

At 3-months follow-up, the PRP groups showed the best outcomes (SMD 27.26; 95% CI 20.54–33.97), followed by Placebo (SMD 28.74; 95% CI 12.36–45.13), CCS (SMD 33.86; 95% CI 27.98–39.74) and HA (SMD 35.08; 95% CI 26.64–43.53). At 6-months follow-up, the PRP groups showed the best outcomes (SMD 32.11; 95% CI 23.90–40.32), followed by HA (SMD 38.01; 95% CI 30.29–45.73), CCS (SMD 43.07; 95% CI 32.64–53.50) and Placebo (SMD 43.80; 95% CI 29.45–58.15). At 12-months follow-up, the PRP groups showed the best outcomes (SMD 33.89; 95% CI 23.88–43.90), followed by Placebo (SMD 34.45; 95% CI 9.58–59.31), HA (SMD 39.12; 95% CI 29.56–48.68) and CCS (SMD 46.99; 95% CI 29.58–64.40). The test for overall inconsistency found transitivity over the 3, 6 and 12-months follow-up ($p > 0.5$). Figure 3 shows a comparison of outcomes based on WOMAC scores at 3, 6 and 12-months follow-up.

Outcome of interest: VAS

At 3-months follow-up, the PRP groups showed the best outcomes (SMD 32.69; 95% CI 27.31–38.06), followed by CCS (SMD 38.80; 95% CI 33.41–44.19), HA (SMD 39.98; 95% CI 34.89–45.08) and Placebo (SMD 42.69; 95% CI 23.90–61.49). At 6-months follow-up, the PRP groups showed the best outcomes (SMD 33.84; 95% CI 28.30–39.38), followed by CCS (SMD 39.44; 95% CI 32.57–46.32), Placebo (SMD 39.90; 95% CI 23.48–56.31) and HA (SMD 40.50; 95% CI 34.40–46.60). At 12-months follow-up, the PRP groups

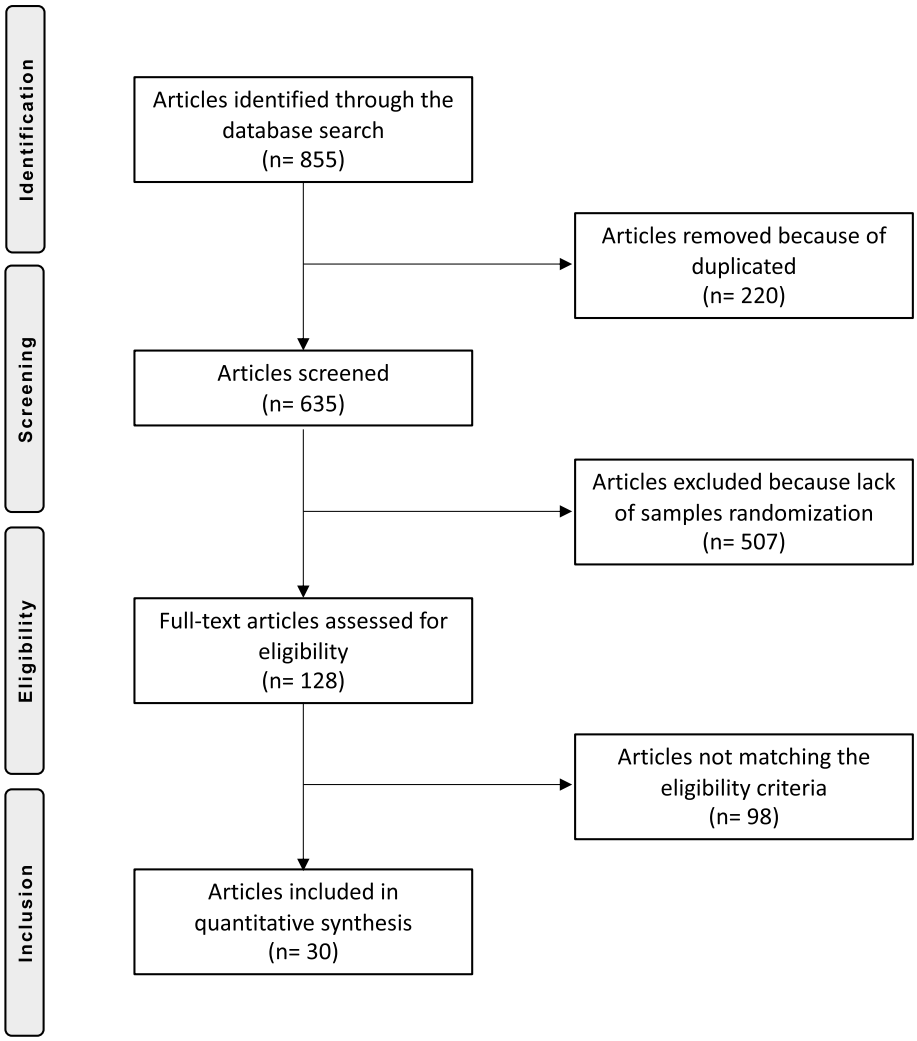

Fig. 1 Literature search flow-chart

showed the best outcomes (SMD 39.04; 95% CI 31.39–46.69), followed by CCS (SMD 49.45; 95% CI 37.75–61.15), Placebo (SMD 49.54; 95% CI 27.21–71.86) and HA (SMD 50.15; 95% CI 43.00–57.31). The test for overall inconsistency found transitivity over the 3, 6 and 12-months follow-up ($p > 0.5$). Figure 4 shows a comparison of outcomes based on VAS scores at 3, 6 and 12-months follow-up.

Discussion

According to the main findings of the present Bayesian network meta-analysis, intra-articular PRP injections resulted in the greatest reduction of pain (VAS score) and the greatest overall outcome (WOMAC) compared to steroids, hyaluronic acid and placebo with follow-up at 3, 6 and 12 months. No significant differences were detected between CCS, hyaluronic acid and placebo.

To the best of our knowledge, this is the first Bayesian network meta-analysis comparing PRP, CCS, HA and placebo. Our results echo the results found by Shen et al. [51] in a meta-analysis pooling data from 1423 patients with up to 12 months follow-up, where the PRP group had significantly better outcomes than HA, CCS and placebo. Other studies have also found better outcomes with PRP compared with HA only [28, 45, 47, 52–56] or with CCS [51], while several others have found no difference between them [25–31]. Importantly, a number of RCTs found that multiple PRP injections resulted in significantly better outcomes than a single injection [24, 25, 28, 45, 55–57]. In a retrospective analysis, Annaniemi et al. analysed the potential for delaying a total knee arthroplasty (TKA) between PRP and HA, and found a significantly greater delay in the PRP cohort [21].

In our analysis, CCS and HA showed similar results, with no measured benefits compared to placebo basd on VAS and WOMAC scores. Current evidence found no relevant differences between HA and CCS [22, 58–60]. HA showed a longer effect duration, while CCS are more cost-effective [22, 58–60]. There is no consensus whether chronic CCS infiltrations can promote articular destruction or if these

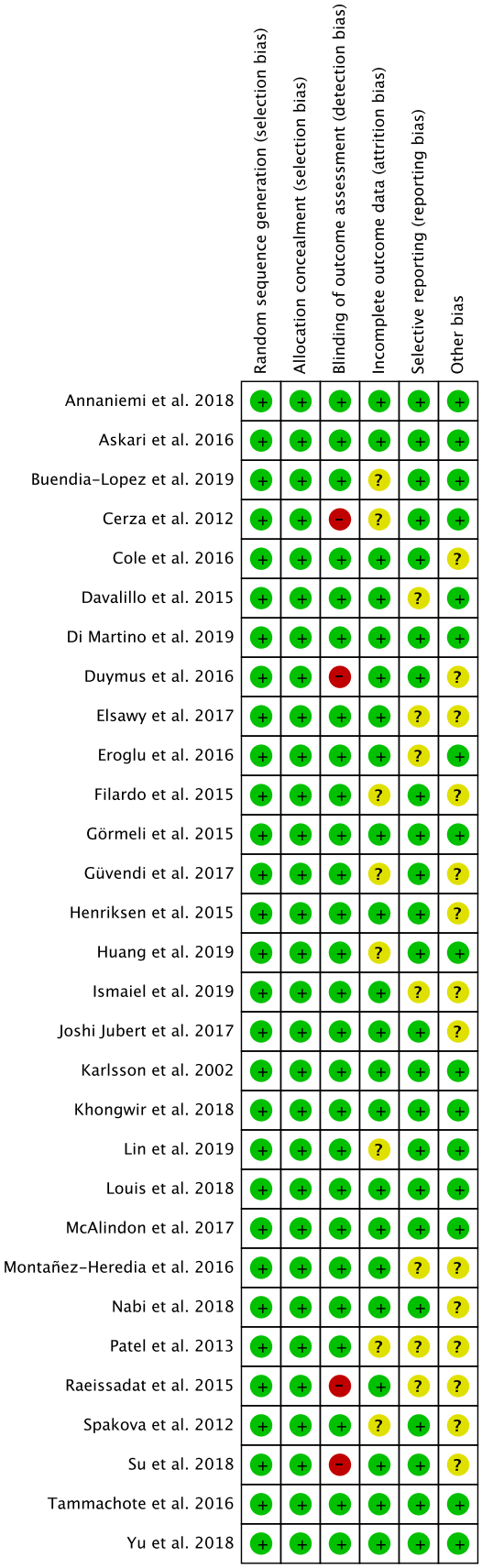

Fig. 2 Methodological quality assessment

changes are more likely due to the underlying OA [61, 62]. Colen et al. [11] performed a systematic review of 74 RCTs comparing HA versus placebo. They found no clinically relevant differences. Similar results were found by Divine et al. [63] when investigating results from published meta-analyses. Arroll et al. [64] performed a meta-analysis on 10 RCTs comparing CCS versus placebo. They found that intra-articular injections of CCS did provide an improvement of symptoms and function. Similar results were found by Godwin et al. on 312 patients in five RCTs [65].

The pathogenesis and progression of OA is influenced by a number of factors, including sex, genetics, biomechanics, dysplasia, obesity, synovitis, complement proteins and many other [66–70]. Regardless of its aetiology, inflammation and progressive destruction of the articular surfaces characterize the disease. Several proinflammatory mediators, e.g., IL-1, TNF-α, IL-6 play a crucial role in the etiogenesis of cartilage damage and [71–73], along with innate immunity via activated macrophages and mast cells [74]. Further tissue degradations, are driven by cartilage matrix catabolic effects (including metalloproteinases, aggrecans, disintegrins, and other activated cartilage-degrading enzymes) and cellular anti-anabolic effects (through enhanced nitric oxide production), and lead to the progressive degradation of the extracellular matrix [75–79]. Intra-articular infiltrations of PRP, and CCS aim to reduce the inflammatory response, HA to promote viscosupplementation to the extracellular matrix. In either case, only PRP achieves clinically demonstrated improvements, according to our analysis, while the effects of CCS and HA are unclear.

This study has several limitations. First, the present network analysis was based on different infiltration protocols. About 35% of the authors performed a single injection. Some authors performed up to five injections. Furthermore, in these groups, the latency time between injections was heterogeneous (from weekly to monthly). This represents the most important limitation of this study. Another important limitation is that the analyses were restricted to 3, 6, and 12-month follow-ups. Further analysis at additional follow-ups were not possible due to lack of data. Longer follow-ups (> 12 months), were reported in only four RCTs [27, 21, 48, 42] with no consistency among them, resulting in poor statistical relevance. Regarding our statistical analysis, the result of the inconsistency test suggests that the null hypothesis cannot be rejected, and the consistency assumption could be accepted at the overall level of each treatment. It is worth mentioning that by increasing the follow-up duration, a proportional reduction in consistency was detected. A possible explanation can be that there is a substantial increase of heterogeneous results after 12 months, that is to say, the benefits of intra-articular infiltrative therapies become more uncertain. The placebo group was quantitatively smaller with regards to the other study groups. Notwithstanding, this did

Table 1 Generalities of the included studies and demographic data of the samples

Author, year	Knees	Inclusion criteria	Exclusion criteria	Type of protocol	Type of injection	Knees	Gender	Age	BMI
Annaniemi et al. [21]	180	(1) Age 18–90 (2) Radiographic confirmation (3) VAS baseline ≥ 30% (4) Kellgren Lawrence I–III	(1) Major systemic disorders (2) Major homolateral symptomatic hip arthrosis (3) Pregnancy (4) Previous intra-articular injections or oral medication other than paracetamol/NSAIDs	Three injections at 10–14 days interval	PRP	94	60 Female 34 male	57.4	28.9
				Either single injection or three injections at 7 days interval	HA	86	50 Female 36 male	65.7	29.7
Askari et al. [22]	140	(1) Age 45–80 (2) Symptoms ≥ 3 months (3) Kellgren Lawrence I–III	(1) History or presence of trauma or surgery or cancer or malignant tumours (2) Infections and sores on the target knee (3) History of vasovagal shock (4) Use of NSAIDs < 2 days prior to injection (5) Previous CCS injection < 6 months (6) Pregnancy (7) Lactation	Single injection	CCS	69	57 Female 12 male	57	
					HA	71	62 Female 9 male	58.5	
Buendia-Lopez et al. [23]	65	(1) Symptomatic knee OA according to the Spanish Society of Rheumatology (2) Kellgren Lawrence I–II	(1) Axis deformity (2) Recent trauma (3) Inflammatory arthritis (4) History of gastrointestinal or cardiovascular disease (5) Concomitant medications of potent analgesics, CCS, anticoagulant, antithrombosis < 12 months (6) Previous spine surgery (7) Previous injection (8) Active local or systemic infection (9) Systemic disorders	Single injection	PRP	33	17 Female 16 male	56.2	24.9
					HA	32	17 Female 15 male	56.6	24.9
Cerza et al. [24]	120	(1) Little benefit from conservative therapies (2) Radiographical confirmation	(1) Previous knee operations (2) Previous knee infiltrations (3) Rheumatoid or autoimmune diseases (4) Kellgren Lawrence IV	Four injections at 7 days interval	PRP	60	35 Female 25 male	66.5	
					HA	60	32 Female 28 male	66.2	
Cole et al. [25]	99	(1) Age 18–80 (2) VAS at baseline ≥ 40% (3) Radiographic confirmation (4) Unilateral symptoms	(1) Knee instability (2) VAS at baseline ≥ 40% (3) Major axial deviation (5) Bilateral symptomatic lesions (6) Systemic disorders such as diabetes, rheumatoid arthritis, haematological diseases, severe cardiovascular diseases, infections, or immunodeficiencies (7) Current use of anticoagulant medications (8) Previous NSAIDs < 5 days (9) Anaemia (10) Previous injection of corticosteroids < 1 month (11) Previous HA injection < 6 months (12) Pregnancy	Single injection	PRP	49	21 Female 28 male	55.9	27.4
					HA	50	30 Female 20 male	56.8	29

Table 1 (continued)

Author, year	Knees	Inclusion criteria	Exclusion criteria	Type of protocol	Type of injection	Knees	Gender	Age	BMI
Davalillo et al. [26]	195	(1) Age 40–85 (2) Kellgren Lawrence II–III (3) BMI < 35 kg/m^2	(1) Any previous knee trauma or surgery (2) Inflammatory arthritis (3) Microcrystalline arthropathies (4) Previous unspecific knee synovitis (5) Infection (6) Leg mal-alignment (7) Neoplasia (8) Diabetes mellitus (9) Metabolic syndrome	Five injections at 7 days interval	CCS	98	57 Female 41 male	62.8	26.3
				Two injections at 4-week interval	HA	97	59 Female 38 male	62.7	28.3
Di Martino et al. [27]	167	(1) Unilateral symptomatic knee, (2) Kellgren Lawrence grade I–III (3) Age 18–80 (4) Symptoms > 4 months	(1) Major axial deviation (2) Focal chondral or osteochondral lesion (3) Any concomitant knee lesion causing pain or swelling (4) Haematological or cardiovascular diseases, infections, and immunodepression (5) Hb > 11 g/dL (6) Thrombocyte > 150,000/mm^3	Three injections at 7 days interval	PRP	85	32 Female 53 Male	52.7	27.2
					HA	82	35 Female 47 Male	57.5	26.8
Duymus et al. [28]	102	(1) Age 47–80 (2) Kellgren–Lawrence II–III (3) BMI < 30 (4) Normal blood results and coagulation profile	(1) Age > 80 (2) Kellgren Lawrence IV (3) Recent history of knee trauma (4) Rheumatic pathology (5) Severe hip OA (6) Systemic or metabolic disease, immunosuppressive or anticoagulant treatment (7) CCS injection < 12 months (8) Previous joint infection (9) Intra-articular effusion on MRI (10) Leg mal-alignment	Two injections at 2 weeks interval	PRP	33	32 Female 1 Male	60.4	27.6
				Single injection	HA	34	33 Female 1 Male	60.3	28.4
Elsawy et al. [29]	60	(1) Kellgren–Lawrence II–III (2) Symptoms > 3 months (4) VAS at baseline > 40%	(1) Secondary OA (2) Previous CCS injections (3) Pregnancy (4) Diabetes mellitus, rheumatic diseases, coagulation disorder	Single injection	CCS	30		50.2	28.3
				Three injections at 7 days interval	HA	30		52.5	28.5
Eroglu et al. [30]	58	(1) Symptoms > 3 months (2) Kellgren Lawrence I–III	(1) Kellgren–Lawrence IV (2) Previous HA < 6 months (3) Previous leg surgery (4) Diabetes, rheumatic diseases, severe cardiovascular diseases, haematological diseases, infections (5) Any concomitant knee lesion causing pain or swelling	Three injections at 7 days interval	PRP	18	15 Female 3 Male	64.16	29.2
						20	19 Female 1 Male	62	29.5

Table 1 (continued)

Author, year	Knees	Inclusion criteria	Exclusion criteria	Type of protocol	Type of injection	Knees	Gender	Age	BMI
Filardo et al. [31]	183	(1) Unilateral symptomatic OA > months (2) Kellgren Lawrence I–III	(1) Age > 80 (2) Kellgren Lawrence > 3 (3) Severe leg mal-alignment (4) focal chondral or osteochondral lesion (5) Any concomitant knee lesion (6) Inflammatory arthropathy (7) Haematological diseases (8) Severe cardiovascular diseases (10) Infections (11) Immunodepression (12) Therapy with anticoagulants or antiaggregant (13) Usage of NSADs < 5 days (14) Hb < 11 g/dL (15) Thrombocyte < 150.000/mm^3	Three injections at 7 days interval	PRP	94	34 Female 60 Male	53.3	26.6
					HA	89	37 Female 52 Male	57.5	26.9
Görmeli et al. [32]	162	(1) Symptoms > 4 months (2) Kellgren Lawrence I–IV	(1) Previous leg surgery (2) Diabetes, rheumatic diseases, severe cardiovascular diseases, haematological diseases, infections (3) Generalized OA (4) Ongoing anticoagulant or antiaggregant therapy (5) NSAIDs < 5 days (6) Hb < 11 g/dL (7) Thrombocyte < 150,000/mm^3	Single injection	PRP	44	25 Female 19 Male	53.8	28.4
				Three injections at 7 days interval	PRP	39	23 Female 16 Male	53.7	28.7
				Single injection	HA	39	22 Female 17 Male	53.5	29.7
				Single injection		40	20 Female 20 Male	52.8	29.5
Güvendi et al. [33]	50	Kellegren Lawrence III	(1) Secondary OA (2) Usage > 3 months of CCS (3) Usage < 7 days of drugs that inhibit Thrombocyte aggregation (non-steroidal anti-inflammatory drugs, acetyl salicylic acid, thienopyridines, cyclopentyltriazolo-pyrimidines, glycoprotein IIB-IIIa complex inhibitors, phosphodiesterase inhibitors) (4) Skin lesions (5) Hb < 12 gr/dL (6) Thrombocyte < 150,000 K/μL (7) Immune suppression or collagen connective tissue disease (8) Previous knee surgery, knee trauma (9) Previous knee injection < 6 months (10) Hip-foot–ankle OA (11) Severe chronic illness (12) Poor general health status (heart failure, chronic bronchitis, etc.)	Single injection	PRP	19	18 Female 1 Male	62.3	31.4
				Three injections at 7 days interval	PRP	14	13 Female 1 Male	60.4	31
				Single injection	CCS	17	15 Female 2 Male	62.8	31.1

Table 1 (continued)

Author, year	Knees	Inclusion criteria	Exclusion criteria	Type of protocol	Type of injection	Knees	Gender	Age	BMI
Henriksen et al. [34]	100	(1) Age < 40 (2) VAS > 40% (3) BMI < 35 kg/m^2	(1) Conservative therapies < 3 months (2) Usage of CCS < 3 months (3) TKA (4) Any contraindications to CCS (5) Fibromyalgia (6) Spinal compression syndromes	Single injection	CCS	50	28 Female 22 Male	61.3	29
						50	33 Female 17 Male	65.5	28.9
Huang et al. [35]	120	(1) Age 40–65 (2) Kellgren Lawrence I–II (3) BMI < 30 mm/kg^2 (4) Stable knees without mal-alignment (5) Thrombocytes 150.000–450.000/l (6) Any previous knee surgery < 2 years	(1) Tricompartmental OA (2) Rheumatoid arthritis (3) Concomitant hip OA (4) Previous high tibial osteotomy (5) Previous cartilage transplantations (6) Blood diseases, systemic metabolic disorders, immunodeficiency, hepatitis B or C, HIV positive status (7) Local or systemic infection (8) Treatment with HA or CCS < 3 months (9) Patellofemoral instability	Three injections at 3 weeks interval	PRP	40	15 Female 25 Male	54.5	25.2
				Three injections at 3 weeks interval	CCS	40	19 Female 21 Male	54.3	24.5
				Three injections at 7 days interval	HA	40	21 Female 19 Male	54.8	24.5
Ismaiel et al. [36]	92	(1) Age 40–80 (2) Kellgren Lawrence III–IV (3) Waiting list for TKA	(1) Previous HA or CCS infiltrations < 12 months (2) Arthroscopic surgery < 3 months (3) Hb < 7.0 g/dl (4) Thrombocytes < 15 000/µl (5) Bleeding dyscrasias (4) Compromised bone metabolism (5) Any autoimmune diseases (6) Documented history of allergy to steroids, or blood products (7) Valgus > 15° or varus > 20° (8) Severe ligamentous instability (9) Flexion deficit < 90° (10) Extension deficit > 20°	Single injection	PRP	52	29 Female 23 Male	62.9	29.4
					CCS	40	31 Female 9 Male	61.1	29.3

Table 1 (continued)

Author, year	Knees	Inclusion criteria	Exclusion criteria	Type of protocol	Type of injection	Knees	Gender	Age	BMI
Joshi Jubert et al. [37]		(1) Age 40–80 (2) Eligibility for total knee arthroplasty (3) Walking ability with or without external support (4) VAS > 60%	(1) Previous surgery < 3 months (2) Compromised bone metabolism (except for osteoporosis) (4) Fibromyalgia (5) Chronic fatigue syndrome (6) Liver disease (7) Clotting deficiency (blood dyscrasias) (8) Thrombocyte < 150,000 mm^3 (9) Hb < 11 g/dL (10) Usage of anticoagulants (11) Active infection, immunosuppression or chronic severe disease (12) Pregnancy (13) Homolateral hip–ankle damage (14) Secondary OA (15) Leg mal-alignment (16) Severe ligamentous instability (17) Limited ROM	Single injection	PRP	35	23 Female 12 Male	65.56	31.2
					CCS	30	24 Female, 6 Male	68	30.98
Karlsson et al. [38]	210	(1) Age > 60 (2) Lequesne Scale > 10 (3) Weightbearing VAS > 40% (4) Good performance status (5) Ahlbäck grade I–II	(1) Ahlbäck grade III–V (2) Secondary OA (3) Previous infiltration or surgery < 6 months (4) Alcohol or drug abuse (5) Any haematological or major organ disorder (6) Any musculoskeletal disorder	One injection at 7 days interval (*Artzal R*)	HA	76	48 Female 28 Male	72	28.4
				One injection at 7 days interval (*Synvisc R*)	HA	77	50 Female 27 Male	70	27.7
				One injection at 7 days interval		57	35 Female 22 Male	71	29
Khongwir et al. [39]		(1) Age > 40 (2) Primary OA (3) Kellgren Lawrence II–III	(1) Secondary OA (2) Local infections (3) Uncontrolled diabetes (4) Severe joint deformity (5) Ongoing anticoagulant therapy (6) Previous knee surgery (7) History of crystalline or neuropathic arthropathy (8) Previous infiltration < 3 months	Three injection at 7 days interval	HA	15			
				Single injection	CCS	15			
				No infiltration		15			

Table 1 (continued)

Author, year	Knees	Inclusion criteria	Exclusion criteria	Type of protocol	Type of injection	Knees	Gender	Age	BMI
Lin et al. [40]	87	(1) Age 20–80 (2) Unilateral or bilateral knee VAS > 40% for > 4 months (3) Ahlbäck I–III (4) No prior knee surgical procedure	(1) Ahlbäck > IV (2) Major axial deviation (3) Concomitant symptomatic knee disorder (4) Systemic inflammatory arthropathy (5) Hematologic disease (6) Severe cardiovascular, neurologic disorder (7) Active infection (8) Immunosuppression (9) Usage of anticoagulant or antiaggregant (10) Use of NSAID and/or chondroprotective supplement < 7 days (11) Prior CCS intra-articular injection < 30 days (12) Prior HA < 6 months (13) Hb < 11 g/dL (14) Thrombocyte < 150.000/mm^3	Three injections at 7 days interval	PRP	31	22 Female 9 Male	61.2	23.9
					HA	29	19 Female 10 Male	62.5	26.3
						27	17 Female 10 Male	62.2	24.9
Louis et al. [41]	48	(1) Age 20–75 (2) Kellgren Lawrence > II (3) Failure of conservative therapies (4) Axial leg deformity (5) BMI 20 to 30 kg/m^2 (6) Hb > 10 g / dL (7) Thrombocyte > 150,000/ mm^3	(1) Knee instability (2) Thrombopathy (3) Infectious disease (4) Current chronic CCS treatment < 2 weeks (5) Intra-articular CCS injection < 8 weeks (6) Intra-articular HA injection < 24 weeks (7) Any NSADs < 2 weeks (8) Autoimmune disease od immunosuppression (9) Inflammatory arthritis (10) Pregnancy	Single injection	PRP	24	10 Female 14 Male	53.2	25.6
					HA	24	13 Female 11 Male	48.5	27
McAlindon et al. [42]	140	(1) Age > 45 (2) OA according to the American College of Rheumatology (3) Ultrasonographic evidence (4) Kellgren Lawrence II–III	(1) Systemic inflammatory (2) Prior sepsis (3) Osteonecrosis (4) Usage of CCS, doxycycline, indomethacin, glucosamine, or chondroitin (5) Intra-articular CCS or HA < 3 moths (6) Severe medical conditions	Injections every 12 weeks for 2 years	CCS	70	37 Female 33 Male	59.1	30.8
						70	Female 38 Male 32	57.2	31.7
Montañez-Heredia et al. [43]	53	(1) Kellgren Lawrence I–III (2) VAS > 50% (3) Age 40 to 80 (3) Thrombocyte > 150.000 (4) Negative serology to Lues, Hepatitis, HIV	(1) Kellgren Lawrence IV (2) Previous surgery < 3 months (4) Previous infiltration of CCS, HA < 3 months (5) Leg deformities (6) Ipsilateral hip–ankle pathology (7) Flexion deficit < 90° (8) Extension deficit > 20° (9) Anticoagulant therapy (10) Fibromyalgia or chronic fatigue syndrome (11) Liver or haematological disease, infection or neoplasm (12) Pregnancy	Three injections at 15 days intervals	PRP	27	15 Female 12 Male	66.3	29
					HA	26	17 Female 9 Male	61.6	30.4

Table 1 (continued)

Author, year	Knees	Inclusion criteria	Exclusion criteria	Type of protocol	Type of injection	Knees	Gender	Age	BMI
Nabi et al. [44]	67	(1) Age 30–75 years (2) OA according to the American College of Rheumatology (3) Kellgren and Lawrence II–III (4) Symptoms > 3 months	(1) Severe joint deformities (2) Malignant (3) Rheumatoid arthritis (4) BMI > 35 kg/m^2 (5) Pregnancy (6) Breastfeeding (7) Acute infection (8) Hb < 11 g/dL (9) Thrombocytes < 150.000 × 109/L (10) Blood disorders (11) Acute knee pain (12) Previous knee surgery (13) Serious neurologic or psychological disorders (14) sciatica pain (15) history of treatment with anticoagulants (16) CCS consumption < 3 months	Three injections at 4 weeks interval	PRP	33	28 Female 5 Male	59.1	28.4
					CCS	34	27 Female 7 Male	58.6	27.8
Patel et al. [45]	75	(1) Ahlback I–II (2) Any leg mal-alignment	(1) Secondary OA (2) Bone metabolic diseases (3) Coexisting backache (4) Intra-articular injections < 3 months (5) Arthroscopic lavage < 12 months in the previous 1 (6) Anticoagulant therapy (7) Hb < 10 md/dL (8) Infection, tumour+r, crystal arthropathies (9) Tense joint effusion	Single injection	PRP	27	16 Female 11 Male	53.1	26.3
				Two injections at 3-week interval	PRP	25	20 Female 5 Male	51.6	25.8
				Single injection		23	17 female 6 male	53.6	26.21
Raeissadat et al. [46]	139	(1) OA according to the American College of Rheumatology criteria (2) Age 40–70 (3) Symptom duration > 3 months (4) Kellgren Lawrence I–IV	(1) Diabetes mellitus, immunodeficiency, collagen and vascular disorders (2) History or presence of malignant disorders, infection or active wound (3) Recent history of severe knee trauma (4) Autoimmune or Thrombocyte disorders (5) Treatment with anticoagulant and antithrombocyte medications < 10 days (6) Usage of NSAIDs < 2 days (7) Previous CCS injections < 3 weeks (8) Usage of systemic CCS < 2 weeks (9) Hb < 12 g/dL (10) Thrombocyte < 150.000/ml (11) Previous vasovagal shock (12) Pregnancy (13) Breastfeeding (14) Severe leg mal-alignments	Two injections at 4 weeks interval	PRP	77	69 Female 8 Male	56.8	28.2
				Three injections at 7 days interval	HA	62	47 Female 15 Male	61.1	27
Spakova et al. [47]	120	(1) Kellgren Lawrence I–III	(1) Thrombocyte < 109/L (2) Hb < 10 g/dl (3) Systemic disease (4) Hematologic disease (5) Previous or active malignant disease (6) Severe cardiovascular disease (7) Infection or immunosuppression (8) Active anticoagulant therapy (9) Intra-articular CCS or HS infiltration < 3 months	Three injection at 7 days interval	PRP	60	27 Female 33 Male	52.8	
					HA	60	29 female 31 male	53.2	

Table 1 (continued)

Author, year	Knees	Inclusion criteria	Exclusion criteria	Type of protocol	Type of injection	Knees	Gender	Age	BMI
Su et al. [48]	82	(1) Unilateral symptomatic OA > 1-month (2) Kellgren Lawrence II–III (3) Age 40 to 73 (4) BMI 18 to 32.5	(1) Secondary OA (2) Kellgren Lawrence > III (3) BMI > 32 (4) Age > 73 (5) Systemic autoimmune rheumatic diseases and blood disorders (6) Immunosuppression or anticoagulant therapy (7) Intra-articular knee injection < 12 months (8) Previous joint infection (8) Usage of CCS < 3 weeks (9) Usage of NSAIDs < 3 weeks	Two injections at 14 days interval (2 mL)	PRP	27	17 Female 10 Male	50.7	28.2
				Two injections at 14 days interval (6 mL)	PRP	25	14 Female 11 Male	54.16	28.2
				Five injections every 7 days (2 mL)	HA	30	18 Female 12 Male	53.1	28.7
Tammachote et al. [49]	99	(1) OA according to the American College of Rheumatology criteria (2) Failure of conservative treatment	(1) Kellegren Lawrence IV (2) Previous fracture or surgery (3) Intra-articular injection < 6 months (4) Active infection (5) Lumbar spondylosis with radiculopathy,	Single injection	CCS	49	36 Female 13 Male	61.0	25.1
					HA	50	43 Female 7 Male	62.6	26.1
Yu et al. [50]	360	(1) OA according to the American College of Rheumatology criteria (2) Age 40–70 (3) Symptoms > 3 months (4) Kellgren Lawrence I–IV	(1) History of diabetes mellitus (2) Immunodeficiency (3) Collagen and/or vascular disorders (4) Previous or active malignant disease (5) Knee infection or active wound (6) Previous severe trauma to the knee (7) treatment with anticoagulant and anti-thrombocyte medications < 10 days b (8) usage of NSAIDs < 2 days (9) Intra-articular CCS injections < 3 weeks (10) Systemic CCS < 2 weeks (11) Hb < 12 g/dL (12) Thrombocyte < 150.000/ml (13) Previous vasovagal shock (14) Pregnancy (15) Breastfeeding (16) Severe leg malalignment	Two injections at 7 days interval	PRP	104	54 Female 50 Male	46.2	
					HA	88	40 Female 48 Male	51.5	
						72	30 Female 42 Male	56.2	

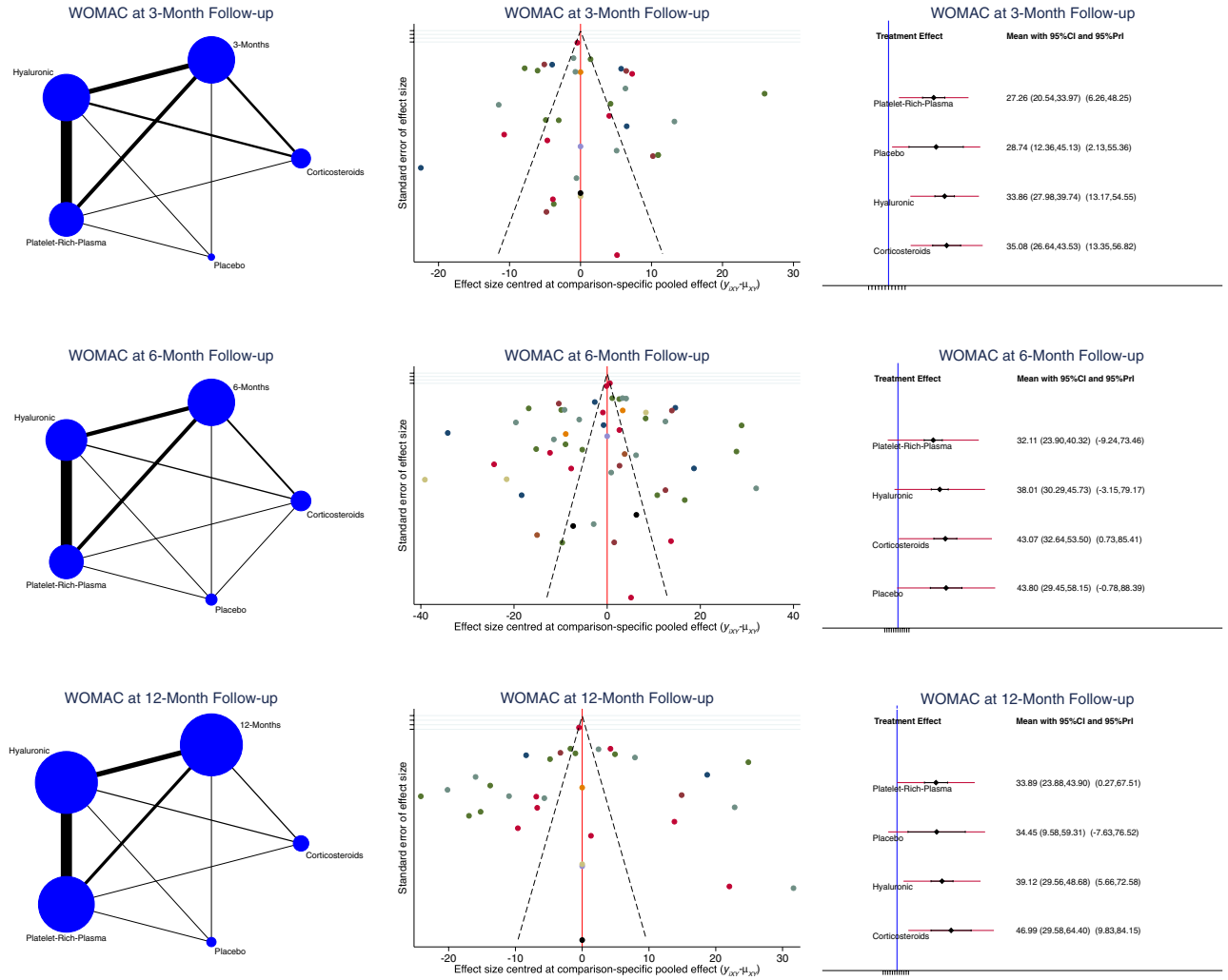

Fig. 3 Overall network comparisons using WOMAC scores

not influence the ranking of the other groups between them. In all the comparisons there was broad CI. The amplitude of the probability value with respect to the CI values that can be assumed by the aleatory variables is large. Hence the distribution of the probability of obtaining a concrete estimated effect of the comparisons is improbable. Data from the present study must therefore be interpreted with caution. Points of strength in the present work include the comprehensive nature of the literature search, the strict eligibility criteria and the quality of the methodological assessment. Further studies should improve the evidence concerning this controversial topic. Whether patients with advanced knee OA can profit from intra-articular infiltrations deserves further investigations through high-quality studies.

Conclusion

According to the main findings of the present Bayesian network meta-analysis, intra-articular injections of PRP demonstrated the best overall outcome compared to steroids, hyaluronic acid and placebo for patients with knee osteoarthrosis at 3, 6 and 12-months of follow-up. Among CCS, hyaluronic acid and placebo, similarity was detected.

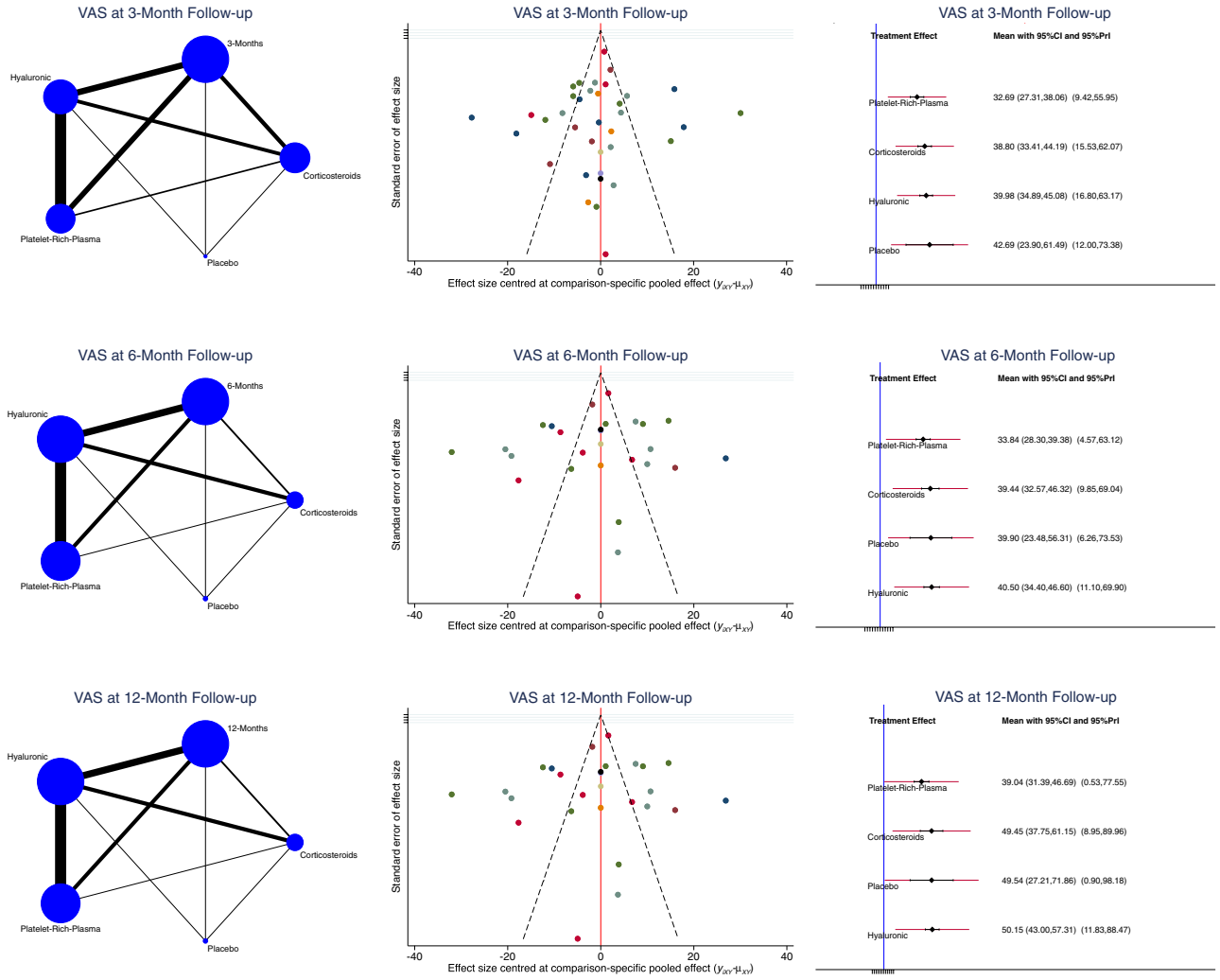

Fig. 4 Overall network comparisons using VAS scores

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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