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Review Paper

Comparison of Clinical Outcomes of Intra-articular Injection of Platelet-rich Plasma Versus Hyaluronic Acid in Patients With Knee Osteoarthritis: A Systematic Review

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ABSTRACT

Background: Intra-articular injections, such as platelet-rich plasma (PRP) and hyaluronic acid (HA), are widely used to manage symptoms of knee osteoarthritis (OA). However, their effectiveness and superiority in patients with degenerative meniscal tears remain controversial.

Objectives: This systematic review aimed to compare the clinical outcomes of leukocyte-rich PRP (LR-PRP) and HA in patients with knee OA.

Methods: We searched PubMed/Medline, Scopus, Embase, and the Cochrane Library databases using relevant MeSH terms, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, to identify articles published between January 2010 and January 2026. Finally, eight studies, including randomized controlled trials and systematic reviews, were included in the qualitative analysis.

Results: Both LR-PRP and HA improved pain, joint function, and duration of therapeutic effect. However, PRP, particularly leukocyte-poor (LP-PRP) formulations, showed a tendency toward reduced reinjection requirements and greater long-term functional improvement. Both treatments were safe and well-tolerated; however, PRP demonstrated potential for more sustained clinical effects.

Conclusion: Based on moderate-to-high-certainty studies, the effects of LR-PRP and HA on clinical outcomes in patients with knee OA were similar. In the long term, PRP may be associated with a reduced need for reinjections and further improvement in functional outcomes. Due to variations in PRP preparation protocols and follow-up durations, it is recommended to conduct large-scale, long-term randomized controlled trials with standardized protocols to better determine the efficacy and optimize treatment strategies.

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Introduction

Osteoarthritis (OA) is among the most prevalent joint disorders and is characterized as a chronic, progressive, and multifactorial condition [1]. It is defined by the gradual degradation of articular cartilage, osteophyte formation, alterations in the subchondral bone, and chronic synovial inflammation, ultimately leading to 'joint failure' [2]. Historically perceived merely as a degenerative process resulting from mechanical wear and tear, OA is now recognized as a complex phenomenon driven by the interplay of biomechanical, inflammatory, and metabolic factors that disrupt the joint tissue's repair capacity [3].

Global reports indicate that OA affects approximately 3.3%-3.6% of the world's population, causing moderate-to-severe disability in over 43 million individuals; consequently, it is identified as the eleventh leading cause of disability worldwide [4]. In 2024, the Osteoarthritis Research Society International published an official report designating OA as a serious disease imposing a significant burden on healthcare systems [5]. Among various joints, the knee is most frequently affected. Knee OA is particularly common in the elderly and has become a primary cause of chronic pain, functional impairment, and mobility disability [6]. Studies indicate that, after age 60, the prevalence of knee OA is higher in women (13%) than in men (10%) [7].

The primary pharmacological management for these patients typically relies on non-steroidal anti-inflammatory drugs (NSAIDs). However, long-term use of NSAIDs is associated with serious adverse effects, including gastrointestinal bleeding, hepatic injury, and other systemic complications [8]. Therefore, intra-articular injection therapies have gained attention as alternatives with a more favorable safety profile. Among these, two widely used approaches are hyaluronic acid (HA) (Hyalgan) and platelet-rich plasma (PRP) injections. HA, a natural component of synovial fluid, functions as a lubricant and shock absorber within the joint [9]. In contrast, PRP is derived from the centrifugation of autologous blood and contains a high concentration of platelets, growth factors, such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), basic fibroblast growth factor (bFGF), and transforming growth factor (TGF)-β1, which stimulate tissue repair, and cartilage regeneration [10, 11].

Recent studies have indicated that PRP injections, by stimulating growth factors and modulating inflammation, can effectively reduce pain and improve knee joint function [12]. In contrast, HA exerts both mechanical and biochemical effects, enhancing joint lubrication and reducing cartilage wear [13]. However, studies have reported inconsistent findings regarding their comparative efficacy. Some studies have reported superior efficacy of PRP in improving outcomes, such as Western Ontario and McMaster universities arthritis (WOMAC), visual analog scale (VAS), and International Knee Documentation Committee (IKDC) scores [14, 15], while others have found no significant difference between PRP and HA or have even reported greater effects with HA [16]. Furthermore, the concurrent combination of PRP and HA has shown promising results in some trials, demonstrating benefits in pain reduction and enhanced cartilage regeneration [17].

Given increasing life expectancy and the rising prevalence of knee OA, the need for non-invasive, low-risk, and cost-effective treatments is more pressing than ever. In this context, comparing the clinical outcomes of intra-articular PRP and HA injections in patients with knee OA represents a significant step towards selecting the optimal therapeutic approach. The aim is to improve joint function, alleviate pain, and enhance patients' quality of life. This systematic review analyzed and compared the efficacy of these two treatment modalities across various functional and clinical indices, including WOMAC, VAS, IKDC, Tegner, and EuroQol (EQ)-VAS scores. By synthesizing scientific evidence, this study aimed to propose an effective strategy to optimize treatment for patients with knee OA.

Methods

This systematic review was designed in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 guidelines [18] to compare the effectiveness of intra-articular injection of PRP and HA in patients with knee OA, and its process was registered in the international prospective register of systematic reviews (PROSPERO).

Literature search

After determining the search strategy based on the patient, problem, population, intervention or exposure, comparison, control or comparator, outcome (PICO) framework, we searched PubMed/Medline, Scopus, Web of Science, and Embase databases using relevant search terms to find relevant articles. Two independent investigators searched. The search was limited to studies published between January 2010 and January 2026

to ensure the inclusion of contemporary evidence. We also searched Google Scholar and the references of the included articles as grey literature. The databases were searched using a combination of the following terms: OA, knee OA, PRP, HA, sodium hyaluronate, injections, intra-articular, intra-articular injection. The search strategy for the sources is reported separately in Supplementary Table 1.

The PICO framework was specified as follows: population: adults with knee OA, exposure: intra-articular injection of PRP, comparison: intra-articular injection of HA, and outcome: clinical and functional outcomes.

Functional or clinical outcomes were assessed using mean pre- and postoperative changes in functional score WOMAC, VAS, IKDC, and knee injury and OA outcome score (KOOS) indices.

Inclusion and exclusion criteria

Studies were selected based on the following criteria: studies that directly compared intra-articular injections of PRP and HA in patients with knee OA, clinical or quasi-experimental studies reporting clinical outcomes, such as WOMAC, VAS, or IKDC scores, studies providing clear information on sample size, injection protocol, follow-up duration, and treatment outcomes, and articles published in English or Persian. The exclusion criteria included editorials, case reports, studies without full-text access, and studies published in non-English/Persian-language journals.

Screening and study selection

The screening and selection of studies were carried out in the following steps.

1. Initial search of databases and aggregation of articles found from the databases using the statistical software EndNote

2. Identification and elimination of duplicate studies between sources using the software EndNote

3. Two independent researchers assessed the remaining articles for relevance to the research question, including the title and, if applicable, the abstract.

4. A third researcher resolved any disagreements in selecting or excluding an article. After applying the inclusion and exclusion criteria, the full texts of the remaining articles were reviewed.

Data extraction

Initially, variables for extraction were identified by a committee of orthopedic surgeons and epidemiologists, as well as by a literature review. Data extraction was performed independently by two investigators using Microsoft Excel. A third investigator resolved any disagreements between the two investigators.

The extracted variables included the following: authors, year of publication, country of origin, study design, sample size, demographic characteristics of the study population (age, sex, body mass index, Kellogg-Lawrence score), type and method of PRP preparation (e.g. leukocyte-rich PRP [LR-PRP]), type and frequency of HA injections, injection protocol, duration of follow-up, and primary functional or clinical outcomes (e.g. WOMAC, VAS, IKDC, KOOS scores). Data were organized in summary tables to facilitate systematic comparison between studies.

Quality assessment

The risk of bias for each included randomized controlled trial (RCT) was assessed using the Cochrane risk of bias 2 (RoB 2) [19], which covers five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each study was rated for risk of bias as low risk, with some concerns, or high risk, based on RoB 2 guidances.

Data analysis and synthesis

The data were analyzed qualitatively. The findings from the included studies were descriptively and comparatively analyzed by intervention type, outcome measures (e.g. WOMAC, VAS, IKDC, and Tegner scores), and follow-up duration. Commonalities, differences, and overall trends in the results were synthesized and presented in tables and analytical interpretations to provide a comprehensive overview of the relative effects of PRP and HA on the alleviation of knee OA symptoms.

Results

The initial search returned 1,064 results from the searched databases. After removing duplicate records, 49 articles were selected for full-text review based on their titles and abstracts. Finally, after applying the inclusion criteria, eight RCT studies were included in this systematic review for qualitative analysis (Figure 1).

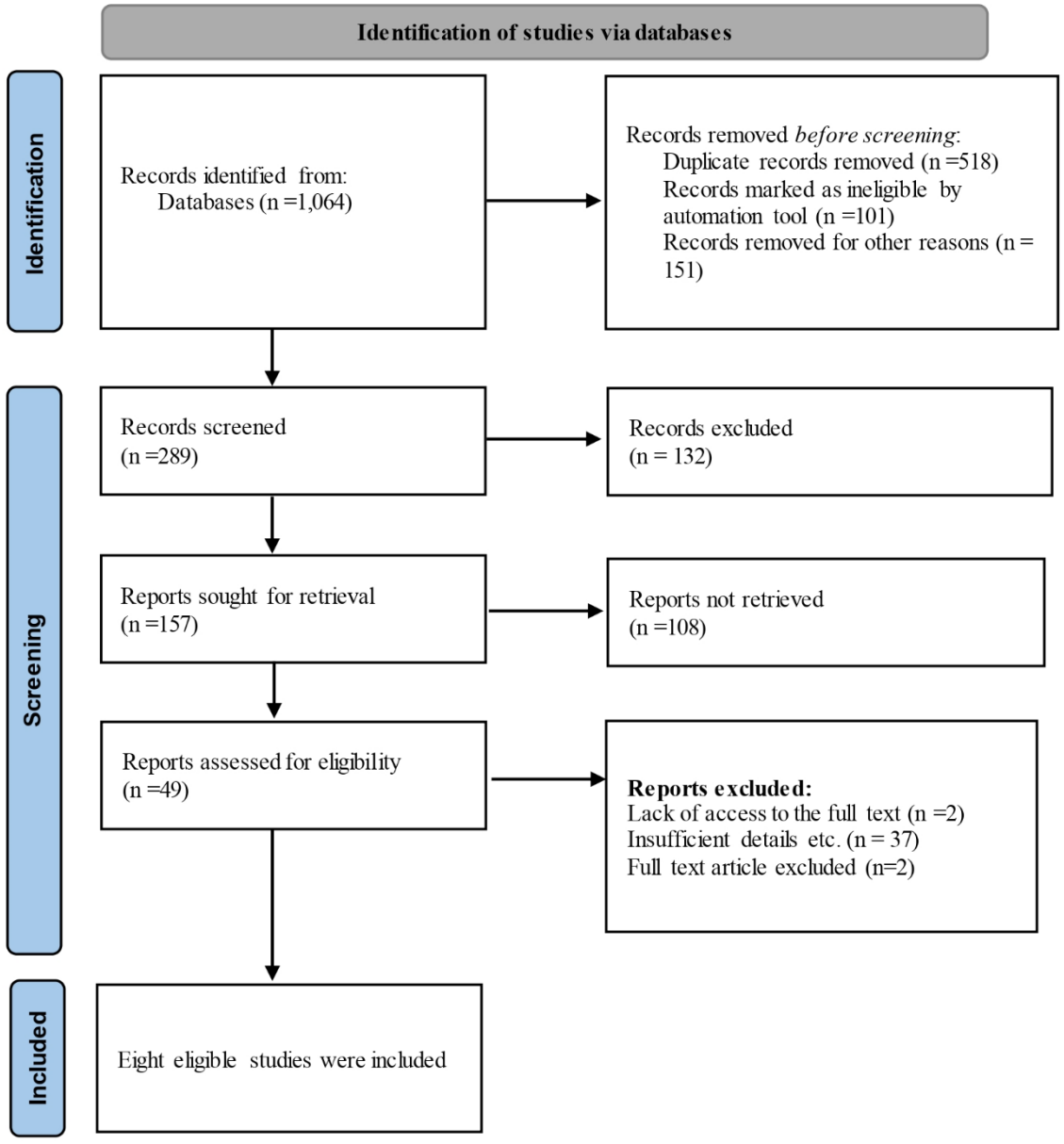

Figure 1. PRISMA flow diagram of study selection

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General characteristics of the included studies

This review, encompassing studies published between 2016 and 2024, evaluated the evidence on the efficacy of PRP injections for patients with mild-to-moderate knee OA or degenerative meniscal tears, with a mean age of 40-65 years (Table 1).

Overall efficacy and relative superiority of PRP

A consensus among the reviewed studies indicates that both PRP and HA injections are effective in significantly reducing pain (measured by indices, such as VAS and the pain subscale of WOMAC) and improving knee function (measured by indices, such as WOMAC, KOOS, and IKDC). However, robust evidence from large-scale meta-analyses [20, 21] demonstrates that PRP is not only a valid therapeutic option but also generally superior in clinical outcomes. This advantage has been reported as a more rapid onset of action in symptom reduction and a longer duration of effect (lasting at least up to 12 months of follow-up) compared to HA [20, 21].

Synergistic effect of combination therapy

A significant finding highlighted in a 2019 systematic review is the potential synergistic effect of combination therapy using both PRP and HA. This finding suggests that the

Table 1. General characteristics of studies on PRP and HA for knee OA

Row	Author(s), Year	Sample Size	Follow-up Duration	Control Group	Intervention Type	Evaluation Indices
1	Montañez-Heredia et al. 2016 [24]	176	6 months	HA	PRP	WOMAC, VAS, KOOS
2	Guenoun et al. 2019 [23]	10	6 months	No control group	Intra-meniscal PRP injection	KOOS, MRI
3	Ivander & Anggono 2024 [25]	23	12 months	HA	PRP	WOMAC, KOOS, EQ-VAS
4	Chen et al. 2023 [20]	2730	12 months	HA	PRP (low-platelet/high-platelet tube)	WOMAC, IKDC, VAS
5	Khalid et al. 2024 [21]	3696	12 months	HA or corticosteroid	PRP	WOMAC, VAS
6	Erdem et al. 2019 [26]	941	12 months	PRP or HA alone	Combined PRP + HA therapy	WOMAC, VAS

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Abbreviations: PRP: Platelet-rich plasma; HA: Hyaluronic acid; WOMAC: Western Ontario and McMaster universities arthritis; VAS: Visual analog scale; IKDC: International Knee Documentation Committee.

combination of these two agents may be more effective than using either agent alone. This phenomenon is likely attributable to complementary mechanisms of action: HA provides immediate lubrication and visco-supplementation, while PRP actively stimulates tissue repair and regeneration processes through the release of numerous growth factors [22].

The challenge of heterogeneity and standardization

A major obstacle to drawing definitive conclusions and making direct comparisons across studies is the substantial heterogeneity in PRP preparation and injection protocols. Variables such as the type of kit used (yielding leukocyte-poor PRP (LP-PRP), versus LR-PRP, the number and intervals of injections, and the injected volume varied considerably among the studies. This heterogeneity is recognized as a key factor contributing to the differences in reported outcomes and underscores the pressing need for standardized treatment protocols in future research.

Although most studies have focused on knee OA, Guenoun et al. (2019) indicated that PRP applications are expanding to include intra-meniscal injuries. This suggests that PRP is also being investigated as a potential regenerative treatment for soft tissue injuries [23].

Therefore, current evidence strongly supports the efficacy of PRP in reducing pain and improving function in patients with knee OA, suggesting that this treatment may have clinical superiority over HA. However, to definitively confirm the superiority of combination therapy and to determine the optimal PRP preparation and injection protocol, it is essential to conduct well-designed clinical trials with standardized protocols.

Clinical outcomes

Comparison of the efficacy of PRP and HA:

Evidence from multiple studies indicates that both injectable treatments, PRP and HA, are effective in reducing pain and improving function in patients with degenerative meniscal tears. However, the pattern and duration of efficacy differ between the two treatments. The study by Montañez-Heredia et al. (2016) showed that although both groups achieved significant improvement by the end of the 6-month follow-up period, the PRP group experienced a faster rate of improvement during the first three months. This finding suggests that PRP may be particularly useful for achieving a rapid clinical response in the early stages of the disease [24].

Table 2. Summary of safety and therapeutic effects

Author(s), Year	Treatment Type	Adverse Effects	Safety Interpretation
Montañez-Heredia et al. 2016 [24]	PRP/HA	Injection site pain	Both methods are safe with limited side effects
Guenoun et al. 2019 [23]	PRP (intra-meniscal)	Pain during injection	Safe; adverse effects resolved spontaneously
Chen et al. 2023 [20]	PRP (LP / LR)	No serious adverse events reported	A safe treatment
Khalid et al. 2024 [21]	PRP	Mild and transient pain	Safe and reliable
Erdem et al. 2019 [26] and Shoma et al. 2019 [22]	PRP + HA	Similar to the control group	The combination regimen has a favorable safety profile

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PRP: Platelet-rich plasma; HA: Hyaluronic acid.

Guenoun et al. (2019), investigating intra-meniscal PRP injection, confirmed its efficacy in a more specialized context. This study reported an increase in the KOOS from 56.6 to 72.7 and observed a quicker return to sports activities. These results position PRP as a promising, minimally invasive intervention for meniscal tissue repair [23].

Long-term superiority of PRP and large-scale studies:

Large meta-analyses with high sample sizes provided stronger evidence of PRP superiority. Chen et al. (2023), which analyzed data from 2,730 patients, consistently showed that PRP led to better WOMAC and IKDC scores compared to HA. An important finding of this study was the impact of PRP preparation type, where LP-PRP demonstrated superior clinical performance compared to LR-PRP. This highlights the importance of standardizing PRP formulations [20].

Similarly, a meta-analysis by Khalid et al. (2024), including 3,696 patients, concluded that PRP is not only more effective than HA in reducing pain and improving function, but these effects remain stable for up to 12 months. This study introduces PRP as a first-line non-surgical option for managing these patients [21].

Potential for synergistic effect of combination therapy:

An interesting area of research is the investigation of combination therapy. A previous systematic review reported that this regimen led to greater improvement in WOMAC and VAS scores than either agent alone. This synergistic effect is likely due to complementary mechanisms of action: HA provides immediate lubrication and cartilage protection, while PRP creates a restorative and anti-inflammatory environment by releasing growth factors [26].

Safety and adverse effects:

The safety profile of both PRP and HA treatments has been evaluated as favorable. As summarized in Table 2, the adverse effects reported across all studies were limited, mild, and transient. The most common adverse effect was temporary pain or swelling at the injection site, which typically resolved spontaneously within 24-72 hours. Large studies, including Chen et al. (2023) [18] and Khalid et al. (2024) [19], reported no serious or systemic treatment-related adverse events. Furthermore, a study on PRP+HA combination therapy showed that adding PRP to HA did not alter the safety profile, and its adverse effects were similar to those of the control group [26]. These findings generally indicate that intra-articular injections of PRP and HA are safe and acceptable interventions with low adverse event rates.

Discussion

This systematic review aimed to evaluate the efficacy and safety of PRP and HA, used as monotherapies or in combination, for the treatment of knee OA. The results indicated that both treatment methods led to significant improvements in patients' clinical indices, including WOMAC, VAS, IKDC, EQ-VAS, and Tegner scores [27-29]. Overall, no significant difference was observed between PRP and HA in terms of pain relief or safety during long-term follow-up, consistent with previous studies [29].

However, subgroup and longitudinal analyses revealed that PRP, particularly LP-PRP formulations, improved total IKDC and WOMAC scores compared to HA and LR-PRP, suggesting that PRP may offer greater long-term functional benefits [30, 31]. These findings are also consistent with biological mechanisms, as PRP contains growth factors that stimulate chondrocyte proliferation, regulate collagenase activity, and promote synthesis of the extracellular matrix. In contrast, HA lacks such regenerative effects [27]. Furthermore, the lower retreatment rate in the PRP group at 24 months may be clinically relevant, even though no significant difference in overall effect duration was observed [32].

The efficacy of PRP is influenced by variables such as leukocyte concentration, preparation method, and number of injections. Laboratory studies have shown that leukocytes may activate catabolic and inflammatory pathways, which can reduce long-term effects, whereas LP-PRP mitigates these negative impacts while preserving growth factor activity [33]. Additionally, using a double-spin centrifugation method for PRP preparation increases platelet and growth factor concentration, thereby enhancing therapeutic efficacy [32]. However, differences in formulations and injection protocols led to variable clinical outcomes, underscoring the necessity for standardization in this field [27].

The combination of PRP and HA may have a synergistic effect; HA contributes through lubrication and mechanical protection, while PRP provides regenerative effects, together aiding in pain reduction and functional improvement. Meta-analyses and previous studies indicate that the PRP + HA combination leads to greater reductions in WOMAC scores and better functional

outcomes compared to either treatment alone, especially at long-term follow-up [34, 35]. The mechanism of this synergy may involve regulation of inflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor (TNF)-α, activation of TGF-β signaling pathways, and enhanced cartilage repair via CD44 and TGF-beta type II receptor (βRII) [36].

Despite these positive results, the study has limitations. Variations in follow-up duration, PRP preparation methods, injection volume, and patient characteristics (age, KL grade, degree of cartilage degeneration) can lead to heterogeneity in the results [37]. Furthermore, the limited number of long-term RCTs and incomplete reporting of adverse events prevent definitive conclusions regarding the absolute superiority of one treatment over the other. Although PRP demonstrated better long-term functional outcomes, no significant differences were observed in pain relief or safety, necessitating further studies with standardized protocols, adequate sample sizes, and follow-up periods exceeding 24 months [38].

In summary, this study confirms the efficacy of both PRP and HA in reducing Knee OA symptoms and improving knee function. LP-PRP, either alone or combined with HA, may provide greater long-term functional benefits and a lower retreatment rate compared to HA or LR-PRP, although further research is essential to optimize PRP formulations and injection strategies. The findings of this study offer important clinical insights for selecting injectable therapies for patients with knee OA and emphasize that treatment decisions should be based on biological mechanisms and individual patient characteristics [37-39].

Conclusion

The present study demonstrated that both LR-PRP and HA improve pain, joint function, and the duration of effect in patients with knee OA. However, PRP, particularly its LP-PRP, showed a tendency toward reduced reinjection requirements and greater long-term functional improvement. Both treatments were safe and well-tolerated; however, PRP's potential for achieving more sustained clinical effects suggests it may be a preferable option for long-term symptom management. Confirming these findings and optimizing treatment strategies requires large-scale, long-term clinical trials with standardized PRP protocols.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization and supervision: Omid Safaee; Methodology: Bushra Zareie; Validation, formal analysis, resources, and data curation: Ali Torkaman, Mohsen Fathi Investigation and writing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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Supplementary Table 1. Search strategy syntax and initial results

Database	Search Query (Adapted for Each Database's Syntax)	Initial Hits (n)
PubMed	([“Osteoarthritis, knee”[mesh] OR “knee osteoarthritis”[title/abstract] OR “knee OA”[title/abstract]] AND [“platelet-rich plasma”[mesh] OR “platelet-rich plasma”[title/abstract] OR “PRP”[title/abstract]] AND [“hyaluronic acid”[mesh] OR “hyaluronic acid”[title/abstract] OR “sodium hyaluronate”[title/abstract] OR “hyalgan”[title/abstract]] AND [“injections, intra-articular”[mesh] OR “intra-articular injection*”[title/abstract] OR “intraarticular injection*”[title/abstract])	352
Scopus	(TITLE-ABS-KEY [“knee osteoarthritis” OR “knee OA”] AND TITLE-ABS-KEY [“platelet-rich plasma” OR “prp”] AND TITLE-ABS-KEY [“hyaluronic acid” OR “sodium hyaluronate” OR “hyalgan”] AND TITLE-ABS-KEY [“intra-articular injection” OR “intraarticular injection”])	498
Web of Science	([TS =[“knee osteoarthritis” OR “knee OA”]] AND TS =[“platelet-rich plasma” OR “PRP”] AND TS =[“hyaluronic acid” OR “sodium hyaluronate” OR “hyalgan”] AND TS =[“intra-articular injection” OR “intraarticular injection”])	287
Google Scholar	A targeted search was performed using key phrases, such as “platelet rich plasma hyaluronic acid knee osteoarthritis trial”. Due to the algorithm-based nature of Google Scholar, the first 200 relevant records were screened for eligibility.	(Screened manually)
Additional sources	Manual search of reference lists	15
Total records identified		1152

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