Relative Efficacy of Intra-articular Injections in the Treatment of Knee Osteoarthritis

A Systematic Review and Network Meta-analysis

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Background: In younger patients and those without severe degenerative changes, the efficacy of intra-articular (IA) injections as a nonoperative modality for treating symptomatic knee osteoarthritis (OA)–related pain while maintaining function has become a subject of increasing interest.

Purpose: To assess and compare the efficacy of different IA injections used for the treatment of knee OA, including hyaluronic acid (HA), corticosteroids (CS), platelet-rich plasma (PRP), and plasma rich in growth factors (PRGF), with a minimum 6-month patient follow-up.

Study Design: Meta-analysis of randomized controlled trials; Level of evidence, 1.

Methods: A systematic review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the following databases: PubMed/MEDLINE, Scopus, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Google Scholar. Mean or mean change from baseline and standard deviation for outcome scores regarding pain and function were recorded at the 6-month follow-up and converted to either a 0 to 100 visual analog scale score for pain or a 0 to 100 Western Ontario and McMaster Universities Osteoarthritis Index score for function. A frequentist network meta-analysis model was developed to compare the effects of HA, CS, PRP, PRGF, and placebo on patient-reported outcomes.

Results: All IA treatments except CS were found to result in a statistically significant improvement in outcomes when compared with placebo. PRP demonstrated a clinically meaningful difference in function-related improvement when compared with CS and placebo due to large effect sizes. Studies evaluating outcomes of PRGF reported significant improvement when compared with placebo due to large effect sizes, whereas a potential clinically significant difference was detected in the same comparison parameters in pain evaluation. With regard to improvements in pain, function, and both combined, PRP was found to possess the highest probability of efficacy, followed by PRGF, HA, CS, and placebo.

Conclusion: PRP yielded improved outcomes when compared with PRGF, HA, CS, and placebo for the treatment of symptomatic knee OA at a minimum 6-month follow-up. Further investigations evaluating different IA and other nonoperative treatment options for patients with knee OA are warranted to better understand the true clinical efficacy and long-term outcomes of nonsurgical OA management.

Keywords: knee; osteoarthritis; platelet-rich plasma; meta-analysis; plasma rich in growth factors

The physical, psychological, and socioeconomic burdens of knee osteoarthritis (OA) on patients is substantial.[40] Although successful outcomes have been reported in patients with advanced knee OA who undergo total knee arthroplasty,[64] patients spend an average of 13.3 years on nonsurgical treatment for symptomatic knee OA before undergoing total knee arthroplasty.[41] As such, in younger patients and those without severe degenerative changes, the efficacy of nonoperative modalities in treating OA-related pain while maintaining function has become a subject of increasing interest.[18,60]

Strong evidence exists for the use of nonsteroidal anti-inflammatory drugs and aerobic exercise, along with

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weight loss for patients with a body mass index >25, in successfully relieving OA-related knee pain based on evidence-based guidelines established by the American Academy of Orthopaedic Surgeons in 2013 in patients with minimum 4-week follow-up.[31] Multiple studies have also reported improvements in pain and physical function for patients undergoing supervised physical therapy.[19,23,55] Although intra-articular (IA) injections consisting of hyaluronic acid (HA) or corticosteroids (CS) are commonly used and have demonstrated positive short-term outcomes, their long-term efficacy is largely unknown.[6,18,42,52] Platelet-rich plasma (PRP), defined as an autologous formulation derived from whole blood that is centrifuged to extract a solution with a platelet concentration 3- to- 5-fold greater in multiple growth factors compared with normal plasma,[24] has become increasingly used for the treatment of knee OA over the past decade by effectively modulating the inflammation process.[7] In contrast, plasma rich in growth factors (PRGF) is similarly obtained from harvested autologous blood but possesses a moderated platelet concentration without leukocytes, minimizing the risk for any proinflammatory events within the joint.[5] However, inconclusive evidence remains regarding the efficacy of PRP and PRGF injections for symptomatic knee OA with >4 weeks of follow-up.[31] As such, an evidence-based method is needed to assess the relative effectiveness of IA injections beyond 4 weeks.

A previous network meta-analysis, which consisted of 53 randomized controlled trials (RCTs) comparing IA treatment modalities for knee OA, reported that IA CS demonstrated superior pain relief compared with IA PRP, HA, and placebo.[32] However, mean patient follow-up time in the included RCTs was limited to 42 days.[32] The purpose of this study was to assess and compare the efficacy of currently available IA injections used in the treatment of knee OA, including HA, CS, PRP, and PRGF, in patients with a minimum 6-month follow-up. We hypothesized there would be no significant differences in treatment outcomes based on the type of IA injection used.

METHODS

Literature Search

We conducted a systematic review and meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using a PRISMA checklist. A comprehensive literature search was conducted by an experienced research librarian (J.C.W.). The following databases were searched: PubMed/MEDLINE, Scopus, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Google Scholar. Both controlled vocabulary (ie, Medical Subject Headings [MeSH] terms) and keywords were searched. No restrictions were placed on the search in terms of language, date of publication, age of study participants, or geography. The search terms included the following: ("Osteoarthritis, Knee"[MeSH] OR KOA OR "(osteoarthritis AND knee)) AND ((("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)). The search was conducted on August 12, 2020.

Study Selection and Quality Assessment

Articles were included in the network meta-analysis and assessed for quality if the study met the following criteria: (1) designed as an RCT; (2) written in English or translated into the English language; (3) included human participants; (4) evaluated treatments, outcomes, and comparisons of interest; (5) evaluated a population with radiographic or clinical evidence of knee OA; (6) included a minimum of 30 patients per study group[32]; and (7) entailed a minimum 6-month follow-up. Treatments of interest included IA HA, CS, PRP, PRGF, and placebo; outcomes of interest included pain and function. After combining the search results and removing duplicates, 2 authors (C.K.E, A.H.B.) independently screened the titles and abstracts of 3943 studies, selecting 1152 studies for full-text review. In cases of disagreement, a third reviewer (D.M.K.) made the final decision. After full-text screening for inclusion criteria, 23 RCTs were selected for the

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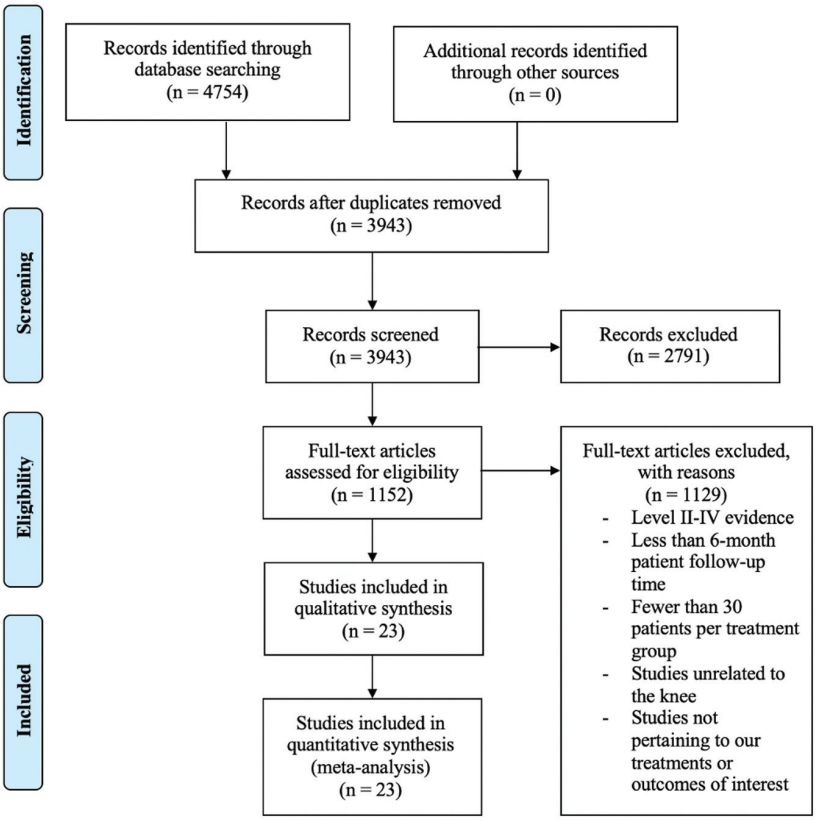

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

network meta-analysis (Figure 1).[‡] Two reviewers (C.K.E, A.H.B.) then extracted data for patients with outcomes reported at a minimum of 6 months of follow-up. Bias assessment for all included RCTs was based on the Cochrane Collaboration risk-of-bias tool.[28] Three reviewers (C.K.E, H.S., S.G.) evaluated each article for bias, including selection, performance, detection, attrition, and reporting biases.

Outcome Assessment

Mean or mean change from baseline and standard deviation of outcome scores for pain and function were recorded. All validated study outcome metrics evaluating pain or function were uniformly converted to either a 0 to 100 visual analog scale (VAS) score for pain or a 0 to 100 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score for function. Subsequently, the uniform scores were converted into minimal clinically important difference (MCID) units. The MCID values used to convert to MCID units were based on previously published literature: reduction of 19.1 units for VAS pain and reduction of 8.0 units for WOMAC function.[4,58,59] The differences in mean MCID converted pain and physical function–related improvement were used to calculate the effect sizes for each treatment.

[‡]References 1-3, 9, 10, 14, 15, 20, 22, 29, 30, 35, 37-39, 44-47, 53, 56, 57, 61.

Statistical Analysis

A frequentist network meta-analysis model was developed to compare the effect of IA HA, CS, PRP, PRGF, and placebo on patient-reported outcomes of function and pain at a minimum of 6 months after injection.[49] A total of 3 RCTs per treatment comparison were needed to perform the statistical analysis. The Q statistic was used to assess the assumptions of homogeneity and consistency under the random-effects model.[66] The assumption of homogeneity refers to the similarity of effect sizes calculated for RCTs within each pairwise treatment comparison. The assumption of consistency pertains to the agreement of direct and indirect evidence within the network for a given treatment. Indirect evidence was extrapolated based on the differences between the mixed (ie, combined direct and indirect) and direct treatment effects within the network. The network meta-analysis model was used to compute mixed effects for each treatment comparison. The magnitude of the mixed effect sizes was defined as representing potentially clinical significance when the value was between 0.5 and 1.0 and likely clinical significance at a value >1.0.[32,33] Outcome metrics reported by the included RCTs were uniformly converted to either a 0 to 100 VAS score for pain or a 0 to 100 WOMAC score for function. Subsequently, the uniform scores were converted into MCID units. The conversion to MCID units was used to enhance interpretability of results. The weighted mean

TABLE 1
Number of Injections and Patient Characteristics in the Included Studies[a]

	Total	HA	PRP	Placebo	CS	PRGF
No. of injections	4604	2371	446	1120	521	146
Age, y	60.0 ± 3.0	61.2 ± 3.1	55.6 ± 3.0	63.3 ± 1.9	63.0 ± 3.4	57.0 ± 3.5
BMI	28.5 ± 1.5	28.5 ± 1.5	27.3 ± 0.6	30.0 ± 2.7	28.6 ± 2.1	28.5 ± 0.6
Male/female, n	1781/2823	910/1461	201/245	394/726	216/305	60/86

[a]Age and BMI are expressed as mean ± SD. BMI, body mass index; CS, corticosteroid; HA, hyaluronic acid; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma.

difference of the MCID conversion results was used to derive the effect sizes of each treatment comparison.

The efficacy of competing treatments in the network was ranked through computation of the *P* value, which is representative of the certainty that a given treatment is superior to other treatments.[50] A total of 5 *P* values were calculated to determine the efficacy of competing treatments in terms of improvement in pain, function, and combined pain and function. The combined efficacy was determined by taking the average *P* value of improvement in pain and function with respect to each treatment. Forest plots comparing treatments were constructed to graphically represent improvements in pain and function. All statistical analyses were performed using R Project for Statistical Computing software (RStudio software Version 1.2.1335; R Foundation for Statistical Computing).

RESULTS

A total of 23 studies meeting inclusion criteria were analyzed for pain and function-related outcomes. Table 1 provides the number of injections and patient characteristics in the included studies. The assumption of between-design consistency assuming a design-by-treatment interaction random-effects model was satisfied for outcomes of both pain and physical function (Q statistic = 0; $P > .999$), indicating no significant difference between direct and indirect evidence within the network (Table 2). With respect to the assumption of homogeneity for pain outcomes, significant heterogeneity was observed for the HA:CS ($Q = 11.1$; $P = .025$), HA:placebo ($Q = 197.9$; $P < .001$), and HA:PRP ($Q = 115.8$; $P < .001$) within-design treatment comparisons but not for HA:PRGF ($Q = 1.4$; $P = .503$). In terms of outcomes for physical function, significant heterogeneity was observed for the HA:CS ($Q = 39.4$; $P < .001$), HA:placebo ($Q = 43.4$; $P < .001$), HA:PRGF ($Q = 6.3$; $P = .043$), and HA:PRP ($Q = 110.8$; $P < .001$) within-design treatment comparisons.

PRP demonstrated the largest difference and CS had the smallest difference regarding pain reduction and function-related improvement relative to placebo using MCID standardized units. Results from this assessment are shown in Figures 2 and 3.

In total, 5 mixed treatment comparisons of pain outcomes were found to be statistically significant, and 3 of these had effect sizes that were large enough to have potential for clinical significance. However, none of the mixed treatment comparisons were deemed clinically significant in terms of pain improvement (Table 3). A total of 5 mixed treatment comparisons of function-related outcomes were found to be statistically significant with large effect sizes (Table 3). Of these, 2 comparisons had potential clinical significance, and 3 had clinical significance. All of the IA treatments except CS were found to have a statistically significant difference in comparison with placebo. PRP had statistical significance over all treatment options except PRGF in terms of outcomes for pain and function.

TABLE 2
Effect Sizes Among RCTs Within Individual Treatment Comparisons (Direct Evidence)[a]

Comparison	Pain Effect Size (95% CI)	Function Effect Size (95% CI)
CS vs HA	–0.07 (–0.31 to 0.16)	–0.33 (–1.13 to 0.47)
PRGF vs HA	0.33 (–0.02 to 0.69)	0.77 (–0.09 to 1.63)
PRP vs HA	0.49 (0.27 to 0.72)	0.85 (0.22 to 1.48)
Placebo vs HA	–0.21 (–0.41 to 0.02)	–0.75 (−1.33 to −0.18)

[a]CS, corticosteroid; HA, hyaluronic acid; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma; RCT, randomized controlled trial.

The 5 competing treatments were subsequently ranked based on pain, function, and combined outcomes. In terms of pain reduction, function-related improvement, and combined improvements, the ranking of the 5 treatments from 1 to 5 (1 being the most efficacious, 5 being the least) was PRP, PRGF, HA, CS, and placebo (Table 4). PRP was the highest ranked treatment for all 3 assessed categories ($P = .94$, .88, and .91, respectively) (Figure 4). Placebo was found to be the least effective treatment when assessed using the same comparison parameters.

Random sequence generation and allocation concealment were evident in all studies except 1 RCT with unclear concealment of allocation (unclear risk of bias)[56] and another RCT in which no concealment was performed (high risk of bias).[45] In our evaluation of performance bias (Figure 5), we found that 2 studies provided an unclear description of blinding measures used for patients and investigators (unclear risk of bias),[1,37] and 6 studies reported no blinding for patients (high risk of bias).[9,38,39,45-47] The risk of attrition bias was unclear in

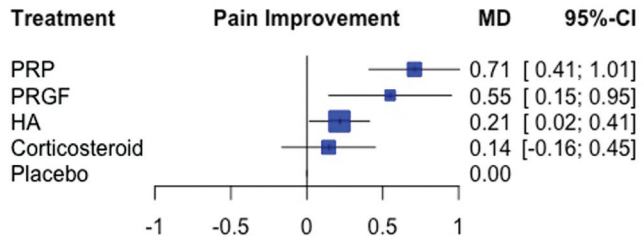

Figure 2. Forest plot demonstrating the mean difference (MD) and 95% CI in clinically significant pain improvement between different treatments relative to placebo for knee osteoarthritis. HA, hyaluronic acid; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma.

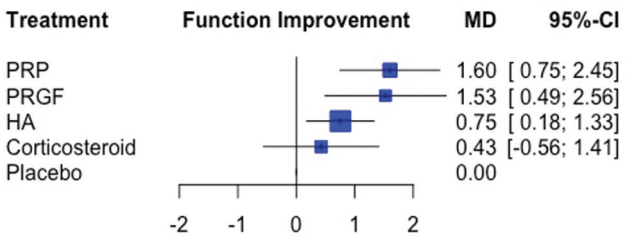

Figure 3. Forest plot demonstrating the mean difference (MD) and 95% CI in clinically significant improvement for function between different treatments relative to placebo for knee osteoarthritis. HA, hyaluronic acid; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma.

TABLE 3
Mixed Effects for Pain and Function[a]

	PRP	PRGF	HA	CS	Placebo
Pain					
PRP		0.16 (–0.26 to 0.58)	**0.49 (0.27 to 0.72)**	**0.56[b] (0.24 to 0.89)**	**0.71[b] (0.41 to 1.01)**
PRGF			0.33 (–0.2 to 0.69)	0.41 (–0.02 to 0.83)	**0.55[b] (0.15 to 0.95)**
HA				0.07 (–0.16 to 0.31)	**0.21 (0.02 to 0.41)**
CS					0.14 (–0.16 to 0.45)
Placebo					
Function					
PRP		0.07 (–0.99 to 1.14)	**0.85[b] (0.22 to 1.47)**	**1.18[c] (0.16 to 2.19)**	**1.60[c] (0.75 to 2.45)**
PRGF			0.77 (–0.09 to 1.63)	1.10 (–0.07 to 2.28)	**1.53[c] (0.49 to 2.56)**
HA				0.33 (–0.47 to 1.13)	**0.75[b] (0.18 to 1.33)**
CS					0.43 (–0.56 to 1.41)
Placebo					

[a]Data are presented as effect size (95% CI). Mixed effects represent a combination of the direct and indirect evidence for each treatment derived from the network. Bolded values indicate a statistically significant difference between the respective treatments. CS, corticosteroid; HA, hyaluronic acid; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma.

[b]Values ≥0.5 indicate a statistically significant difference between treatments that also represents a potential clinically important difference.

[c]Values ≥1.0 indicate a statistically significant difference between treatments that is clinically meaningful.

10 studies: minor loss to follow-up was reported (between 6% and 20%) without explanation.[§]

DISCUSSION

The main findings of this network meta-analysis were that at a minimum 6-month patient follow-up after IA injection, (1) PRP significantly improved pain and functional status compared with HA, CS, and placebo for patients with symptomatic knee OA; (2) PRGF provided superior improvements in pain and function compared with placebo; and (3) CS showed no statistically significant improvement in measured outcomes compared with placebo.

When compared with HA, CS, and placebo, PRP showed significant improvements in patient-reported pain and function. In recent years, PRP injections have demonstrated significant promise in the treatment of various orthopaedic diseases, including OA, rotator cuff tears, and tendinopathies.[12,16,21,22,36,62,63] Our results indicate that PRP had a statistically greater effect in reducing pain and improving function compared with HA. Furthermore, when compared with CS and placebo, PRP led to statistically significant improvements in pain and function.

[§]References 2, 3, 9, 20, 30, 38, 44, 46, 47, 53.

TABLE 4
Final Cumulative Rank of All Treatments and Outcomes[a]

Treatment Rank	Pain Improvement	Function-Related Improvement	Function and Pain Improvement
1	PRP	PRP	PRP
2	PRGF	PRGF	PRGF
3	HA	HA	HA
4	CS	CS	CS
5	Placebo	Placebo	Placebo

[a]CS, corticosteroid; HA, hyaluronic acid; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma.

Multiple studies comparing PRP, HA, CS, and placebo have reported similar outcomes.[8,13,27,37] A recent meta-analysis reported PRP to result in significant improvements in pain and function when compared with HA at an average follow-up of 11.1 months.[8] Another meta-analysis of 14 RCTs reported significant reduction of pain and improvement of functional outcomes from 3 to 12 months when comparing PRP with CS, HA, and placebo.[54] The authors also found the greatest improvement in mean difference based on pain reduction in favor of PRP at 6 months (mean difference, −3.82; 95% CI, −6.40 to −1.25; $P = .004$). In contrast, Jevsevar et al[32] reported no statistically significant difference between pain and function when comparing PRP and placebo at a mean follow-up of 42 days. As such, it is possible that to experience the true benefits of PRP, longer patient follow-up is required; however, this requires further investigation.

Substantial variations in PRP formulations exist, primarily in regard to platelet concentration, white blood cell concentration, and growth factor quantity.[7,51] Outcomes based on PRP leukocyte concentration have previously shown that leukocyte-poor PRP formulations result in significantly improved outcomes compared with leukocyte-rich PRP for the treatment of knee OA,[48] whereas platelet concentrations <5 times baseline have similarly been shown to correlate with improved results.[43] However, there remains a wide degree of variability between PRP preparation systems; in a systematic review, Chahla et al[11] reported that only 11.5% of studies reported on the variables necessary to reliably repeat the protocol. As such, further investigations minimizing PRP formulation heterogeneity by standardizing PRP preparation and classification are warranted to better understand the true efficacy of PRP on clinical outcomes.

In the current study, PRGF was found to result in statistically greater improvement in pain and function when compared with placebo for knee OA. With respect to reduction of pain, the difference had the potential to be clinically significant; in terms of improvement of function, a clinically meaningful difference was observed. In addition, PRGF demonstrated the second (after PRP) largest mean differences in clinically significant pain and function-related improvements in comparison with placebo. However, no significant differences in outcomes were seen when PRGF was compared with HA and CS. Believed to promote growth factor proliferation without furthering cytokine

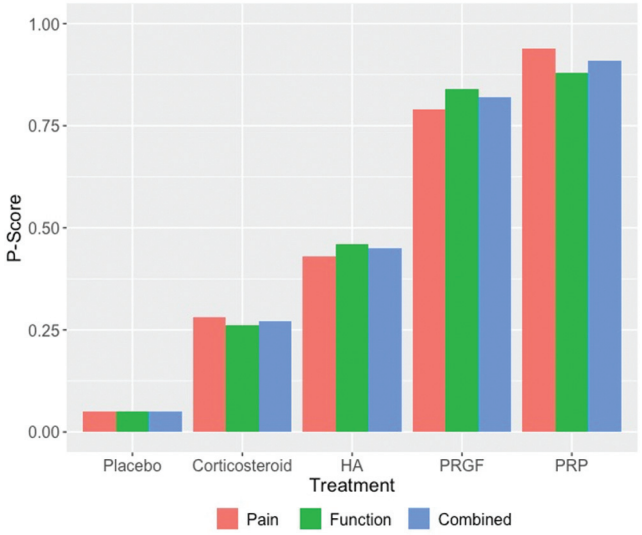

Figure 4. Bar plot demonstrating the rankings based on *P* value for the most effective treatments. The ''combined'' *P* value reflects the treatment rankings based on the efficacy of improvement in pain and function. A higher *P* value indicates a more efficacious treatment. HA, hyaluronic acid; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma.

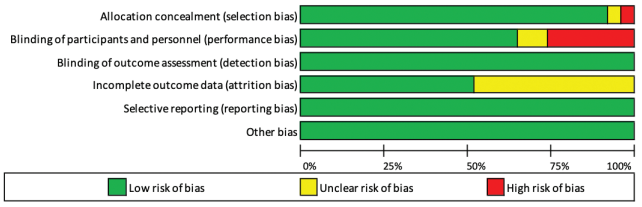

Figure 5. Risk-of-bias graph. Risk of bias is presented as a percentage across all included randomized controlled trials.

damage, PRGF has been used extensively in ulcer treatment and tissue engineering.[5] Currently, 4 different types of autologous PRGF have been reported: (1) the supernatant, which can be used as eye drops and for cell culture media; (2) a liquid version used during surgery as well as dental procedures to bioactivate implants; (3) the scaffold-like PRGF, which may assist in tissue regeneration; and (4) fibrin that stimulates epithelization of soft tissues.[5] As such, the role of PRGF for the treatment of OA remains relatively new, with the absence of leukocytes potentially minimizing any further proinflammatory reactions, improving injection efficacy.[5] The findings from the present study demonstrate the potential for PRGF to be included in the nonsurgical treatment regimen for knee OA; however, further investigations examining the long-term efficacy and outcomes of PRGF are warranted.

We found that IA CS provided no statistically significant improvements in pain and function when compared with placebo. This finding is in contrast to the results

reported in the network meta-analysis by Jevsevar et al,[32] in which IA CS was reported to possess the greatest efficacy in reducing pain when compared with IA PRP, HA, and placebo. The difference in study results may be due to the longer patient follow-up time evaluated in the RCTs included in our network meta-analysis. Previous studies have validated the shorter duration of symptomatic relief using IA CS for knee OA.[6,25,26] A meta-analysis of 312 patients found IA CS to have no significant difference in pain reduction when compared with placebo after 6 weeks.[25] Although the use of IA CS remains common for the treatment of symptomatic knee OA, its long-term efficacy remains questionable.

In our probability rankings for reducing pain and improving function, PRP was found to demonstrate the greatest efficacy. Previous studies have established the relative absence of adverse effects after PRP injections.[17,34,54] PRGF was ranked second in terms of improving pain and function. HA was third in our probability rankings, and unlike the previous network meta-analysis by Jevsevar et al,[32] we found HA to possess a statistically significant difference in decreasing pain and improving function when compared with placebo. IA CS was fourth in our probability rankings. This may be due to its shorter duration of action, consistent with findings by Godwin and Dawes,[25] who reported on its lack of efficacy when compared with placebo at 6 weeks of follow-up. Additionally, as described by Wernecke et al,[65] IA CS may have a time-dependent deleterious effect on articular cartilage, resulting in decreased efficacy when compared with other intra-articular treatment options for knee OA.

This investigation was not without limitations. Due to the lack of RCTs examining nonsteroidal anti-inflammatory drugs and acetaminophen with minimum 6-month follow-up, oral medications were not included in our network meta-analysis. Furthermore, although physical therapy and exercise are commonly prescribed for the treatment of knee OA, outcomes related to these treatments were not included in our analysis due to the lack of data on specific protocols, precluding any meaningful analysis between studies. This limitation is similar to the contemporary meta-analysis by Jevsevar et al[32] evaluating nonsurgical management of knee OA, in which exercise, physical therapy, and lifestyle changes were not examined. Because PRP and PRGF are rarely reimbursed by insurance and require out-of-pocket payment, there exists a potential bias whereby patients receiving PRP or PRGF may report increased improvement or satisfaction due to the financial investment in their treatment. Leukocyte concentration was infrequently reported in studies evaluating PRP outcomes, preventing any analysis comparing differences in outcomes using leukocyte-rich versus leukocyte-poor PRP formulations. Substantial heterogeneity was observed in the reported outcomes between injection types, limiting the number of variables that could be analyzed. However, similar to the network meta-analysis performed by Jevsevar et al, who also reported a high degree of heterogeneity between studies, we performed direct comparisons between treatment types whenever possible to minimize heterogeneity. Last, due to the strict inclusion and exclusion criteria, a small number of studies was included in the final analysis, which can be attributed to the limited number of studies available assessing IA injections with >6 months of follow-up. This emphasizes the need for further studies that evaluate outcomes with minimum 2-year follow-up.

Our study has strengths as well. Our network meta-analysis included the highest quality available RCTs with a minimum 6-month patient follow-up time, and we evaluated treatment modalities with a minimum of 3 studies per treatment comparison.

CONCLUSION

PRP yielded improved outcomes when compared with PRGF, HA, CS, and placebo for the treatment of symptomatic knee OA at a minimum 6-month follow-up. Further investigations evaluating different IA and other nonoperative treatment options for patients with knee OA are warranted to better understand the true clinical efficacy and long-term outcomes of nonsurgical OA management.

REFERENCES

1. Ahmad HS, Farrag SE, Okasha AE, et al. Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma treatment for knee osteoarthritis. *Int J Rheum Dis*. 2018;21(5):960-966.
2. Altman RD, Akermark C, Beaulieu AD, Schnitzer T; Durolane International Study Group. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. *Osteoarthritis Cartilage*. 2004;12(8):642-649.
3. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). *Semin Arthritis Rheum*. 2009;39(1):1-9.
4. Angst F, Aeschlimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. *J Rheumatol*. 2002;29(1):131-138.
5. Anitua E, Sánchez M, Orive G, Andía I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. *Biomaterials*. 2007;28(31):4551-4560.
6. Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. *World J Orthop*. 2014;5(3):351-361.
7. Beitzel K, Allen D, Apostolakos J, et al. US definitions, current use, and FDA stance on use of platelet-rich plasma in sports medicine. *J Knee Surg*. 2015;28(1):29-34.
8. Belk JW, Kraeutler MJ, Houck DA, Goodrich JA, Dragoo JL, McCarty EC. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Am J Sports Med*. 2021;49(1):249-260.
9. Bisicchia S, Bernardi G, Tudisco C. HYADD 4 versus methylprednisolone acetate in symptomatic knee osteoarthritis: a single-centre single blind prospective randomised controlled clinical study with 1-year follow-up. *Clin Exp Rheumatol*. 2016;34(5):857-863.
10. Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. *Clin Orthop Relat Res*. 2001;385:130-143.
11. Chahla J, Cinque ME, Piuzzi NS, et al. A call for standardization in platelet-rich plasma preparation protocols and composition reporting: a systematic review of the clinical orthopaedic literature. *J Bone Joint Surg Am*. 2017;99(20):1769-1779.

12. Chahal J, Van Thiel GS, Mall N, et al. The role of platelet-rich plasma in arthroscopic rotator cuff repair: a systematic review with quantitative synthesis. *Arthroscopy*. 2012;28(11):1718-1727.
13. Chen P, Huang L, Ma Y, et al. Intra-articular platelet-rich plasma injection for knee osteoarthritis: a summary of meta-analyses. *J Orthop Surg Res*. 2019;14(1):385.
14. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis*. 2010;69(1):113-119.
15. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic acid versus platelet-rich plasma: a prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis. *Am J Sports Med*. 2017;45(2):339-346.
16. Cook CS, Smith PA. Clinical update: why PRP should be your first choice for injection therapy in treating osteoarthritis of the knee. *Curr Rev Musculoskelet Med*. 2018;11(4):583-592.
17. Dai W-L, Zhou A-G, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. *Arthroscopy*. 2017;33(3):659-670.e1.
18. DeRogatis M, Anis HK, Sodhi N, et al. Non-operative treatment options for knee osteoarthritis. *Ann Transl Med*. 2019;7(suppl 7):S245.
19. Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med*. 2000;132(3):173-181.
20. Di Martino A, Di Matteo B, Papio T, et al. Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: results at 5 years of a double-blind, randomized controlled trial. *Am J Sports Med*. 2019;47(2):347-354.
21. Di Sante L, Villani C, Santilli V, et al. Intra-articular hyaluronic acid vs platelet-rich plasma in the treatment of hip osteoarthritis. *Med Ultrason*. 2016;18(4):463-468.
22. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. *Am J Sports Med*. 2015;43(7):1575-1582.
23. Foley A, Halbert J, Hewitt T, Crotty M. Does hydrotherapy improve strength and physical function in patients with osteoarthritis—a randomised controlled trial comparing a gym based and a hydrotherapy based strengthening programme. *Ann Rheum Dis*. 2003;62(12):1162-1167.
24. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med*. 2009;37(11):2259-2272.
25. Godwin M, Dawes M. Intra-articular steroid injections for painful knees: systematic review with meta-analysis. *Can Fam Physician*. 2004;50:241-248.
26. Gossec L, Dougados M. Intra-articular treatments in osteoarthritis: from the symptomatic to the structure modifying. *Ann Rheum Dis*. 2004;63(5):478-482.
27. Han Y, Huang H, Pan J, et al. Meta-analysis comparing platelet-rich plasma vs hyaluronic acid injection in patients with knee osteoarthritis. *Pain Med*. 2019;20(7):1418-1429.
28. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. Cochrane Collaboration; 2011.
29. Housman L, Arden N, Schnitzer TJ, et al. Intra-articular hylastan versus steroid for knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(7):1684-1692.
30. Huang T-L, Chang C-C, Lee C-H, Chen S-C, Lai C-H, Tsai C-L. Intra-articular injections of sodium hyaluronate (Hyalgan®) in osteoarthritis of the knee. a randomized, controlled, double-blind, multicenter trial in the Asian population. *BMC Musculoskelet Disord*. 2011;12:221.
31. Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. *J Am Acad Orthop Surg*. 2013;21(9):571-576.
32. Jevsevar DS, Shores PB, Mullen K, Schulte DM, Brown GA, Cummins DS. Mixed treatment comparisons for nonsurgical treatment of knee osteoarthritis: a network meta-analysis. *J Am Acad Orthop Surg*. 2018;26(9):325-336.
33. Johnston BC, Thorlund K, Schünemann HJ, et al. Improving the interpretation of quality of life evidence in meta-analyses: the application of minimal important difference units. *Health Qual Life Outcomes*. 2010;8:116.
34. Kanchanatawan W, Arirachakaran A, Chaijenkij K, et al. Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(5):1665-1677.
35. Lana JFSD, Weglein A, Sampson SE, et al. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *J Stem Cells Regen Med*. 2016;12(2):69-78.
36. Le ADK, Enweze L, DeBaun MR, Dragoo JL. Current clinical recommendations for use of platelet-rich plasma. *Curr Rev Musculoskelet Med*. 2018;11(4):624-634.
37. Leighton R, Akermark C, Therrien R, et al. NASHA hyaluronic acid vs. methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. *Osteoarthritis Cartilage*. 2014;22(1):17-25.
38. Leopold SS, Redd BB, Warme WJ, Wehrle PA, Pettis PD, Shott S. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee: a prospective, randomized trial. *J Bone Joint Surg Am*. 2003;85(7):1197-1203.
39. Lisi C, Perotti C, Scudeller L, et al. Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid: a randomized controlled trial. *Clin Rehabil*. 2018;32(3):330-339.
40. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. *Br Med Bull*. 2013;105:185-199.
41. Losina E, Paltiel AD, Weinstein AM, et al. Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. *Arthritis Care Res (Hoboken)*. 2015;67(2):203-215.
42. Migliore A, Granata M. Intra-articular use of hyaluronic acid in the treatment of osteoarthritis. *Clin Interv Aging*. 2008;3(2):365-369.
43. Milants C, Bruyère O, Kaux JF. Responders to platelet-rich plasma in osteoarthritis: a technical analysis. *Biomed Res Int*. 2017;2017:7538604.
44. Pham T, Le Henanff A, Ravaud P, Dieppe P, Paolozzi L, Dougados M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. *Ann Rheum Dis*. 2004;63(12):1611-1617.
45. Raeissadat SA, Rayegani SM, Ahangar AG, Abadi PH, Mojgani P, Ahangar OG. Efficacy of intra-articular injection of a newly developed plasma rich in growth factor (PRGF) versus hyaluronic acid on pain and function of patients with knee osteoarthritis: a single-blinded randomized clinical trial. *Clin Med Insights Arthritis Musculoskelet Disord*. 2017;10:1179544117733452.
46. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Knee osteoarthritis injection choices: platelet-rich plasma (PRP) versus hyaluronic acid (a one-year randomized clinical trial). *Clin Med Insights Arthritis Musculoskelet Disord*. 2015;8:1-8.
47. Raynauld J-P, Torrance GW, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (part 1 of 2): clinical results. *Osteoarthritis Cartilage*. 2002;10(7):506-517.
48. Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. *Am J Sports Med*. 2016;44(3):792-800.
49. Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods*. 2012;3(4):312-324.
50. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015;15:58.
51. Russell RP, Apostolakos J, Hirose T, Cote MP, Mazzocca AD. Variability of platelet-rich plasma preparations. *Sports Med Arthrosc Rev*. 2013;21(4):186-190.

52. Rutjes AWS, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(3):180-191.
53. Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy*. 2012;28(8):1070-1078.
54. Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. *J Orthop Surg Res*. 2017;12(1):16.
55. Silva LE, Valim V, Pessanha APC, et al. Hydrotherapy versus conventional land-based exercise for the management of patients with osteoarthritis of the knee: a randomized clinical trial. *Phys Ther*. 2008;88(1):12-21.
56. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil*. 2012;91(5):411-417.
57. Tammachote N, Kanitnate S, Yakumpor T, Panichkul P. Intra-articular, single-shot hylan G-F 20 hyaluronic acid injection compared with corticosteroid in knee osteoarthritis: a double-blind, randomized controlled trial. *J Bone Joint Surg Am*. 2016;98(11):885-892.
58. Thorlund K, Walter SD, Johnston BC, Furukawa TA, Guyatt GH. Pooling health-related quality of life outcomes in meta-analysis—a tutorial and review of methods for enhancing interpretability. *Res Synth Methods*. 2011;2(3):188-203.
59. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis*. 2005;64(1):29-33.
60. Vaishya R, Pariyo GB, Agarwal AK, Vijay V. Non-operative management of osteoarthritis of the knee joint. *J Clin Orthop Trauma*. 2016;7(3):170-176.
61. Van der Weegen W, Wullems JA, Bos E, Noten H, van Drumpt RAM. No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: a randomized, controlled, double-blind trial. *J Arthroplasty*. 2015;30(5):754-757.
62. Vander Doelen T, Jelley W. Non-surgical treatment of patellar tendinopathy: a systematic review of randomized controlled trials. *J Sci Med Sport*. 2020;23(2):118-124.
63. Vannabouathong C, Del Fabbro G, Sales B, et al. Intra-articular injections in the treatment of symptoms from ankle arthritis: a systematic review. *Foot Ankle Int*. 2018;39(10):1141-1150.
64. Varacallo M, Luo TD, Johanson NA. Total knee arthroplasty (TKA) techniques. StatPearls Publishing; 2020. Accessed October 19, 2020. http://www.ncbi.nlm.nih.gov/books/NBK499896/
65. Wernecke C, Braun HJ, Dragoo JL. The effect of intra-articular corticosteroids on articular cartilage: a systematic review. *Orthop J Sports Med*. 2015;3(5):2325967115581163.
66. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods*. 2012;3(2):111-125.