# Platelet-Rich Plasma, Bone Marrow Aspirate Concentrate, and Hyaluronic Acid Injections Outperform Corticosteroids in Pain and Function Scores at a Minimum of 6 Months as Intra-Articular Injections for Knee Osteoarthritis: A Systematic Review and Network Meta-analysis

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**Purpose:** To compare the efficacy of common intra-articular injections used in the treatment of knee osteoarthritis, including corticosteroid (CS), hyaluronic acid (HA), platelet-rich plasma (PRP), and bone marrow aspirate concentrate (BMAC), with a minimum follow-up of 6-months. **Methods:** A literature search was conducted using the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines in August 2022 in the following databases: PubMed/MEDLINE, Scopus, Cochrane Database of Controlled Trials, and the Cochrane Database of Systematic Reviews. Level I to II randomized clinical trials with a minimum follow-up of 6 months that investigated the treatments of interest were included. Patient-reported outcome scores for pain and function at baseline and at latest follow-up were extracted, and the change in scores was converted to uniform 0 to 100 scales. Arm-based Bayesian network meta-analysis using a random-effects model was created to compare the treatment arms in pain and function. **Results:** Forty-eight studies comprising a total of 9,338 knees were included. The most studied intra-articular injection was HA (40.9%), followed by placebo (26.2%), PRP (21.5%), CS (8.8%), and then BMAC (2.5%). HA and PRP both led to a significant improvement in pain compared with placebo. HA, PRP, and BMAC all led to a significant improvement in function scores when compared with placebo. Surface under the cumulative ranking curves (SUCRAs) of the interventions revealed that PRP, BMAC, and HA were the treatments with the highest likelihood of improvement in both pain and function, with overall SUCRA scores of 91.54, 76.46, and 53.12, respectively. The overall SUCRA scores for CS and placebo were 15.18 and 13.70, respectively. **Conclusions:** At a minimum 6-month follow-up, PRP demonstrated significantly improved pain and function for patients with knee osteoarthritis compared with placebo. Additionally, PRP exhibited the highest SUCRA values for these outcomes when compared with BMAC, HA, and CS. **Level of Evidence:** Level II, meta-analysis of Level I to II studies.

Intra-articular (IA) injections are utilized in the treatment of knee osteoarthritis (OA) to decrease pain, improve function, and hopefully delay the need for a total knee arthroplasty (TKA). While prolonging the time to surgery is preferable to most patients, this also substantially reduces the lifetime health care costs

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*Received February 27, 2023; accepted January 28, 2024.*

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*0749-8063/23297/$36.00*

*https://doi.org/10.1016/j.arthro.2024.01.037*

associated with knee OA.[1] Accordingly, the subject of IA injections for the treatment of knee OA has been of increasing interest, and various studies have been performed to better understand the efficacy of each injection type.

Intra-articular injections of corticosteroids (CS) or hyaluronic acid (HA) are commonly used to reduce inflammation and pain in the knee joint, with studies demonstrating both to be viable options to improve short-term outcomes.[2,3] More recently, "orthobiologic" treatments include hematopoietic stem cells, mesenchymal stem cells, plasma rich in growth factors (PRGF), platelet-rich plasma (PRP), and bone marrow aspirate concentrate (BMAC). PRP and BMAC in particular have become of great interest due to their potential to modulate the inflammatory response.[4,5] PRP is created by centrifuging autologous blood to extract concentrated platelets that have the potential to modify inflammatory responses, stimulate proliferation of local progenitor cells, and direct cell differentiation.[5-7] Similarly, BMAC, which is normally extracted from either iliac crest or tibial bone marrow and then mixed with anticoagulants, provides anti-inflammatory benefits in injected tissues as well as low concentrations of progenitor cells.[8,9] An additional added benefit of BMAC may be that it also contains IL-1 antagonists, which may enable it to further diminish the inflammatory response.[10] A recent systematic review and network meta-analysis by Singh et al.[11] evaluated the efficacy of HA, CS, PRP, and PRGF in the treatment of knee OA. They found that while all treatments showed significant improvements in outcomes (except CS at minimum 6-month follow-up), PRP demonstrated the greatest clinically meaningful improvement in outcomes.[11] However, BMAC was not included in this comparative analysis despite previous studies showing the likely benefit in knee OA.[9,12,13] Furthermore, several new studies have been published since the compilation of included studies used, which have yet to be evaluated in a network meta-analysis.

Therefore, the purpose of this current study was to compare the efficacy of common intra-articular injections used in the treatment of knee osteoarthritis, including CS, HA, PRP, and BMAC, with a minimum follow-up of 6-months. We hypothesized that PRP would lead to significantly improved outcomes in terms of pain and function when compared with the most commonly used IA injections. Additionally, we hypothesized that BMAC would have comparable results to PRP given its related mechanism.

## Methods

### Literature Search and Study Selection

We conducted a systematic review of the literature using the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] A comprehensive literature search was conducted by a medical librarian in August 2022 using the following databases: PubMed/MEDLINE, Scopus, Cochrane Database of Controlled Trials, and the Cochrane Database of Systematic Reviews. Google Scholar was searched as well. Both controlled vocabularies (e.g., MeSH terms) and keywords in the title or abstract fields were searched. There were no restrictions on geography or age of participants. Animal studies were excluded. Additionally, a search was conducted of the reference lists of selected articles. A reproducible search strategy is included (Appendix).

The treatments of interest included CS, HA, PRP, BMAC, and normal saline (NS; considered placebo). Inclusion criteria for the studies were English language, studies designed as randomized clinical trials, level of evidence I to II, studies that measured patient-reported outcomes for pain and/or function, studies that evaluated patients with radiographic or clinical evidence of knee osteoarthritis, studies that compared at least 2 of the treatments of interest, studies with a minimum 6-month follow-up, and studies with a minimum of 20 patients per treatment group. Following removal of duplicates, 2 independent authors (H.J. and A.A.W.) performed abstract and title screening and subsequent full-text review of the articles based on the inclusion criteria. In cases of disagreement, a third reviewer made the final decision (G.R.J.). The following article- and patient-based data were then extracted: title, publication year, level of evidence, type of injection, number of injections, grade of osteoarthritis, patient number, patient age, patient sex, patient body mass index, final follow-up, preoperative outcome measures for pain and function, and postoperative outcomes measures for pain and function at latest follow-up with a minimum of 6 months. Bias assessment was conducted using the Cochrane risk of bias tool for all studies included.[15]

### Outcomes

Preinjection and postinjection outcome scores at latest follow-up were recorded for each study. These scores were converted to a universal 0 to 100 scale for both pain and function separately, with 100 indicating complete function or no pain and 0 indicating no function or worst pain as previously described in Singh et al.[11]

### Risk of Bias Assessment

Risk of bias assessment was completed by a single author (H.J.) using the Cochrane Risk of Bias tool, which evaluates the methodologic quality of studies in 5 main domains: bias arising from randomization, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Aggregate results of the risk of bias assessment are summarized in Figure 2, and individual risk of bias

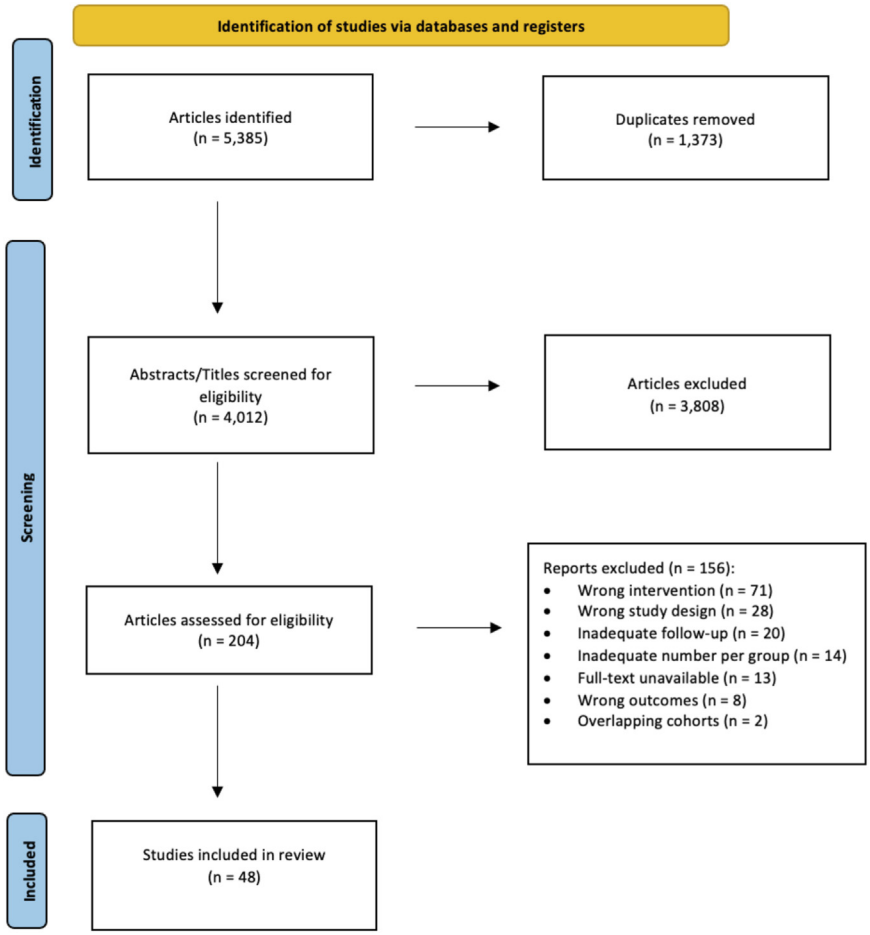


**Fig 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

assessment for all included studies is illustrated in Figure 3.

## Statistical Analysis

Arm-based network meta-analyses were fit with Bayesian methods using the R package "pcnetmeta."[16] Analyses were run based on the mean improvement (score at latest final follow-up − preoperative score). In cases where the standard deviation for the change in score was not available, the formula outlined in Cochrane was used and assumed a correlation of 0.5 between pre and post measurements.[17] In a limited number of studies that provided medians, interquartile range, and ranges, the methods in Luo et al.[18] and Wan et al.[19] were used to provide estimated means and standard deviations, respectively. Model results are presented as estimated absolute differences against the placebo treatment. Surface under the cumulative

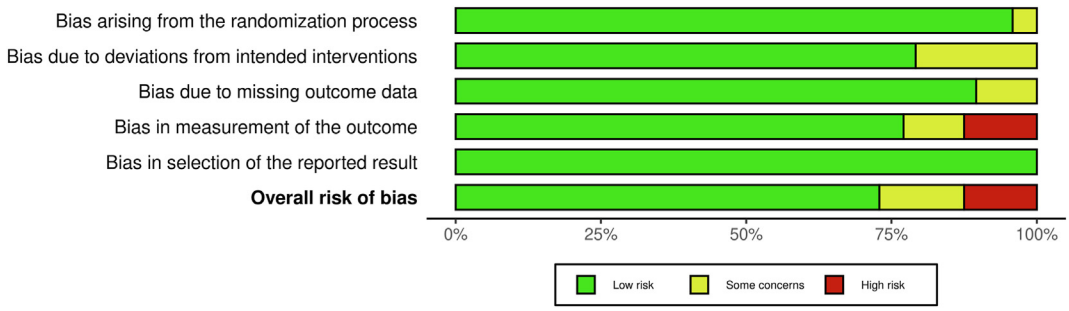


**Fig 2.** Cochrane risk of bias assessment summary of included studies within network meta-analysis.


**Fig 3.** Cochrane risk of bias assessment for individual studies included within network meta-analysis.

ranking curves (SUCRAs) were calculated for each of the interventions for pain and function separately and then averaged for an overall ranking. SUCRA values can range from 0 to 1, and higher values represent higher likelihood that a certain treatment is the best.[20]

## Results

### Included Studies

Initial literature search identified a total of 5,385 studies. After screening, a total of 204 articles were assessed for full-text eligibility, and 48 studies[21-68] were included for this review (Fig 1). There was an overall low risk of bias in 35 (72.9%) studies, some risk of bias in 7 (14.6%) studies, and high risk of bias in 6 (12.5%) studies.

The 48 included studies comprised a total of 9,338 knees, of which 3,815 (40.9%) received HA, 2,451 (26.2%) received placebo, 2,011 (21.5%) received PRP, 824 (8.8%) received CS, and 237 (2.5%) received BMAC. Table 1 details demographics for each included study.

Figure 4 visualizes the network geometry of included study groups. Direct comparisons were available for all injection pairs, excluding BMAC versus corticosteroid injections. The most commonly compared injection groups were PRP versus hyaluronic acid, whereas the least commonly compared group was BMAC versus placebo. The network geometry of available studies was satisfactory for arm-based network meta-analysis fit with Bayesian methods of both pain and function outcomes, with enough direct evidence to extrapolate indirect evidence comparing BMAC versus corticosteroid injections.

Figure 5 depicts the effect sizes of the mean difference in pain from baseline to follow-up among each injection type, with positive effect differences indicating symptomatic improvement in pain. There was no significant change in pain from baseline between the CS and BMAC groups, whereas HA and PRP treatment led to significant reduction in pain. BMAC ranked as the second-best intervention by mean effect difference, but it exhibited the greatest variability in outcomes.

Figure 6 depicts the effect sizes of the mean difference in function from baseline to follow-up among each injection type, with positive effect differences indicating symptomatic improvement in function. There was no significant change in function among patients receiving corticosteroid injections. However, patients receiving HA, BMAC, and PRP injections achieved significant function improvement at follow-up. While BMAC ranked as the second-best intervention by mean effect difference, it exhibited the greatest variability in outcomes, which could be attributed to the number of studies or sample size available.

Cumulative ranking of injection types based on pain and function effect differences was calculated using the SUCRA of interventions values depicted in Table 2. For

**Table 1.** Demographics for Each Included Study

| First Author, Year | Level of Evidence | Type of IA Injection | Number of Knees | Age, Mean ± SD (Range), y | Male/Female, n | Latest Follow-Up | Pain Scale Used | Function Scale Used |
|---|---|---|---|---|---|---|---|---|
| Ahmad, 2018[21] | I | HA | 44 | 56.8 ± 7.4 | 14/30 | 6 mo | VAS pain | IKDC |
| | | PRP | 45 | 56.2 ± 6.8 | 14/31 | 6 mo | VAS pain | IKDC |
| Altman, 2004[22] | I | HA | 172 | 62.9 (41-85) | 93/79 | 26 wk | WOMAC pain | WOMAC function |
| | | Placebo | 174 | 63.3 (35-85) | 63/111 | 26 wk | WOMAC pain | WOMAC function |
| Altman, 2009[23] | I | HA | 293 | 62.5 (11.0) | 107/184 | 26 wk | VAS pain | WOMAC function |
| | | Placebo | 295 | 60.8 (10.0) | 109/186 | 26 wk | VAS pain | WOMAC function |
| Anz, 2022[24] | II | BMAC | 45 | 55.8 ± 11.3 | 27/18 | 24 mo | WOMAC pain | WOMAC function |
| | | PRP | 39 | 52.2 ± 12.4 | 22/17 | 24 mo | WOMAC pain | WOMAC function |
| Bansal, 2021[25] | I | HA | 68 | 65.8 (54-73) | 42/26 | 12 mo | WOMAC pain | WOMAC function |
| | | PRP | 64 | 64.4 (52-74) | 39/25 | 12 mo | WOMAC pain | WOMAC function |
| Basnaev, 2021[26] | I | HA | 38 | NR | NR | 6 mo | VAS pain | Lequesne Index |
| | | PRP | 47 | NR | NR | 6 mo | VAS pain | Lequesne Index |
| Bennell, 2021[27] | I | Placebo | 144 | 61.6 ± 6.6 | 60/84 | 12 mo | Numerical 0-10 | NR |
| | | PRP | 144 | 62.2 ± 6.3 | 59/85 | 12 mo | Numerical 0-10 | NR |
| Bisicchia, 2016[28] | I | CS | 75 | 68.6 ± 9.9 | 25/50 | 52 wk | VAS pain | WOMAC total |
| | | HA | 75 | 71.5 ± 10.6 | 22/53 | 52 wk | VAS pain | WOMAC total |
| Boffa, 2021[29] | I | BMAC | 56 | 57.8 ± 8.9 | 53/21 | 24 mo | VAS pain | IKDC |
| | | HA | 56 | 57.8 ± 8.9 | 53/21 | 24 mo | VAS pain | IKDC |
| Brandt, 2001[30] | I | HA | 66 | 65 ± 8.2 | 26/40 | 27 wk | WOMAC pain | WOMAC function |
| | | Placebo | 69 | 67 ± 8.4 | 26/43 | 27 wk | WOMAC pain | WOMAC function |
| Chevalier, 2010[31] | I | HA | 124 | 63.6 ± 9.64 | 32/92 | 26 wk | WOMAC pain | WOMAC function |
| | | Placebo | 129 | 62.5 ± 9.17 | 41/88 | 26 wk | WOMAC pain | WOMAC function |
| Chu, 2022[32] | I | Placebo | 302 | 54.5 ± 5.1 | 127/175 | 60 mo | VAS pain | WOMAC function |
| | | PRP | 308 | 53.9 ± 5.0 | 123/185 | 60 mo | VAS pain | WOMAC function |
| Cole, 2017[33] | I | HA | 50 | 56.8 ± 10.5 | 20/30 | 52 wk | VAS pain | IKDC |
| | | PRP | 49 | 55.9 ± 10.4 | 28/21 | 52 wk | VAS pain | IKDC |
| Davalillo, 2015[65] | I | CS | 98 | 62.8 (0.6) | 41/57 | 12 mo | WOMAC pain | WOMAC function |
| | | HA | 97 | 62.7 (0.6) | 38/59 | 12 mo | WOMAC pain | WOMAC function |
| Di Martino, 2019[35] | I | HA | 82 | 57.5 ± 11.7 | 47/36 | 24 mo | EQ-VAS pain | IKDC |
| | | PRP | 85 | 52.7 ± 13.2 | 53/33 | 24 mo | EQ-VAS pain | IKDC |
| Di Martino, 2022[34] | I | PRP | 90 | 55.2 ± 9.8 | 62/28 | 12 mo | EQ-VAS pain | IKDC |
| | | PRP | 85 | 55.7 ± 10.7 | 50/35 | 12 mo | EQ-VAS pain | IKDC |
| Dulic, 2021[36] | I | BMAC | 111 | 56.9 ± 10.8 | 57/54 | 12 mo | KOOS pain | WOMAC total |
| | | HA | 30 | 59.4 ± 14.0 | 13/17 | 12 mo | KOOS pain | WOMAC total |
| | | PRP | 34 | 58.8 ± 11.2 | 15/19 | 12 mo | KOOS pain | WOMAC total |
| Filardo, 2015[37] | I | HA | 89 | 57.55 ± 11.8 | 52/37 | 12 mo | EQ-VAS pain | IKDC |
| | | PRP | 94 | 53.32 ± 13.2 | 60/34 | 12 mo | EQ-VAS pain | IKDC |
| Görmeli, 2017[38] | I | HA | 39 | 53.5 ± 14 | 22/17 | 6 mo | EQ-VAS pain | IKDC |
| | | Placebo | 40 | 52.8 ± 12.8 | 20/20 | 6 mo | EQ-VAS pain | IKDC |
| | | PRP | 39 | 53.7 ± 13.1 | 23/16 | 6 mo | EQ-VAS pain | IKDC |
| | | PRP | 44 | 53.8 ± 13.4 | 25/19 | 6 mo | EQ-VAS pain | IKDC |
| Housman, 2014[39] | I | CS | 132 | 60.1 ± 9.3 | 41/91 | 26 wk | WOMAC pain | NR |
| | | HA | 129 | 62.0 ± 9.7 | 38/91 | 26 wk | WOMAC pain | NR |
| | | HA | 130 | 60.6 ± 9.9 | 51/79 | 26 wk | WOMAC pain | NR |

(continued)

**Table 1.** Continued

| First Author, Year | Level of Evidence | Type of IA Injection | Number of Knees | Age, Mean ± SD (Range), y | Male/Female, n | Latest Follow-Up | Pain Scale Used | Function Scale Used |
|---|---|---|---|---|---|---|---|---|
| Huang, 2011[40] | I | HA | 100 | 65.9 ± 8.1 | 26/74 | 25 wk | VAS pain | WOMAC physical function |
| | | Placebo | 100 | 64.2 ± 8.4 | 22/78 | 25 wk | VAS pain | WOMAC physical function |
| Huang, 2019[42] | I | CS | 40 | 54.3 ± 1.4 | 21/19 | 12 mo | VAS pain | WOMAC total |
| | | HA | 40 | 54.8 ± 1.1 | 19/21 | 12 mo | VAS pain | WOMAC total |
| | | PRP | 40 | 54.5 ± 1.2 | 25/15 | 12 mo | VAS pain | WOMAC total |
| Huang, 2021[41] | I | HA | 71 | 56.6 ± 12.6 | 25/46 | 52 wk | VAS pain | WOMAC function |
| | | HA | 69 | 56.0 ± 9.7 | 20/50 | 52 wk | VAS pain | WOMAC function |
| Joshi Jubert, 2017[43] | II | CS | 30 | 68 ± 7.17 | 6/24 | 6 mo | VAS pain | KOOS function |
| | | PRP | 35 | 65.56 ± 8.6 | 12/23 | 6 mo | VAS pain | KOOS function |
| Karlsson, 2002[44] | I | HA | 76 | 72 ± 7 | 22/54 | 26 wk | VAS pain | Lequesne Index |
| | | HA | 77 | 71 ± 7 | 25/52 | 26 wk | VAS pain | Lequesne Index |
| | | Placebo | 57 | 71 ± 6 | 20/37 | 26 wk | VAS pain | Lequesne Index |
| Ke, 2021[45] | I | HA | 220 | 61.5 ± 7.9 | 50/170 | 26 wk | WOMAC pain | NR |
| | | Placebo | 220 | 61.6 ± 7.8 | 48/172 | 26 wk | WOMAC pain | NR |
| Leighton, 2014[46] | I | CS | 215 | 61.5 ± 9.9 | 113/102 | 26 wk | WOMAC pain | WOMAC function |
| | | HA | 218 | 61.9 ± 9.6 | 107/111 | 26 wk | WOMAC pain | WOMAC function |
| Leopold, 2003[47] | I | CS | 50 | 64 (40-83) | 22/28 | 6 mo | VAS pain | WOMAC total |
| | | HA | 50 | 66 (39-79) | 24/26 | 6 mo | VAS pain | WOMAC total |
| Lewis, 2022[48] | I | Placebo | 28 | 60.1 ± 9.3 | 12/16 | 12 mo | VAS pain | KOOS |
| | | PRP | 47 | 55.1 ± 12.6 | 20/27 | 12 mo | VAS pain | KOOS |
| | | PRP | 27 | 59.4 ± 8.9 | 9/18 | 12 mo | VAS pain | KOOS |
| Lin, 2019[49] | I | HA | 29 | 62.53 ± 9.9 | 10/19 | 12 mo | NR | IKDC |
| | | Placebo | 27 | 62.23 ± 11.71 | 10/17 | 12 mo | NR | IKDC |
| | | PRP | 31 | 61.17 ± 13.08 | 9/22 | 12 mo | NR | IKDC |
| Lisi, 2018[50] | I | HA | 31 | 57.1 ± 10 | 16/12 | 12 mo | VAS pain | Lysholm |
| | | PRP | 31 | 53.5 ± 15.1 | 20/10 | 12 mo | VAS pain | Lysholm |
| Migliore, 2021[51] | I | HA | 347 | 63.7 ± 8.7 | 115/232 | 24 wk | VAS pain | Lequesne Index |
| | | Placebo | 345 | 63.8 8.1 | 115/230 | 24 wk | VAS pain | Lequesne Index |
| Nabi, 2018[52] | I | CS | 34 | 58.55 ± 8.79 | 7/27 | 12 mo | VAS pain | KOOS function |
| | | PRP | 33 | 59.09 ± 7.79 | 5/28 | 12 mo | VAS pain | KOOS function |
| Nunes-Tamashiro, 2022[53] | I | CS | 33 | 65.8 ± 6.1 | 3/30 | 52 wk | VAS pain | WOMAC function |
| | | Placebo | 33 | 68 ± 6.2 | 3/30 | 52 wk | VAS pain | WOMAC function |
| | | PRP | 34 | 67.6 ± 7.4 | 4/30 | 52 wk | VAS pain | WOMAC function |
| Park, 2021[54] | I | HA | 55 | 62.3 ± 9.6 | 8/47 | 6 mo | VAS pain | WOMAC function |
| | | PRP | 55 | 60.6 ± 8.2 | 16/39 | 6 mo | VAS pain | WOMAC function |
| Patel, 2013[55] | I | Placebo | 46 | 53.65 ± 8.17 (37-70) | 6/17 | 6 mo | VAS pain | WOMAC function |
| | | PRP | 54 | 53.11 ± 11.55 (33-80) | 11/16 | 6 mo | VAS pain | WOMAC function |
| | | PRP | 50 | 51.64 ± 9.22 (34-70) | 5/20 | 6 mo | VAS pain | WOMAC function |
| Petterson, 2019[56] | I | HA | 184 | 59.5 ± 8 | 75/109 | 26 wk | VAS pain | WOMAC function |
| | | Placebo | 185 | 58.7 ± 9.2 | 79/106 | 26 wk | VAS pain | WOMAC function |
| Pham, 2004[57] | I | HA | 131 | 64.9 ± 8.4 | 38/93 | 12 mo | VAS pain | Lequesne Index |
| | | Placebo | 85 | 64.9 ± 7.7 | 33/52 | 12 mo | VAS pain | Lequesne Index |
| Qamar, 2021[58] | I | Placebo | 50 | 58.7 ± 3.9 | 20/30 | 6 mo | VAS pain | NR |
| | | PRP | 50 | 60.03 ± 4.7 | 17/33 | 6 mo | VAS pain | NR |

(continued)

**Table 1.** Continued

| First Author, Year | Level of Evidence | Type of IA Injection | Number of Knees | Age, Mean ± SD (Range), y | Male/Female, n | Latest Follow-Up | Pain Scale Used | Function Scale Used |
|---|---|---|---|---|---|---|---|---|
| Raeissadat, 2015[59] | I | HA | 62 | 61.13 ± 7.48 | 15/47 | 12 mo | WOMAC pain | WOMAC function |
| | | PRP | 77 | 56.85 ± 9.13 | 8/69 | 12 mo | WOMAC pain | WOMAC function |
| Sdeek, 2021[60] | I | HA | 94 | 59.5 | 16/78 | 36 mo | VAS pain | IKDC |
| | | PRP | 95 | 60.2 | 15/80 | 36 mo | VAS pain | IKDC |
| Shapiro, 2017[61] | II | BMAC | 25 | 60 (42-68) | 7/18 | 6 mo | VAS pain | NR |
| | | Placebo | 25 | 60 (42-68) | 7/18 | 6 mo | VAS pain | NR |
| Shoma, 2021[62] | I | HA | 68 | 52.7 ±5.4 | 29/39 | 6 mo | VAS pain | NR |
| | | PRP | 65 | 51.3 ±6.5 | 27/38 | 6 mo | VAS pain | NR |
| Spaková, 2012[63] | I | HA | 60 | 53.2 ± 14.53 | 31/29 | 6 mo | Numeric rating scale (0-11) | WOMAC total |
| | | PRP | 60 | 52.8 ± 12.43 | 33/27 | 6 mo | Numeric rating scale (0-11) | WOMAC total |
| Tammachote, 2016[64] | I | CS | 49 | 61 | 13/36 | 6 mo | VAS pain | Modified WOMAC |
| | | HA | 50 | 62.6 | 7/43 | 6 mo | VAS pain | Modified WOMAC |
| Vaishya, 2017[66] | I | CS | 68 | NR | 15/25 | 24 wk | VAS pain | KSS function |
| | | HA | 72 | NR | 13/29 | 24 wk | VAS pain | KSS function |
| van der Weegen, 2015[67] | I | HA | 99 | 58.7 ± 9.6 | 49/50 | 6 mo | VAS pain | WOMAC total |
| | | Placebo | 97 | 60.1 ± 10.1 | 50/47 | 6 mo | VAS pain | WOMAC total |
| Yaradilmis, 2020[68] | I | HA | 30 | 63 ± 9.17 | 4/26 | 12 mo | VAS pain | WOMAC total |
| | | PRP | 30 | 60.3 ± 7.65 | 4/26 | 12 mo | VAS pain | WOMAC total |
| | | PRP | 30 | 58.93 ± 6.25 | 3/27 | 12 mo | VAS pain | WOMAC total |

BMAC, bone marrow aspirate concentrate; CS, corticosteroid; EQ-VAS, EuroQol visual analogue scale; HA, hyaluronic acid; IA, intra-articular; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; KSS, Knee Society Score; NR, not reported; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

the treatment of pain in patients with knee osteoarthritis, PRP ranked as the best IA injection, followed by BMAC, then HA, then CS. For function improvement, PRP similarly ranked as the best IA injection, followed by BMAC, then HA. CS ranked worse than placebo in function improvement, indicating a net-negative effect.

## Discussion

The most important finding from the network meta-analysis found that PRP demonstrated the highest SUCRA value compared with the other IA injection options. Additionally, although PRP, BMAC, and HA demonstrated improvements in pain and function compared with placebo, this was not seen for the CS injection cohort. Furthermore, although the BMAC cohort did not demonstrate significantly improved pain compared with NS patients, its SUCRA value for both evaluated outcomes of pain and function was higher than those of HA and CS.

The results of the current study suggest PRP was the most efficacious IA injection in terms of pain and function. These findings are similar to those of Singh et al.,[11] who recently conducted a similar network meta-analysis of 23 randomized controlled trials (RCTs) and demonstrated that PRP yielded superior outcomes compared with the additional IA injections evaluated. Analysis from the current investigation builds from these findings by reporting on over twice the number of studies and approximately twice the number of patients receiving IA injections. Furthermore, the authors of the previous study did not evaluate the utility of BMAC injections. Although the authors did evaluate PRGF and found superior improvements in both pain and function compared with placebo,[11] this IA injection was excluded from the current analysis given the relatively low number of patients among currently available Level I and Level II studies receiving this injection (n = 146).

Corticosteroid injections did not provide significant improvement in pain or function compared with placebo at a minimum of 6 months and even had a lower SUCRA value for function than placebo. These results are similar to those reported by Singh et al.[11] Of note, there is prior evidence that, despite small to moderate benefit relative to placebo at 1 to 6 weeks following CS injection, there is no evidence of effect beyond 13 to 26 weeks, as highlighted in a comprehensive review by Jüni et al.[69] This short-term exclusive benefit is further corroborated by the findings of our present study, the scope of which is focused at a 6-month minimum follow-up. Given the increasing body of evidence demonstrating superiority of PRP compared with CS for the treatment of knee OA, it is interesting that the updated Clinical Practice Guideline released by the American Academy of Orthopaedic Surgeons indicates that CS remains appropriate for all evaluated patient scenarios. Similarly, these guidelines stated that PRP was rarely appropriate for the management of knee OA and that there was not enough evidence to identify patients for whom HA should be appropriately given.[70] BMAC was not addressed by these recommendations, likely due to its relatively novel use for knee OA management. However, given the findings regarding the utility of PRP, BMAC, and HA, coupled with the relative lack of efficacy shown for CS, the present analysis suggests it is reasonable to consider alternative IA injections as first-line treatment options for patients with knee OA.

Multiple systematic reviews have found that PRP remains an effective and often superior treatment option for osteoarthritis of the knee[11,71,72] as well as for other arthritic joints and tendinopathies.[72-76] However, previous studies have suggested that the superior effects of PRP demonstrate a time-dependent relationship. Shen et al.[72] found that although the greatest improvements in Western Ontario and McMaster Universities Arthritis Index (WOMAC) functional scores were seen at 3-month follow-up, the effect for WOMAC pain scores was most pronounced at 6 months when compared with placebo. Time-dependent improvement was also observed in a prior meta-analysis of RCTs by Dai et al.,[77] revealing no differences in outcomes between PRP and HA at 6 months but statistically significant superiority in WOMAC, International Knee Documentation Committee (IKDC), and Lequesne scores at 12-month follow-up, as well as clinically significant superiority in WOMAC scores. Of note, a similar Bayesian network meta-analysis by Migliorini et al.[78] revealed superior outcomes following the use of PRP relative to alternative IA injections at 3-, 6-, and 12-month follow-up marks. Additionally, multiple studies have indicated that there are various patient-related factors that may impact the effectiveness of PRP injections, with more advanced OA grade frequently associated with poorer treatment response.[79,80] Therefore, as the cost-effectiveness of PRP injections remains a subject of debate,[81-83] the authors feel that appropriate patient selection taking into consideration patient factors, including body mass index (BMI), age, degree of osteoarthritis, timing of symptoms, and more, may influence decisions regarding PRP use.

BMAC was found to have function and pain SUCRA values above those of CS injections and HA injections. As a source of numerous growth factors, including bone morphogenetic protein (BMP) 2, BMP-7, and platelet-derived growth factor, BMAC has demonstrated therapeutic anti-inflammatory effects for the management of various orthopaedic conditions.[8,84,85] Although PRP demonstrated the highest improvements in outcomes when compared with placebo, some evidence suggests comparable if not superior outcomes for patients receiving BMAC when compared directly with PRP cohorts.[24,36] Notably, the article by Anz et al.[24] included in our analysis found that WOMAC and IKDC values

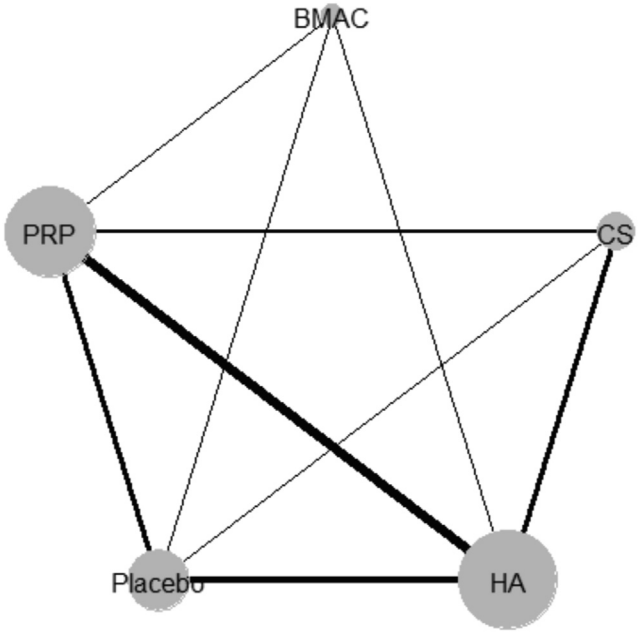


**Fig 4.** Node plot of injection types included in network meta-analysis. (BMAC, bone marrow aspirate concentrate; CS, corticosteroid; HA, hyaluronic acid; PRP, platelet-rich plasma.)

were significantly improved for both PRP and BMAC patients, with no differences demonstrated at 24-month follow-up. However, similar to PRP, the harvesting process, cost, and variation in injection protocols for BMAC have contributed to its limited use for knee OA.[86,87] As analysis of the current investigation suggests that BMAC is a promising option for patients managing knee OA, it is important that future evaluations focus on standardized treatment algorithms and appropriate patient selection to optimize the use of this biologic.[88] While BMAC ranked as the second-best intervention by mean effect difference, it exhibited the greatest variability in outcomes, which could be attributed to the number of studies or sample size available. Another possible source for the variability is the heterogeneity of formulations used in the literature. As the body of evidence increases, it is hoped that future research will be able to determine what concentrations are optimal for each orthopaedic pathology.

## Limitations

The findings of this study must be interpreted through the context of its limitations. While the network meta-analysis only included data from high-quality studies, variations among included cohorts among utilized adjuvant treatments, such as anti-inflammatory medications and physical therapy regimens, may affect patient response to therapy. Related to this notion, the higher cost associated with PRP and BMAC may result in expectation bias among unblinded patients, which could affect patient-reported outcome measures. The study did not perform a cost-benefit analysis, and biologic injections such as PRP and BMAC are not currently covered by government or private insurances. Furthermore, HA injections may only be approved by certain insurances at specific time intervals. The length of efficacy of each of these injections warrants further study, and an ongoing issue in the literature pertains to the volume and formulation of various injections, particularly for PRP,[89] as well as their associated dosing schedule. For example, multiple HA injections available on the market may require up to 3 injections staged over multiple weeks. Similarly, the impact of different platelet and leukocyte concentrations among PRP

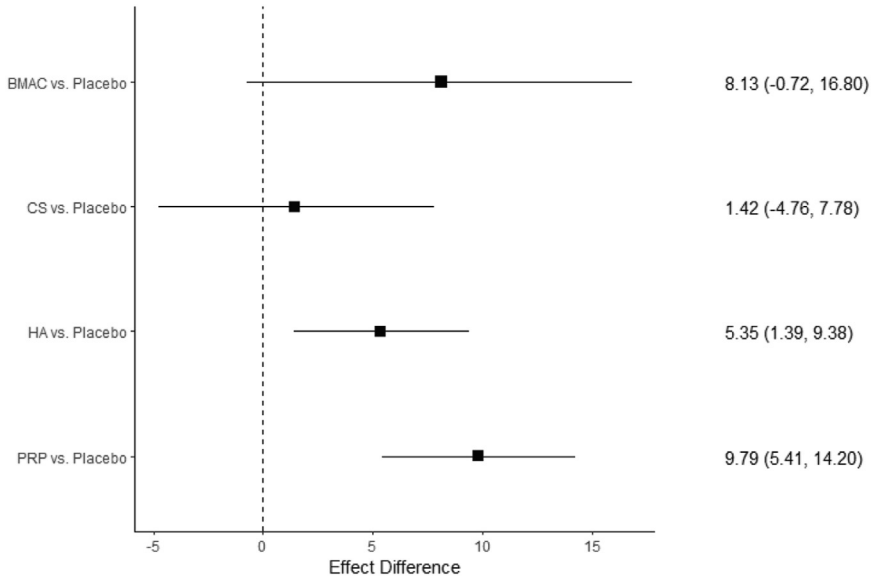


**Fig 5.** Forest plot depicting effect difference in pain from baseline among injection groups compared to placebo. Positive numbers denote symptomatic pain improvement. (BMAC, bone marrow aspirate concentrate; CS, corticosteroid; HA, hyaluronic acid; PRP, platelet-rich plasma.)

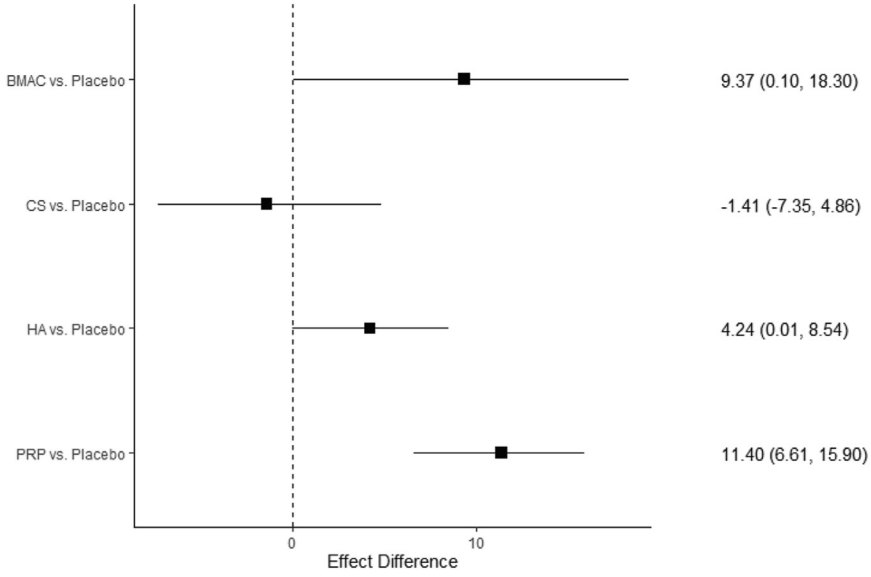


**Fig 6.** Forest plot depicting effect difference in function from baseline among injection groups compared to placebo. Positive numbers denote function improvement. (BMAC, bone marrow aspirate concentrate; CS, corticosteroid; HA, hyaluronic acid; PRP, platelet-rich plasma.)

injections and outcomes continues to be evaluated[90,91]—with emerging evidence suggesting superior outcomes for leukocyte-poor PRP in knee OA populations.[71] The various preparation methods of PRP and BMAC among the 48 included studies is a significant limitation for our study. When pooling results from various studies without analysis of a standardized composition of these injectables, the results must be interpreted with caution. While our analysis included commonly utilized IA injections individually, it is important to note that increased evidence has suggested a synergistic effect when multiple IA injections are given in combination.[92] It is also important to note that there were significant differences in patient characteristics in the pooled intervention groups, namely, lower age and slightly lower (with unlikely clinical significance) BMI in the PRP group. Additionally, although the conversion of values from multiple pain and function scales allowed for comparison and creation of a network for a large number of studies, there is inherent heterogeneity with pooling the data in this fashion. The use of SUCRA scores does allow for a ranking system of the injections utilized, but given the prior statement, the results must be interpreted with caution. Furthermore, although our analysis evaluated pain and function given their importance in the management of knee OA symptoms, additional outcomes may be considered when deciding on which IA injection to implement, including their respective complications and resulting safety profile, as well as their efficacy in delaying conversion to a TKA.[93] The present review included only studies with a minimum follow-up of 6 months, with no analysis of the shorter-term efficacy of the analyzed IA injection options.

**Table 2.** Surface Under the Cumulative Ranking (SUCRA) Scores of Interventions

| Characteristic | Pain | Function | Mean |
|---|---|---|---|
| Platelet-rich plasma | 91.00 (1) | 92.07 (1) | 91.54 (1) |
| Bone marrow aspirate concentrate | 74.02 (2) | 78.92 (2) | 76.46 (2) |
| Hyaluronic acid | 54.40 (3) | 51.83 (3) | 53.12 (3) |
| Corticosteroid | 21.31 (4) | 9.04 (5) | 15.18 (4) |
| Placebo (normal saline) | 9.26 (5) | 18.13 (4) | 13.70 (5) |

NOTE. Higher SUCRA values denote higher likelihood that a given intervention is the best treatment modality for each respective outcome. Numbers in parentheses denote the rank of that injection type for each outcome.

## Conclusions

At a minimum 6-month follow-up, PRP demonstrated significantly improved pain and function for patients with knee osteoarthritis compared to placebo. Additionally, PRP exhibited the highest SUCRA values for these outcomes when compared with BMAC, HA, and CS.

## Disclosures

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

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## Appendix: Search Strategy

(((“Osteoarthritis, Knee”[Mesh] OR KOA)
OR ((“Knee”[Mesh] OR “Knee Joint”[Mesh] OR knee)
AND (“Osteoarthritis”[Mesh] OR osteoarthriti* OR osteoarthros* OR arthros* OR arthriti* OR gonarthros* OR gonitis OR gonarthritis)))
AND ((BMAC OR bone marrow aspirate OR “Hyaluronic Acid”[Mesh] OR hyaluron* OR hylan OR “Adrenal Cortex Hormones”[Mesh] OR “Adrenal Cortex Hormones” OR corticoid* OR cortical OR corticosteroid* OR “cortico steroid” OR corticotherapy OR “Platelet-Rich Plasma”[Mesh] OR “platelet rich plasma” OR “Ibuprofen”[Mesh] OR ibuprofen OR ibuprophen OR “Naproxen”[Mesh] OR naproxen OR “Acetaminophen”[Mesh] OR acetaminophen OR paracetamol OR “Celecoxib”[Mesh] OR celecoxib OR “Diclofenac”[Mesh] OR diclofenac OR steroid* OR triamcinolone OR hexacetonide))
AND ((“randomized controlled trial”[pt]))
NOT (animals [mh] NOT humans [mh]))