Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2024 Mar 15; 12(1):156-164.
https://doi.org/10.3889/oamjms.2024.11860
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Systematic Review Article*

Platelet-rich Plasma Superiority over Hyaluronic Acid as a Conservative Treatment for Early Knee Osteoarthritis: A Systematic Review

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Edited by: Mirko Spiroski
Citation: Ivander G, Riantho A, Anggono Y. Platelet-rich Plasma Superiority over Hyaluronic Acid as a Conservative Treatment for Early Knee Osteoarthritis: A Systematic Review. Open Access Maced J Med Sci. 2024 Mar 15; 12(1):156-164. https://doi.org/10.3889/oamjms.2024.11860
Keywords: Platelet-rich plasma; Hyaluronic acid; Knee osteoarthritis; Conservative treatment
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Received: 10-Jan-2024
Revised: 25-Jan-2024
Accepted: 30-Jan-2024

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

AIM: This study aimed to perform a systematic review (SR) of SR to elucidate prior findings regarding favorable outcomes between platelet-rich plasma (PRP) and hyaluronic acid (HA) injections for early knee osteoarthritis (KOA).

MATERIALS AND METHODS: We conducted a thorough literature search adhering to the Preferred Reporting Items for SR and Meta-analyses only for SRs from PubMed, ScienceDirect, and Google Scholar from 2020 to 2023. The inclusion and exclusion criteria were determined using the population, intervention, comparison, outcome, and study design model. A measurement tool to assess SR-2 was used to grade the included SRs. Two researchers independently searched, extracted, and assessed the risk of bias in the included studies. Cohen's kappa coefficient was used to calculate the inter-observer disparities in study eligibility and risk of bias. The corrected covered area (CCA) metric addressed the overlap issue with the original studies.

RESULTS: One SR yielded high methodological quality whereas three SRs yielded moderate methodological quality. The overall CCA among the four SRs was 30.77%, and all SRs used the Western Ontario and McMaster Universities Osteoarthritis Index score as a patient-reported outcome (PRO) and revealed that the PRP group improved more than the HA group. One SR used the Tegner score as a PRO and found no distinction between the PRP and HA groups. The incidence of substantial pain was lower in the PRP group than in the HA group. One SR reported considerably lower local pain post-injection in the HA groups. Overall, three SRs showed that PRP yielded better outcomes than the HA, and one showed that PRP showed advantages over HA injections for knee pain at 6 and 12 months; however, the clinical outcomes were not different.

CONCLUSION: Our findings supported the superiority of PRP over HA as a long-term alternative therapy for early-stage KOA.

Level of Evidence: Therapeutic Level II.

What is already known

- No consensus regarding conservative treatment for early knee osteoarthritis
- Viscosupplementation such as platelet-rich plasma and hyaluronic acid yields benefits for the treatment of knee osteoarthritis.

What are the new findings

- Intra-articular platelet-rich plasma is superior to hyaluronic acid in long-term therapy for knee osteoarthritis.

Platelet-rich plasma should be considered the main conservative treatment for early knee osteoarthritis.

Introduction

Knee osteoarthritis (KOA) is a prevalent chronic degenerative joint disease characterized by wear and tear involving the progressive deterioration and thinning of cartilage, reduction in joint space, and subchondral sclerosis [1]. It is caused by the complex combination of biomechanical and mechanical insults that exceed the joint's ability to repair itself [2]. KOA is estimated to have a prevalence of 3.3–3.6% globally, resulting in significant disability for around 43 million individuals worldwide, and it ranks as the 11th most prevalent condition that contributes to disability-related diseases [3], [4].

Conservative treatment is preferred over surgery as the primary treatment for early KOA [5], [6]. Conservative treatment options for this condition encompass a variety of approaches, including exercise, weight reduction, physiotherapy, and medication. The pharmacological treatments include non-steroidal anti-inflammatory drugs, opioids, and injectable therapies [5], [6]. The primary injectable therapies used in clinical practice include corticosteroids and viscosupplementation using hyaluronic acid (HA) and platelet-rich plasma (PRP) [5], [7]. The clinical

effectiveness of PRP compared with HA injections has recently garnered considerable interest as a non-surgical therapeutic alternative for KOA [8], [9].

HA, a glycosaminoglycan that occurs naturally in synovial fluid, can potentially modulate the cellular milieu and promote the viscoelastic features of synovial fluid intra-articularly [10], [11]. The benefit of HA injection for KOA has been demonstrated by a prior meta-analysis [12]. PRP is a substance harvested from a patient's own blood (autologous), comprising a diverse range of growth factors, including vascular endothelial growth factor, fibroblast growth factor (FGF), and platelet-derived growth factor [13], [14], [15]. Previous research has demonstrated that PRP can enhance the proliferation of chondrocytes, mitigate inflammatory responses, and thus regulate the microenvironment within the articular cavity [16]. This potential effectiveness in regenerating cartilage has drawn rising attention [17]. Therefore, PRP is considered superior to HA.

Prior systematic reviews (SRs) have analyzed the benefits of PRP versus HA injections in managing KOA. The utilization of SR of SRs has garnered increasing attention as a novel form of evidence synthesis. This methodology facilitates the comparison of data gathered from various interventions or situations, thereby offering decision-makers to make comprehensive overviews of the existing information. This approach has the potential to address the limitations of SRs [18]. Based on the available information, it appears that there is currently a lack of comprehensive SR that integrates the clinical outcome data comparing PRP to HA for KOA. Therefore, the objective of this study was to consolidate and synthesize the findings from previous SRs.

Materials and Methods

Eligibility criteria

This SR involved a comprehensive examination of previously conducted SRs using a pre-determined method and aligned to the fundamentals described in the Preferred Reporting Items for SR and Meta-analyses (PRISMA) statement [19]. This review was not registered on the online SR protocol. This study used the population, intervention, comparison, outcome, and study design models for inclusion selection. The population (P) was patients diagnosed with early KOA who underwent radiographic testing using a standardized scoring method to establish their diagnosis. The intervention (I) was PRP intra-articularly. The control (C) was HA intra-articularly with or without the control group. The outcomes (O) were multiple patient-reported outcomes (PROs) that can measure clinical improvement and adverse effects (AEs). The study design (S) was the SRs that included only randomized controlled trials (RCTs) written in English. Any SRs that did not fit the previously stated requirements were excluded.

Literature search and study selection

Boolean search operators were used with the following keywords: "Knee Osteoarthritis" OR "Knee OA" AND "Hyaluronic Acid" OR "HA" AND "Platelet-rich Plasma" OR "PRP" AND "Systematic Review." The literature was searched using three international databases, including PubMed, Science Direct, and Google Scholar, from year 2020 to 2023.

Two independent reviewers (G.I. and A.R.) performed a literature search. A comprehensive evaluation of the literature was conducted, where titles and/or abstracts were carefully reviewed to ascertain eligibility for inclusion based on the aforementioned criteria. In the case of disparities, Y.A. as the third reviewer made the final decision.

Data extraction and quality assessment

The authors reached a consensus regarding the formulation of the extraction plan. The data were arranged in a tabular format, followed by narrative synthesis. Two independent reviewers (G.I. and A.R.) determined the quality of the literature using the "A Measurement Tool to Assess SR-2" (AMSTAR-2) tool, which prioritizes the detection of significant faults within the important domains rather than placing sole emphasis on an overall score. These identified flaws potentially affect the quality of the literature [20]. The AMSTAR-2 quality evaluation tool comprises a checklist consisting of 16 items or domains. Seven items were considered critical: Protocol registration, adequacy of search strategy, a reason to exclude studies, each individual study's risk of bias, proper meta-analytical methods, risk of bias of review results, and assessing bias that likely impacts publication [20]. The scores were 0 (no), 1 (yes), and 0.5 (partial yes). Quality was considered low when one critical domain was met, moderate when 2–5 domains were met, and high when ≥6 domains were met [20]. The corrected covered area (CCA) metric was computed to address the issue of overlap among the original studies included in each separate SR. The CCA was calculated and analyzed in accordance with the methodologies and recommendations proposed by Pieper *et al*. [21] The CCA metric quantifies the degree of overlap between the original studies included, and the higher score (≥15%) signifies more overlap [21], [22].

Evidence synthesis

All available evidence for each included SR and meta-analyses were summarized, including the pooled risk ratio (RR), pooled mean differences (MD),

pooled weighted MD, standardized MD (SMD), and risk difference (RD).

Statistical analysis

SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used to perform statistical analysis. Cohen's kappa coefficient was used to evaluate inter-observer differences and the bias risk.

Results

Study selection and characteristics

A primary search using the PRISMA method found a total of 896 articles. After removing the duplicate entries, 101 articles were thoroughly examined. A comprehensive search was performed using abstracts and titles, specifically focusing on SR. Subsequently, 12 full-text articles satisfying the eligibility criteria were retrieved. Of the 12 articles that were assessed, four satisfied the predetermined criteria for inclusion and exclusion in this study. [16], [23], [24], [25] (Figure 1). The inter-observer reliability for study selection was excellent (kappa score 0.824, 95% confidence interval [CI]: 0.49–1) [26].

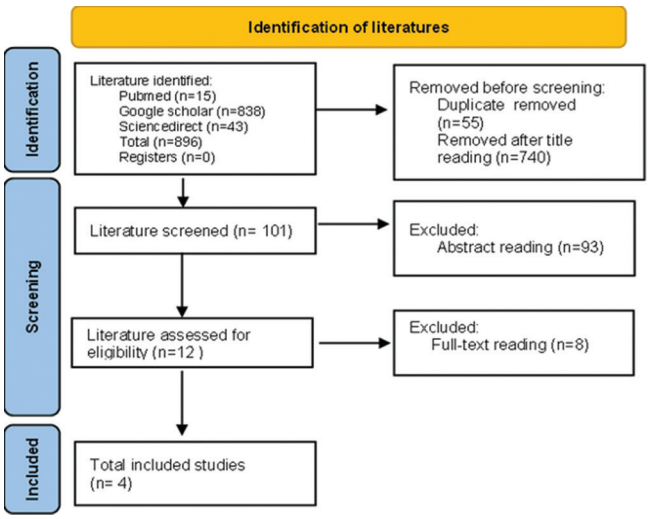

Figure 1: Flow of search strategy

This SR included four SRs that focused on comparing the efficacy of PRP versus HA on multiple PROs measures in patients with KOA [16], [23], [24], [25]. These four SRs consisted of 50 RCTs with a range of 6–18 RCTs and a follow-up period of 3–24 months. These PROs included the visual analog scale for pain (VAS) (n = 3), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score (n = 4), international knee documentation committee score (n = 4), euro quality of life VAS (n = 2), Tegner activity score (n = 1), knee injury and osteoarthritis outcome score (KOOS) (n = 1), and AEs (n = 2). In addition, all of the included SRs also performed a meta-analysis (Table 1).

AMSTAR-2

Qualitative evaluation using AMSTAR-2 revealed the distinct qualities of the included SRs. The outcome showed that one SR was deemed of high quality, and the others were of moderate quality. Among the four SRs, only one SR by Hohmann *et al*. investigated a publication bias [25]. Only Hohmann *et al*. and Belk *et al*. assessed the potential bias of each individual study using a meta-analysis that may impact the results [16], [25]. In addition, all four SRs used a comprehensive literature search strategy but only fulfilled the partial yes criteria (Table 2) [16], [23], [24], [25]. The kappa score for literature appraisal was excellent (kappa score = 0.876, 95% CI: 0.71–1).

CCA

The overall CCA result for all SRs was 30.77%, implying a very high degree of overlap [16], [23], [24], [25]. Among the four SRs, two SRs by Hohman *et al*. and Belk *et al*. had the highest CCA result of 60%, indicating a very high overlap of the included studies [16], [25]. In addition, SRs by Hohman *et al*. and Gong *et al*. had the lowest CCA result of 12.5% yet still indicated high overlap (Table 3) (Appendix 1) [23], [25].

KOA treatment result

The primary therapeutic intervention was to compare intra-articular PRP with HA. All four SRs included WOMAC scores as PROs, and all studies reported that the PRP group showed statistically significant improvement in WOMAC scores compared to the HA group [16], [23], [24], [25] One SR by Gong *et al*. included Tegner score as PROs and reported no statistically significant difference between PRP and HA group (MD = −0.10, 95% CI = −0.23–0.43, p = 0.55) [23]. The SR by Hohmann *et al*. included KOOS as one of the PROs and reported that the PRP group statistically significantly improved in knee pain compared to the HA group at 6 (SMD = 0.380, 95% CI = −2.044–−0.553, p = 0.001) and 12 months (SMD = 0.466, 95% CI = −2.517–−0.69, p = 0.001) [25]. The pain was assessed in three SRs, all involving VAS as PROs, and statistically significant pain reduction was reported in the PRP group compared to the HA group [16], [24], [25]. Two SRs observed AEs where Gong *et al*. reported no statistically significant differences between PRP and HA group (RR = 0.88, 95% CI = 0.60–1.29, p = 0.52); meanwhile, Li *et al*., reported that the HA group had statistically significant lower local pain

Table 1: Characteristics of each study

Author's name and year of publication	Included studies	Method	Population	Inclusion criteria	Exclusion criteria	Intervention	Follow-up (months)	Outcome measure	Results	Conclusion
Hohmann *et al.* (2020)	12 RCTs	Systematic review and meta-analysis	1248 (PRp=63, HA=612)	Level 1 and 2 studies ranging from the year 2010–2019 PRP versus HA in KOA patients, Minimal 6 months follow-up	Level 3 and 4 studies and/or retrospective studies	Intra-articular injections of PRP and HA	6–12 months follow-up	WOMAC IKDC KOOS VAS	PRP>HA for knee pain in VAS, WOMAC, KOOS at 6 months (SMD=0.380, 95%CI = −2.044–−0.553, p=0.001) PRP>HA for knee pain in VAS, WOMAC, KOOS at 12 months (SMD=0.466, 95% CI = −2.517–−0.69, p=0.001) PRP=HA in clinical outcome in VAS, WOMAC, IKDC, and KOOS at 6 months (SMD=0.362, 95%CI = −1.366–0.052, p=0.069) PRP=HA in clinical outcome in VAS, WOMAC, IKDC, and KOOS at 12 months (SMD=0.684, 95%CI = −2.242–0.44, p=0.188)	PRP>HA for knee pain at 6 and 12 months PRP=HA in clinical outcomes at both 6 and 12 months
Belk *et al.* (2021)	18 RCTs	Systematic review and meta-analysis	1608 (PRP=81, HA=797)	P: diagnosed KOA with grade radiographically I: PRP C: HA O: Efficacy and AEs Study design: Level 1 trials in English	Level 2–5 studies that did not satisfy the inclusion list	Intra-articular injections of PRP and HA	3–24 months follow-up	VAS WOMAC Subjective IKDC	PRP=HA in VAS at>12 months (MD = −9.8, 95% CI = −20.5–0.89, p=0.07) PRP=HA in VAS at<12 months (MD = −0.5, 95% CI = −23.1–22.0, p=0.96) PRP>HA in WOMAC at>12 months (MD = −13.6, 95% CI = −18.2–−9.1, p<0.0001) PRP>HA in WOMAC at<12 months (MD = −18.4, 95% CI = −33.8–−3.00, p<0.0001) PRP>HA in IKDC at>12 months (MD=6.7, 95% CI=2.1–11.2, p=0.004)	PRP>HA in clinical outcome
Gong *et al.* (2021)	6 RCTs	Systematic review and meta-analysis	660 (PRP=33, HA=323)	Level 1 RCT comparing PRP versus HA for KOA	Retrospective and non-randomized studies Unavailable result	Intra-articular injections of PRP and HA	6–12 months follow-up	WOMAC Subjective IKDC TAS EQ-VAS AEs	PRP>HA in WOMAC score at 1 month (MD=1.33, 95% CI=0.43–2.23, p=0.004) PRP>HA in WOMAC score at 6 months (MD=4.79, 95% CI=4.00–5.59, p=0.05) PRP>HA in WOMAC score at 12 months (MD=3.85, 95% CI=2.66–5.04, p=0.05) PRP=HA in IKDC score at 2 months (MD = −0.58, 95% CI = −5.78–4.62, p=0.83) PRP=HA in IKDC score at 6 months (MD=6.51, 95% CI = −0.01–13.03, p=0.05) PRP=HA in IKDC score at 12 months (MD=5.72, 95% CI = −5.16–16.59, p=0.30) PRP=HA in Tegner score post-injection (MD = −0.10, 95% CI = −0.23–0.43, p=0.55) PRP=HA in EQ-VAS score at 6 months (MD=6.26, 95% CI = −2.76–15.27, p=0.17) PRP=HA in AEs. (RR=0.88, 95% CI=0.60–1.29, p=0.52)	PRP>HA in WOMAC score PRP=HA, in IKDC, Tegner scores, EQ-VAS scores, and AEs
Li *et al*. (2022)	14 RCTs	Systematic review and meta-analysis	1512 (PRP=78, HA=731)	RCTs Intra-articular viscosuplemmentation of KOA Multiple injection Unpublished studies deemed relevant Written in English Proper method described	Animal studies Not RCTs Not written in English Duplication Recent knee surgery No outcome interest	Intra-articular injections of PRP and HA	6–24 months follow-up	VAS WOMAC IKDC EQ-VAS AEs	PRP>HA in VAS score at 3 months (WMD = −0.25, 95% CI= −0.40–−0.10, p=0.0009) PRP>HA in VAS score at 12 months (WMD = −0.64, 95% CI = −0.79–−0.49, p<0.00001) PRP>HA in WOMAC score at 1 month (WMD = −1.23, 95% CI = −2.17–−0.29, = 0.01) PRP>HA in WOMAC score at 3 months (WMD = −5.34, 95% CI = −10.41–−0.27, p=0.04) PRP>HA in WOMAC score at 6 months (WMD = −11.02, 95% CI = −18.09–−3.95, p=0.002) PRP>HA in WOMAC score at 12 months (WMD = −7.69, 95% CI = −12.86–−2.52, p=0.004) PRP>HA in IKDC score at 3 months (WMD=7.45, 95% CI=2.50–12.40, p=0.003) PRP>HA in IKDC score at 6 months	PRP>HA for relieving pain, improve QoL, increase joint function

(Contd...)

Table 1: *(Continued)*

Author's name and year of publication	Included studies	Method	Population	Inclusion criteria	Exclusion criteria	Intervention	Follow-up (months)	Outcome measure	Results	Conclusion
									(WMD=5.06, 95% CI=1.94–8.18, p=0.001) PRP>HA in EQ-VAS at 12 months (WMD=2.90, 95% CI=1.29–4.51, p=0.0004) PRP=HA for AEs (complications). (RD=0.07, 95% CI = −0.05–0.20, p=0.24) PRP>HA for AEs (local pain after injection). (RD=0.10, 95% CI=0.01–0.18, p=0.02) PRP=HA for AEs (local swelling). (RD=0.06, 95% CI = −0.02–0.15, p=0.16)	

MD: Mean difference, CI: Confidence interval, KOA: Knee osteoarthritis, HA: Hyaluronic acid, PRP: Platelet-rich plasma, FGF: Fibroblast growth factor, PDGF: Platelet-derived growth factor, RCTs: Randomized controlled trials, RD: Risk difference, RR: Risk ratio, VAS: Visual Analog Scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, IKDC: International Knee Documentation Committee, EQ-VAS: Euro quality of life-VAS, TAS: Tegner activity score, KOOS: Knee injury and osteoarthritis outcome score, AEs: Adverse effects, SMD: Standardized MD, WMD: Weighted MD.

post-injection compared to PRP group (RD = 0.10, 95% CI = 0.01–0.18, p = 0.02) [23], [24]. Overall, three SRs concluded a statistically significant improvement in clinical outcomes in the PRP group when compared to the HA group [16], [23], [24]. However, one SR by Hohmann *et al*. concluded that the PRP group showed better improvement in knee pain at 6 (p = 0.001) and 12 months (p = 0.001), yet the clinical outcome is not statistically significant between both groups at 12 months (SMD = 0.684, 95% CI = −2.242–0.44, p = 0.188) [25].

Discussion

This SR of SRs supported the use of intra-articular PRP as a long-term therapeutic choice for patients with KOA, as opposed to HA injections. In summary, all four SRs assessed clinical outcomes using several PROs. Four SRs concluded that the PRP group lowered the WOMAC score significantly compared to the HA group [16], [23], [24], [25]. Two SRs mentioned AEs, and Gong *et al*. reported that there is no statistically significant difference between the PRP and HA groups (RR = 0.88, 95% CI = 0.60–1.29, p = 0.52). However, Li *et al*. found that the HA group had significantly lower post-injection local pain than the PRP group (RD = 0.10, 95% CI = 0.01–0.18, p = 0.02) [23], [24]. Three SRs by Belk *et al*., Li *et al*., and Hohmann *et al*. elaborated on the type of HA and their volume and frequency of injections [16], [24], [25]. In addition, only Hohmann *et al*. mentioned the brand name of viscosupplement injected in their SR [25]. Minor contradictions are found in terms of measurable PROs, symptoms, and follow-up periods. All four SRs consistently reported congruent results, indicating that using intra-articular PRP is beneficial for optimal long-term outcomes.

Major inconsistencies exist in PRP injections, including the optimal amount, time, method, and preparation quality. Within the scope of this review, several studies have provided information regarding the quantity of autologous blood extracted, the centrifugation technique employed, centrifugation duration, injection site, and time intervals between injections. The study conducted by Gong *et al*. failed to provide specific details regarding the characteristics of the PRP and HA [23]. In addition, the study by Belk *et al*. reported a further profile of PRP, whether it contains leukocyte-rich or leukocyte-poor PRP [16]. A comparative analysis was conducted on three centrifuge systems, revealing statistically significant variations in the concentrations of leukocytes and growth factors across samples [27]. These parameters may suggest varied levels of healing properties in plasma concentrations acquired from distinct separation systems. Regardless of the numerous methods of preparing PRP in the studies,

Table 2: Evaluation of the quality of the literature

Question	Hohmann *et al*. (2020)	Belk *et al*. (2021)	Gong *et al*. (2020)	Li *et al*. (2023)
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes
Did the review report explicitly state that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	Yes	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	Yes
Did the review authors use a comprehensive literature search strategy?	PY	PY	PY	PY
Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	Yes
Did the review authors perform data extraction in duplicate?	Yes	Yes	Yes	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes	Yes	Yes
Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes
Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?	Yes	Yes	Yes	Yes
Did the review authors report on the sources of funding for the studies included in the review?	Yes	Yes	Yes	Yes
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	No	No
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes	Yes	Yes	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	No	No	No
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes
Overall methodological quality (CL, low, high, moderate)	High	Moderate	Moderate	Moderate

RoB: Risk of bias, CL: Critically low, PY: Partially yes, PICO: Population, intervention, comparison, outcome.

PRP still showed a positive effect on treating KOA to the extent that some studies revealed that PRP is superior to HA. However, whether PRP preparation is crucial in affecting outcomes is yet to be elucidated. Therefore, standardization of PRP preparation is required to provide a clear and consistent PRP profile.

Injection therapies, such as PRP and HA, possess numerous advantageous characteristics relevant to the field of therapeutic practice. The postulated mechanisms and their impact on tissues exhibited notable variations. The introduction of exogenous HA can potentially augment the production of endogenous HA and proteoglycans by chondrocytes, thereby inhibiting cartilage breakdown and facilitating regenerative processes. In addition, it attenuates nerve conductivity and sensibilities linked to chronic KOA pain [28], [29]. PRP usage aims to downregulate inflammatory cascade and mitigate the catabolic environment within the joint [30]. The suggested mechanisms involve suppression of catabolic cytokines, including interleukin-1beta and tumor necrosis factor-alpha, as well as FGF, transforming growth factor-β, and various other factors [27], [31], [32]. Moreover, it is likely to influence the regulation of matrix breakdown and concurrently attenuate nuclear factor kappa B pathway initiation, a main mechanism implicated in the development of osteoarthritis. The growth factors that present in PRP play a crucial role in supporting the proliferation and maturation of chondrocytes, regulating collagenase activity, and ultimately facilitating cartilage tissue regeneration [33]. Considering the inevitable degenerative process in KOA, it is plausible that PRP injections could offer greater advantages owing to their possible regenerative attributes.

Based on our bias risk evaluation, this study demonstrated varying degrees of quality, from moderate to high. All SRs in this study used identical procedures for PRP and HA injections. Nevertheless, there was variation among the studies regarding the precise methods used to prepare PRP and the specific type of HA injectable medication employed. During the process, all of the SRs included in this study conducted an extensive literature search, implemented measures to confirm the precision and dependability of the selection and extraction of data, established a set of criteria for the inclusion and exclusion of studies, employed rigorous scientific evaluation methods to assess the quality of the articles, integrated their findings to derive conclusions, and acknowledged the potential impact of publication bias [16], [23], [24], [25]. Furthermore, a significant proportion of the studies (75%) reported no conflicts of interest in their respective reviews [23], [24], [25].

The consistent findings across all four SRs may be attributed to a high CCA, which suggests a significant overlap in the original research included in each SR. The studies by Hohmann *et al*. and Belk *et al*. exhibited the highest CCA scores (60%), an expected result, given the temporal proximity of the studies.

However, it is important to acknowledge that these findings have certain limitations. One limitation of our study was that we exclusively included only English-language articles. This language limitation could increase the risk of systematic bias and exclusion of relevant studies. Another aspect to consider is the diversity in the composition and preparation methods of both PRP and HA injections across all trials, such as blood collection method, centrifugation, the use of single- or double-spin method, and site of injection, which may increase inter-study heterogeneity and decrease external validity. The third pertains to the individual limitations of the SRs included in this study, primarily stemming from the limited sample size of participants in the selected research, which may undermine the internal validity. Moreover, it is essential to note that there is a significant degree of overlap between each SR. Therefore, establishing more effective inclusion and exclusion criteria is imperative to

Table 3: Overlap between each study

Study	Review			
	Hohmann et al.	Belk et al.	Gong et al.	Li at al.
Cerza et al.				
Filardo et al. (2012)				
Sanchez et al.				
Spakova et al.				
Vaquerizo et al.				
Filardo et al. (2015)				
Raeissadat et al. (2015)				
Lana et al.				
Smith et al.				
Cole et al.				
Duymus et al.				
Lin et al.				
Ahmad et al.				
Di Martino et al.				
Gormeli et al.				
Lisi et al.				
Montanes-Heredia et al.				
Paterson et al.				
Reissadat et al. (2017)				
Su et al.				
Vasavilbaso et al.				
Yu et al.				
Huang et al.				
Xu et al.				
Dulick et al.				
Reissadat et al. (2021)				

reduce the extent of this overlap. Additional investigation is warranted to examine particular processes, including PRP preparation, centrifugation, concentration, and injection procedures, which can provide the best evidence of whether a specific protocol yields better outcomes in reducing pain and enhancing functional outcomes. In addition, it is recommended that future studies incorporate extended follow-up periods to comprehensively assess the long-term impact of PRP injections, particularly the duration of their effects. Based on the evidence presented in these SRs, it can be concluded that PRP is more beneficial over a longer timeframe as a therapeutic modality for the reduction of pain and improvement of functional outcomes in individuals diagnosed with KOA.

Conclusion

Our findings support the superiority of PRP over HA as a long-term therapeutic alternative for early KOA. Studies with longer follow-up periods (>6 months) showed a higher efficacy of PRP. Intra-articular PRP appears to reduce pain and improve functional outcomes.

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Appendix

Appendix 1: Coorected covered area

Parameter	Times studies appeared in reviews (N)	Number of rows (r)	Number of reviews (c)	CCA values	
				Proportion	Percentage
Overall	50	26	4	0.308	30.80
Review 1 versus 2	30	21	2	0.6	60
Review 1 versus 3	18	16	2	0.125	12.50
Review 1 versus 4	26	21	2	0.238	23.80
Review 2 versus 3	24	20	2	0.2	20
Review 2 versus 4	32	23	2	0.391	39.10
Review 3 versus 4	20	15	2	0.333	33.30

$$CCA = \frac{N - r}{(r \times c) - r}$$

CCA: Corrected covered area.