Treating Knee Osteoarthritis With Platelet-Rich Plasma and Hyaluronic Acid Combination Therapy

CME

A Systematic Review

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Background: Platelet-rich plasma (PRP) and hyaluronic acid (HA) are injectable treatments for knee osteoarthritis. The focus of previous studies has compared their efficacy against each other as monotherapy. However, a new trend of combining these 2 injections has emerged in an attempt to have a synergistic effect.

Purpose: To systematically review the clinical literature examining the combined use of PRP + HA.

Design: Systematic review.

Methods: A systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using PubMed and Embase. The following search terms were used: knee osteoarthritis AND platelet rich plasma AND hyaluronic acid. The review was performed by 2 independent reviewers who applied the inclusion/exclusion criteria and independently extracted data, including methodologic scoring, PRP preparation technique, HA composition, and patient-reported outcomes (PROs).

Results: A total of 431 articles were screened, 12 reviewed in full, and 8 included in the final analysis: 2 case series, 3 comparative, and 3 randomized studies. Average follow-up was 9 months. The modified Coleman Methodology Score was 38.13 ± 13.1 (mean ± SD). Combination therapy resulted in improved PROs in all studies. Of the comparative and randomized studies, 2 demonstrated that combination therapy was superior to HA alone. However, when PRP alone was used as the control arm (4 studies), combination therapy was not superior to PRP alone.

Conclusion: Combination therapy with PRP + HA improves PROs and is superior to HA alone but is not superior to PRP alone.

Keywords: knee; articular cartilage; platelet-rich plasma

Knee osteoarthritis (OA) is a leading cause of pain and disability worldwide.[21,25] Standard-of-care treatments include therapeutic exercise, weight management, dietary supplements (eg, glucosamine), nonsteroidal anti-inflammatory drugs, and injections such as corticosteroid and hyaluronic acid (HA) / viscosupplement.[30,34,38]

Platelet-rich plasma (PRP) is another injection option, with growing data supporting its use for OA.[9,13,15,18,27,29,32,35] It is an injectable solution of platelets derived from autologous whole blood and concentrated over baseline.[26] Although the therapeutic mechanism of action is not completely understood, PRP contains many anti-inflammatory and anabolic proteins that have in vitro evidence of chondroprotection, chondrogenesis, and the ability to decrease chondrocyte apoptosis.[27,28] Clinically, several randomized studies and meta-analyses demonstrated that PRP was safe and effective in treating OA and, in some studies, had better outcomes when compared directly with HA.[8,13,18,29,32,35,39,40]

An emerging concept in the treatment of OA is to combine PRP and HA in an attempt to achieve a synergistic therapeutic effect.[4] The rationale underlying this approach is that because the 2 solutions have distinct mechanisms of action, combining them may be more effective than either treatment in isolation.[41] While theoretically plausible, the increased cost of this approach necessitates a clear advantage of combination therapy as compared with monotherapy before its use is recommended widely. Several recent clinical trials have studied combination therapy with PRP + HA for knee OA. The purpose of this systematic review is to synthesize the clinical data for combination therapy.

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TABLE 1
Study Inclusion and Exclusion Criteria

Inclusion criteria
Human clinical injection study (case series, comparative study, or randomized trial)
Knee osteoarthritis
Combination therapy with platelet-rich plasma and hyaluronic acid
Documentation of patient-reported outcome measure
Written in English
Indexed in Medline or Embase
Exclusion criteria
Basic science or animal study
Poster or abstract only
Case reports
Review articles
Noninjection study (surgical intervention)

We hypothesize that the combined use of PRP + HA (1) will result in improved patient-reported outcomes (PROs) and (2) will be superior to HA alone but not superior to PRP alone.

METHODS

Using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for standardized reporting, a search of Medline/PubMed and Embase was conducted up to March 19, 2020, using the following Medical Subject Headings terms: (osteoarthritis OR arthritis OR gonarthrosis) AND (platelet rich plasma OR plasma rich in growth factors OR autologous conditioned plasma OR PRP) AND (hyaluronic acid OR sodium hyaluronate OR viscosupplement). The resulting studies were screened for title and abstract by 2 independent reviewers (M.R.B., W.K.V.) according to previously determined inclusion and exclusion criteria (Table 1). The full texts of the resulting studies were reviewed by the same 2 individuals, again applying the inclusion/exclusion criteria. The resulting full texts were reviewed independently for methodology grading (using the modified Coleman Methodology Score) and extraction of details, including PRP preparation method, HA volume and composition, injection and dosing strategy, and PROs. If there was disagreement between reviewers during this process, they met to reach a consensus. If no consensus was reached, a third reviewer was used as the tiebreaker (R.A.M.). In an attempt to perform a quantitative analysis of the data, all corresponding authors were contacted, and raw data were requested when not available in the article.

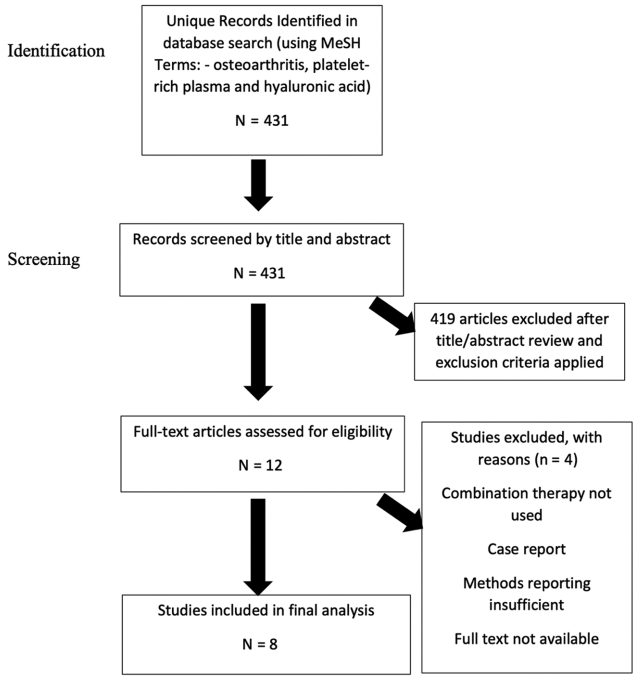

Figure 1. Study screening process. We initially conducted a MeSH (Medical Subject Headings) search on PubMed/Medline and Embase, which identified 431 studies. After application of the inclusion/exclusion criteria, 8 studies were included in this systematic review.

RESULTS

After the initial search, the titles and abstracts of 431 articles were reviewed. Twelve articles passed the initial screening and were reviewed in full, which resulted in 8 articles that met criteria for inclusion and full data extraction (Figure 1).

Eight studies evaluated the effect of combination therapy on PROs for knee OA, with 6 studies comparing combination versus monotherapy (with either HA or PRP alone).[1,2,6,19,20,23,24,33] There were 2 case series, 3

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TABLE 2
Details for Studies of the Knee Joint[a]

First Author, Year	Methods and Groups	Coleman Score	Age, y, Mean ± SD (Range)	KL Stage	Follow-up, mo
Abate,[1] 2015	Retrospective cohort study: 40 patients received PRP + HA; 40 patients received PRP alone	34	56.7 ± 11.2; 60.9 ± 9	2-3	6
Abbassy,[2] 2019	Retrospective case series: 25 patients received PRP + HA	22	57 ± 11	1-3	6
Barac,[6] 2019	Prospective double-blind RCT: 19 patients received PRP + HA; 19 received HA (Arthrovisc); 19 received HA (Ostenil)	53	61.3 ± 10.9; 61.3 ± 10.9; 66.2 ± 6.8	1-3	12
Guo,[19] 2016	Retrospective study: 63 patients received PRP + HA; 63 received PRP	41	61.2 ± 9.6; 60.7 ± 10.1	0-3	12
Jacob,[20] 2017	Prospective RCT: 17 patients received PRP + LMW HA; 14 received PRP + HMW HA; 20 received PRP alone	39	Not reported	0-3	6
Kurapati,[23] 2018	Prospective case series: 12 patients received PRP + HA	41	52.8 ± 4.9 (KL 1); 49.8 ± 9.8 (KL 2)	1-2	12
Lana,[24] 2016	Prospective double-blind RCT: 33 patients received PRP + HA; 36 received PRP; 36 received HA	56	62 ± 6.1; 60.9 ± 7; 60 ± 6.6	1-3	12
Saturveithan,[33] 2016	Retrospective cohort study: 56 knees received PRP + HA; 47 received HA alone	19	For all, 66 (50-87)	3-4	6

[a]HA, hyaluronic acid; HMW, high molecular weight; KL, Kellgren-Lawrence; LMW, low molecular weight; PRP, platelet-rich plasma; RCT, randomized controlled trial.

nonrandomized comparative studies, and 3 randomized controlled trials (RCTs), 2 of which were double blind. Average follow-up was 9 months. The modified Coleman Methodology Score was 38.13 ± 13.1 (mean ± SD) (Table 2). Study details are presented in Table 3, including PRP preparation, HA composition, PROs, and study conclusion. There was significant heterogeneity in data reporting among studies, and no corresponding authors responded to the request for raw data, which precluded a quantitative analysis of outcomes.

PRP Preparation and HA Combination Details

Of the 8 studies, 4 used an independent laboratory process to concentrate PRP.[20,23,24,33] The other 4 studies used the same commercial device, called Cellular Matrix (CM; RegenLab).[1,2,6,19] This proprietary system utilizes a gel separator tube, which is preloaded with 2 mL of nonavian, non–cross linked low molecular weight (LMW) HA. When whole blood is processed in this system, the PRP is separated using the thixotropic gel and simultaneously combined with the HA during the centrifugation process.

Case Series

Abbassy et al[2] and Kurapati et al[23] treated 37 patients with combination PRP + HA therapy. Abbassy et al used the CM device, while Kurapati et al manually prepared the PRP and provided no details about the HA. Patients in both case series experienced a significant improvement in their PROs. Abassy et al reported a mean change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) of 65.9 ± 13.5 to 24.4 ± 20.2 ($P < .001$) and >50% improvement in the WOMAC scores in 68% of patients. Kurapati et al reported a significant improvement in visual analog scale (VAS): for stage I OA, 3.00 ± 0.49 to 1.57 ± 0.41 ($P = .031$); and for stage II OA, 3.60 ± 0.51 to 2.10 ± 0.29 ($P = .031$). However, these improvements waned between 6 and 12 months. Additionally, all other outcomes—Oxford Knee Score, WOMAC, International Knee Documentation Committee (IKDC) questionnaire, and Knee injury and Osteoarthritis Outcome Score (KOOS)—showed a statistically significant improvement ($P < .05$) at 6 months, which was consistent through 12-month follow-up.

Comparative Studies

Six studies (3 retrospective, 3 prospective) compared combination therapy with another active treatment arm. In the retrospective studies, Abate et al[1] and Guo et al[19] studied combination therapy versus PRP alone and concluded that combination therapy was not superior to PRP alone. Abate et al reported a change in KOOS from 60.7 ± 14.7

TABLE 3
Injectate Preparation and Administration Details[a]

First Author, Year, Study Type	Treatment Arm	Procedural Details	Mean Final Outcomes	Conclusion
Abbassy,[2] 2019, case series	PRP + HA	10-mL whole blood placed in tube preloaded with natural, non–cross linked HA; single spin at 3500 rpm for 5 min using the Cellular Matrix device; yield, PRP (no details provided) + 2-mL HA	WOMAC, 65.9 to 24.2 ($P < .001$)	PRP + HA improves PRO
Kurapati,[23] 2018, case series	PRP + HA	150-mL whole blood processed via double spin (first, 1800 rpm for 15 min; second, 3500 rpm for 10 min). Resultant PRP divided into 5-mL aliquots and frozen. Yield: PRP (platelets, 6×, no other cells reported). At time of injection, 3-mL PRP mixed with 2-mL HA.	Significant improvement in VAS, WOMAC, OKS, KOOS, and IKDC at 6 and 12 mo	PRP + HA results in improved PROs
		No independent description of preparation in Methods section. Performed as a single injection	Absolute values only reported for VAS at 6 mo (3 to 1.57, KL 1; 3.6 to 2.1, KL 2)	
Barac,[6] 2019, comparative with HA as control	PRP + HA	6-mL whole blood placed in tube preloaded with natural, non–cross linked HA; single spin at 3600 rpm for 5 min using the Cellular Matrix device; yield, 3-mL LP-PRP (platelets, 1.5-1.6×) + 2-mL HA	WOMAC, 42.5 to 82.4; IKDC, 28 to 66.2; VAS, 75.8 to 17.2; KOOS, 38.5 to 80.2	PRP + HA is superior to HA alone
	HA (Arthrovisc)	2% non–cross linked HA	53.7 to 59.1, 36.4 to 37.5, 70.2 to 62.4, 49.7 to 51.1	
	HA (Ostenil)	2% non–cross linked HA with mannitol	45.3 to 58.7, 25.3 to 35.8, 68.9 to 61.8, 41 to 46.3	
		All administered as series of 3 injections 2 wk apart	PRP + HA demonstrates significantly greater improvement in all PROs	
Saturveithan,[33] 2016, comparative with HA as control	PRP + HA	30-mL whole blood mixed with unspecified anticoagulant. Processed via double spin (first, 2500 rpm for 5 min; second, 3200 rpm for 10 min). Yield: 2.5-3 mL of PRP (platelet concentration reported, 1.4-1.6 million/μL) with 4 mL of HMW HA.	IKDC, 49.5 to 73.9; VAS, change of –1.9	PRP + HA is superior to HA alone
	HA alone	4-mL of HMW HA	53.3 to 65.4, change of –1	
			Mean difference in IKDC of –12.1 favors PRP + HA	
Abate,[1] 2015, comparative with PRP as control	PRP + HA	4-mL whole blood placed in tube preloaded with natural, non–cross linked LMW (1550 kDa) HA; single spin at 3500 rpm for 5 min; yield, 2-mL LP-PRP (platelets, 1.6-1.8×) + 2-mL HA	VAS-rest, 2.9 to 1.3; VAS ADL, 6.3 to 3.6; KOOS, 60.7 to 67	PRP + HA is not superior to PRP alone
	PRP alone	8-mL whole blood; single spin at 3500 rpm for 5 min; yield, 4- to 5-mL LP-PRP (platelets, 3×)	3.1 to 1.6, 6.3 to 3.8, 53.5 to 65.5	
		Both administered as series of 3 injections 1 wk apart	No significant difference between groups	

(continued)

TABLE 3
(continued)

First Author, Year, Study Type	Treatment Arm	Procedural Details	Mean Final Outcomes	Conclusion
Guo,[19] 2016, comparative with PRP as control	PRP + HA	4-mL whole blood placed in tube preloaded with natural non–cross linked, LMW (1550 kDa) HA; single spin at 3500 rpm for 5 min; yield, 2-mL LP-PRP (platelets, 1.6-1.8 ×) + 2-mL HA	WOMAC, 39.9 to 14.6; VAS, 7.2 to 1.3	PRP + HA is not superior to PRP alone
	PRP alone	8-mL whole blood; single spin at 3500 rpm for 5 min; yield, 4-5-mL LP-PRP (platelets, 3 ×)	41.1 to 15.7, 6.9 to 1.6	
		Both administered as series of 3 injections 1 wk apart. No independent description of preparation in Methods section; see Abate et al	No significant difference in either outcome between groups (WOMAC, P = .082; VAS, P = .392)	
Jacob,[20] 2017, comparative with PRP as control	PRP + LMW HA	For all procedures, 20-mL whole blood mixed with 5-mL citrate phosphate dextrose; centrifuged at 3500 rpm for 7 min, buffy coat manually extracted, and then spun again at 3000 rpm for 5 min	IKDC, 34.1 to 44.3; VAS, 7.65 to 5.71	PRP + HA is not superior to PRP alone
	PRP + HMW HA	No details provided on HA composition or how it was combined with PRP	38.7 to 47.3, 7.14 to 5.57	
	PRP alone	Performed as a single injection	34.7 to 43.4, 7.8 to 5.95	
			No significant difference among groups for any PRO	
Lana,[24] 2016, comparative with PRP as control	PRP + HA	60-mL whole blood mixed with 8.5-mL ACD and was processed via double spin (first, 300g for 5 min, plasma and buffy coat extracted, then second spin at 700g for 17 min). Yield: 5 mL of LR-PRP (platelets, 5-8 ×). 2 mL of HMW, nonavian, non–cross-linked HA (Euflexxa) injected immediately before PRP (but not mixed with PRP outside the body).	VAS, –5; WOMAC PA, –825	PRP + HA is not superior to PRP alone
	PRP alone	Identical preparation as above	–5, –775	
	HA	2 mL of HMW, nonavian, non–cross linked HA (Euflexxa)	–2, –450	
		All administered as series of 3 injections 2 wk apart	Median changes. PRP + HA and PRP alone both superior to HA alone at 12 mo. No difference in outcomes between PRP + HA and PRP alone	

[a]For PRP, preparation description is presented as follows: whole blood volume used, centrifugation technique, commercial kit if used, resultant PRP volume and composition (LR vs LP), and the number and timing of the injections. For HA, details include molecular weight, cross-linking, and brand name if available. ACD, acid citrate dextrose; ADL, activities of daily living; HA, hyaluronic acid; HMW, high molecular weight; IKDC, International Knee Documentation Committee; KL, Kellgren-Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; LMW, low molecular weight; LP, leukocyte poor; LR, leukocyte rich; OKS, Oxford Knee Score; PRO, patient-reported outcome; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

to 67 ± 12.7 with combination therapy versus 53.5 ± 16.3 to 65.5 ± 14.6 with PRP alone and a change in VAS for activities of daily living from 6.3 ± 2.0 to 3.6 ± 1.5 with combination therapy versus 6.3 ± 2.6 to 3.8 ± 2.4 with PRP alone. There were no significant differences between groups. Guo et al demonstrated that WOMAC improved from 39.9 ± 13.50 to 14.6 ± 6.9 with combination therapy versus 41.1 ± 12.7 to 15.7 ± 8.5 with PRP alone. Additionally, VAS decreased from 7.2 ± 3.2 to 1.3 ± 1.1 with combination therapy versus 6.9 ± 3.8 to 1.6 ± 1.9 with PRP alone. The differences between groups were not significant (WOMAC, $P = .082$; VAS, $P = .392$). Saturveithan et al[33] compared combination therapy with HA alone and found superior IKDC scores in the combination therapy group: an improvement of 24.3 ± 13.7 with combination therapy vs 12.1 ± 8.2 with HA alone.

There were 3 prospective RCTs. Jacob et al[20] studied combination therapy using 2 combinations—PRP + high molecular weight (HMW) HA and PRP + LMW HA—versus PRP alone. At final follow-up, there was no significant difference among groups for any PRO. IKDC mean differences were 8.66 for PRP alone, 10.15 for PRP + LMW HA, and 8.64 for PRP + HMW HA, with no significant difference. Mean differences for VAS at final follow-up were 1.85 for PRP, 1.94 for PRP + LMW HA, and 1.57 for PRP + HMW HA without any significant difference.

Lana et al[24] performed a 3-arm trial comparing combination therapy versus PRP alone versus HA alone. At final follow-up, HA alone had the worst PROs, and there was no difference between combination therapy and PRP alone. Combination therapy and PRP alone outperformed HA alone in median VAS change (–5, –5, –2, respectively) and the WOMAC physical activity scale (–825, –775, –450). However, when combination therapy was compared with PRP alone, there was no difference between groups in any outcome measure at 1 year (VAS, $P = .6783$; WOMAC pain, $P = .3057$; WOMAC stiffness, $P = .7537$; WOMAC physical activity, $P = .1982$).

Barac et al[6] performed a double-blind comparison of combination therapy versus 2 HA formulations and found superior PROs in the combination therapy group. The WOMAC score improved by 39.9 points with combination therapy versus 5.4 and 13.4 in the HA groups. Additionally, KOOS improved by 41.7 with combination therapy versus 1.4 and 5.3 in the HA groups. These differences were statistically significant ($P < .01$).

DISCUSSION

The most significant finding of this systematic review is that combination therapy with PRP + HA is not superior to PRP alone. That is, the addition of HA to PRP injections did not provide additional benefit when compared with PRP monotherapy. This review included 6 comparative studies: 2 used HA alone as the control, and 4 compared combination therapy with PRP alone. In the 2 HA-controlled studies, each found that combination therapy was superior to HA alone.[6,33] However, when PRP alone was the control arm, the addition of HA to PRP did not result in improved PROs.[1,19,20,24] There are currently no compelling data to suggest that combination therapy is more beneficial than PRP alone for knee OA.

The reason why combination therapy consistently outperformed HA alone but not PRP alone may be explained by previous studies directly comparing PRP versus HA. Several recent meta-analyses demonstrated that when compared head-to-head for knee OA, PRP consistently yields better clinical results than HA.[8,10,12,14,39] Therefore, for studies showing that PRP + HA is better than HA alone, it is possible that they are demonstrating just the superior effect of PRP over HA rather than a synergistic effect. This is supported by the fact that the studies in this review that controlled for PRP by using it as monotherapy failed to demonstrate that the addition of HA provided consistent benefit. The work of Lana et al[24] provides the best study design to test this hypothesis. The authors compared PRP monotherapy versus HA monotherapy versus combination therapy and concluded that HA had the worst outcomes, although there was no difference between PRP monotherapy and the combination injection.

While this systematic review did not find any compelling reason to combine PRP + HA, it should be noted that Zhao et al[42] recently published a systematic review and meta-analysis that favored combination therapy over PRP alone. These conflicting conclusions can be explained by differences in methodology, including inclusion/exclusion criteria. While they analyzed 7 studies (vs 8 in the present work), we held only 2 studies in common.[1,19] They did not include the prospective RCTs by Lana et al[24] or Jacob et al,[20] both of which demonstrated that combination therapy is not superior to PRP alone. Likewise, we did not include the works of Yu et al,[41] Zhao,[43] Ding et al,[16] and Ke et al[22] because they were not available in English, which was part of our predetermined exclusion criteria. Although we did not include these studies, we reviewed the work of Yu et al because it had the largest sample size. While potentially helpful, there are significant limitations of that work. For example, they describe a complex PRP + HA dose titration schedule with 6 options for PRP and 5 for HA; they also state that "most" were enrolled with a specific dose, but they do not provide the exact sample size of each dosing regimen. While this approach may have value in moving toward precise dosing, definitive conclusions about combination therapy cannot be made given the significant number of variables introduced by this dosing scheme. Including such studies in a systematic review has potential to introduce imprecise outcome data.

The basic science rationale of combining PRP + HA is compelling. The 2 solutions have distinct and complementary effects on the OA environment. The goal of combination therapy is to leverage these unique effects and maximize the number of therapeutic targets treated. For example, while PRP is purely biologic in its mechanisms, HA has mechanical and biologic effects that may add to the benefit of PRP. In OA, synovial fluid loses its viscoelasticity,

thereby exposing cartilage and bone to more mechanical stress.[11] Treatment with normalized HA therefore aims to restore the viscoelastic properties of synovial fluid—hence, the term *viscosupplementation*.[3,4] PRP and HA are both anti-inflammatory, but this occurs through unique pathways. For example, both solutions reduced tumor necrosis factor expression, but only HA reduces interleukin 6.[37] Since the pathophysiology of OA is complex, the goal of combination therapy is to treat as many degradative pathways as possible. In addition to treating a broader range of targets, in vitro models have shown synergistic effects. A human fibroblast model showed a 335% increase in fibroblast motility when combination therapy was compared with monotherapy.[5] Another study demonstrated that the addition of HA to PRP prolonged the half-life of anabolic proteins such as bone morphogenetic protein 2 by protecting them from proteolytic degradation.[36] Based on maximizing the number of therapeutic targets treated and the potential for additive effect, the notion of using combination therapy is scientifically sound. However, these basic science mechanisms do not seem to be realized in clinical benefit according to the studies presented in this review—perhaps because in vitro models are an incomplete picture of the in vivo response and the human joint is complex and not easily reproduced in the laboratory setting.

For future clinical and research efforts, several practical considerations should be considered. A major difficulty in synthesizing PRP clinical research is the heterogeneity of PRP preparation, content, and application strategies.[17] The use of differing preparation methods and commercial kits make it difficult to reach firm conclusions, and results of a single study can be extended to clinical practice only if the same preparation method is being employed. The advent of combination PRP + HA therapy introduces another realm of profound heterogeneity. The HA products vary in their molecular weight, cross-linking, source, volume, and how they are mixed with the PRP—all of which may influence clinical outcomes. The CM device is the only proprietary device currently available that creates the PRP + HA combination in a single step, which may be beneficial in future research studies because of the preparation uniformity. Of the 4 studies that used this device, 2 compared it with PRP alone and failed to demonstrate any difference.[1,19] Jacob et al[20] had the only study to include 2 combination therapy arms with different HA formulations (HMW vs LMW). There was no difference between the treatment groups, but this study was underpowered to detect a difference. This highlights the need to consider that HA composition differences may influence clinical outcomes in the same way as they do for PRP.

Using combination therapy in the United States comes with increased logistical complexity. First, the CM device is not currently approved for use in the United States, so physicians have to use separate PRP and HA preparations. From a technique perspective, regulation surrounding the practice of combining these biologic therapies before administration (ie, outside of the body) is debatable.[7,31] Therefore, it may be most prudent to administer the injections using separate syringes, as performed by Lana et al.[24] Billing also adds a layer of complexity. Most insurers provide coverage for HA. However, despite data demonstrating the safety and efficacy of PRP for knee OA, most insurers still consider it experimental; as such, it is an out-of-pocket expense. Because of these coverage differences, clinics must decide whether to designate the entire procedure (including HA) as cash pay or to issue separate charges (1 cash, 1 third-party payer) for the 2 injections.

This systematic review has several limitations. First, the heterogeneity of PRO data reporting precluded a formal meta-analysis. For example, some studies presented raw data, while others reported median changes or mean differences in the PROs. Ideally, these would be reported consistently using a standard reference, such as the minimal clinically important difference for each outcome measure, which would allow for a statistical synthesis of the data. In an attempt to do this, we contacted each corresponding author to obtain raw data but received no responses. A second limitation is that the highest-level prospective RCTs were relatively small. It is possible that combination therapy provides a therapeutic advantage over PRP monotherapy, but the included studies were underpowered to detect a difference. Finally, the studies included in this review have varying degrees of methodologic quality. Each was graded using the modified Coleman Methodology Score, which assigns point values for different elements of study design (sample size, randomization, blinding, description of intervention, follow-up duration, use of accepted outcome measures, etc). The average Coleman score in this review was 38.13 ± 13.1 (range, 19-56). This large range reflects the varying study designs that were included, from retrospective cohort to RCT. Because combination therapy is relatively new with limited original data, this review was intentionally more inclusive to present a more comprehensive overview of the clinical data. Certainly, as additional higher-level studies are performed, a minimum Coleman score could be used as inclusion/exclusion criteria, which would improve the strength of future analyses and recommendations.

CONCLUSION

This systematic review failed to demonstrate a clear benefit of adding HA to PRP as compared with PRP monotherapy. Larger studies may be able to detect a difference, and increasing the sample size should be the focus of future studies. Because of the lack of compelling evidence plus the additional complexity of performing combination therapy, we cannot recommend this practice over PRP monotherapy.

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