REVIEW ARTICLE

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Effects of the intra-articular injection of platelet-rich plasma versus hyaluronic acid on the inflammatory process and histopathological characteristics of cartilage and synovium in animals with osteoarthritis: a systematic review

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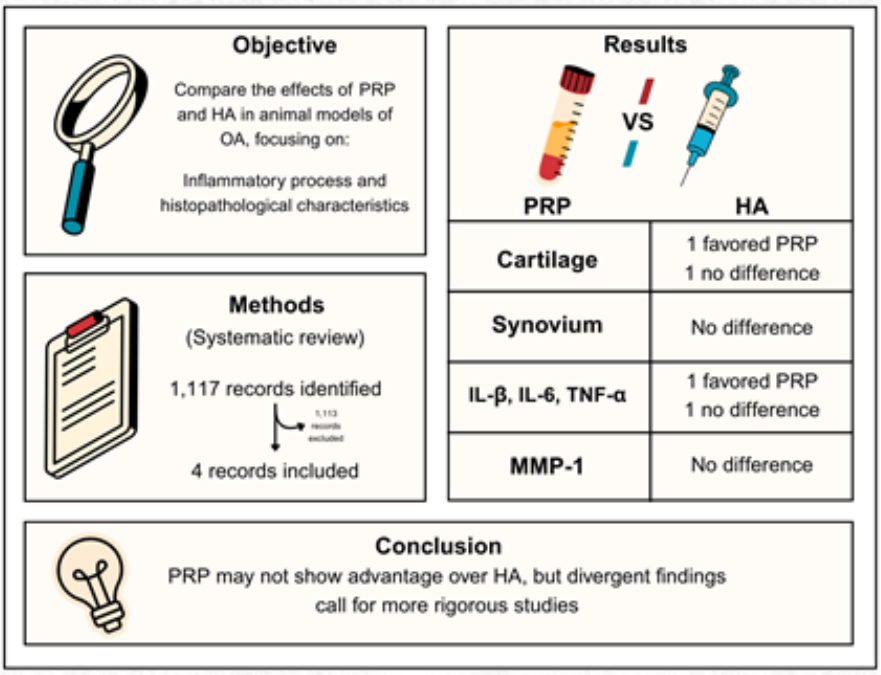

Abstract: The objective of this systematic review was to assess the effectiveness of platelet-rich plasma (PRP) injection versus hyaluronic acid (HA) injection for the management of osteoarthritis (OA) in animal models, with a specific focus on the inflammatory process and histopathological features of cartilage and the synovium. A comprehensive electronic search was conducted of the Medline/PubMed, Embase, and Web of Science databases for articles published up to June 2025 that performed a comparative analysis of the effects of PRP versus HA injection therapy in animal models of OA and also assessed the inflammatory process and histopathological characteristics of cartilage and the synovium. The review adhered to the PRISMA guidelines and recommendations outlined by the Cochrane Collaboration. Risk of bias was assessed using the SYRCLE RoB tool. Although 1,117 articles were retrieved from the databases, only four met all inclusion criteria. Among these, three reported no significant difference between PRP and HA in terms of the histological analysis of cartilage and the synovium or levels of interleukin 1, interleukin 6, tumor necrosis factor alpha, and matrix metalloproteinase-1. In contrast, one study indicated that treatment with PRP yielded superior outcomes compared to HA concerning cartilage histology and interleukin 1β levels. The scarcity of studies exploring intra-articular PRP injections versus intra-articular HA injections in animal models of OA underscores the need for further research to enable a more comprehensive comparison.

PROSPERO registration: CRD42024599465

Keywords: Cartilage; Platelet-rich plasma; Synovitis; Interleukins

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Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by the progressive deterioration of articular cartilage that affects various joint structures, including the synovium, ligaments, and subchondral bone[1] of the hands, knees, hips, and feet[18]. OA results in pain, stiffness, and impaired mobility, significantly impacting quality of life, mental well-being, and daily functioning[18]. With an estimated 250 million individuals affected by OA throughout the world[18], this condition poses a substantial public health challenge[20]. Given its association with aging the prevalence of OA is likely to increase with the rise in life expectancy, leading to an increase in healthcare costs and the burden of premature patient retirement.

Current treatment modalities for OA encompass pharmacological, non-pharmacological, and surgical interventions[31]. Non-pharmacological approaches include weight management, exercise, and physical therapy[30]. However, adherence to changes in lifestyle is often suboptimal[31]. Pharmacological management involves the use of analgesics, anti-inflammatory drugs, and intra-articular injections[30-33]. These two approaches are intended to reduce pain and improve physical functioning[1]. In cases refractory to conservative measures, joint replacement surgery offers relief from pain and the restoration of function[1-30].

Recent attention has focused on intra-articular injections of platelet-rich plasma (PRP) and hyaluronic acid (HA) as non-surgical therapeutic options for OA [33-4]. PRP derived from autologous whole blood via centrifugation has a high concentration of platelets [19-9] containing growth factors, such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF), along with other bioactive proteins implicated in modulating the inflammatory process, tissue repair, and chondrocyte proliferation [21-12-5]. A recent systematic review and meta-analysis reported that PRP injections significantly improved cartilage and synovial histology compared to control groups in animal models of OA, with reductions in proinflammatory markers, such as interleukin 1 (IL-1), interleukin 6 (IL-6), or tumor necrosis factor alpha (TNF-α).

HA is a glycosaminoglycan naturally found in joints that contributes to synovial fluid viscosity and elasticity[29]. In OA, a reduction occurs in HA molecular weight and concentration, leading to synovial fluid degradation. Intra-articular injections of HA are hypothesized to stimulate endogenous HA production, regulate inflammation, exert chondroprotective effects, and relieve pain[23-32].

Despite the potential advantages, such as enhanced local bioavailability and fewer systemic side effects, the effectiveness of intra-articular injections remains inconclusive [16-17] and consensus with regards to the superiority of HA or PRP therapy is lacking[12]. Therefore, the aim of the present systematic review was to investigate and compare the effects of PRP versus HA injections in animal models of OA, with a focus on the inflammatory process and histopathological changes in cartilage and the synovium.

Material and Methods

Protocol and Registration

This review followed PRISMA guidelines[27] and recommendations outlined by the Cochrane Collaboration[14]. To ensure thorough study and transparency of the methods and results, the protocol was filed in the International Prospective Register of Systematic Reviews (PROSPERO) (registration code: CRD42024599465).

Eligibility Criteria

Types of Studies

Preclinical trials assessing the inflammatory process and histopathological features subsequent to the intra-articular administration of PRP and HA in animal models of osteoarthritis OA were deemed eligible. Only articles published in English, Portuguese, or Spanish were considered. No restriction was imposed with regards to year of publication.

Types of Participants

Studies involving any animal model of OA induced either physiologically, genetically, surgically, or pharmacologically, irrespective of the anatomical site affected, were considered eligible.

Types of Comparators

Studies featuring comparison groups receiving intra-articular injections of PRP and HA were deemed eligible.

Types of Interventions

Studies employing intra-articular injections of PRP and HA as therapeutic modalities were considered eligible. No restrictions were imposed with regards to PRP and HA dosage, concentration, or production method.

Outcome Measures

Primary studies reporting outcomes related to modulation (improvement, deterioration, or stability) of the inflammatory process (inflammatory markers) and/or histopathological variables (rate of chondrocyte and synoviocyte proliferation, glycosaminoglycan synthesis, cartilage and/or synovium thickness) were included.

Exclusion Criteria

Clinical trials and case studies, animals with concomitant multiple diseases, in vitro or ex vivo experiments.

Data Collection and Analysis

Databases and Search Strategies

An electronic search was conducted of the Medline/PubMed, Embase, and Web of Science databases for relevant articles published up to June 2025. Search terms were chosen considering the controlled vocabulary of the Medical Subject Headings (MeSH) database and uncontrolled vocabulary. The search strategy comprised terms pertinent to the research theme. Thus, the following search combination was used: ("Platelet-Rich Plasma" OR "Platelet Gel" OR "Autologous Platelet Concentrate" OR "Autologous Conditioned Plasma" OR ACP) AND ("Hyaluronic Acid") AND (Osteoarthritis) AND (Animals OR "Models, Animal" OR "Animal Experimentation") AND (Inflammation OR "Intercellular Signaling Peptides and Proteins" OR Cartilage OR "Synovial Membrane"). Grey literature was not included. A manual search of the reference lists of the primary studies included in the review was performed to identify potentially relevant studies not retrieved during the electronic search.

Study Selection

Two independent reviewers (H.G.M. and G.E.S) screened the titles and abstracts of the retrieved publications based on the inclusion criteria. Potentially relevant studies were submitted to full-text analysis. Consensus was sought throughout the selection process, with a third reviewer (C.C.) consulted in cases of disagreement. The Rayyan reference management software (http://rayyan.qcri.org) was used to facilitate the study selection process [26].

Data Extraction

After consensus and the selection of articles, the reviewers worked independently. Data extraction was performed with a standardized form adapted from the template proposed by the Cochrane Collaboration, capturing information on study design, animal characteristics, intervention and control groups, and outcomes [14].

Risk of Bias Appraisal

Risk of bias was appraised using the SYRCLE RoB tool for animal studies[15], with the assessment of the risk of selection, performance, detection, attrition, and other biases. Two reviewers (M.S.O.S. and H.G.M.) independently assessed the items. Divergences of opinion were resolved through consultation with a third reviewer (C.C.).

Results

The search of the database yielded 1,117 articles. After excluding 53 duplicates, the titles of the remaining 1,064 articles were screened, resulting in the exclusion of 1,033 articles. Subsequent abstract screening led to the selection of 7 articles for full-text analysis, 4 of which met all inclusion criteria [22-13-7-8]. The article selection process is illustrated in Figure 1.

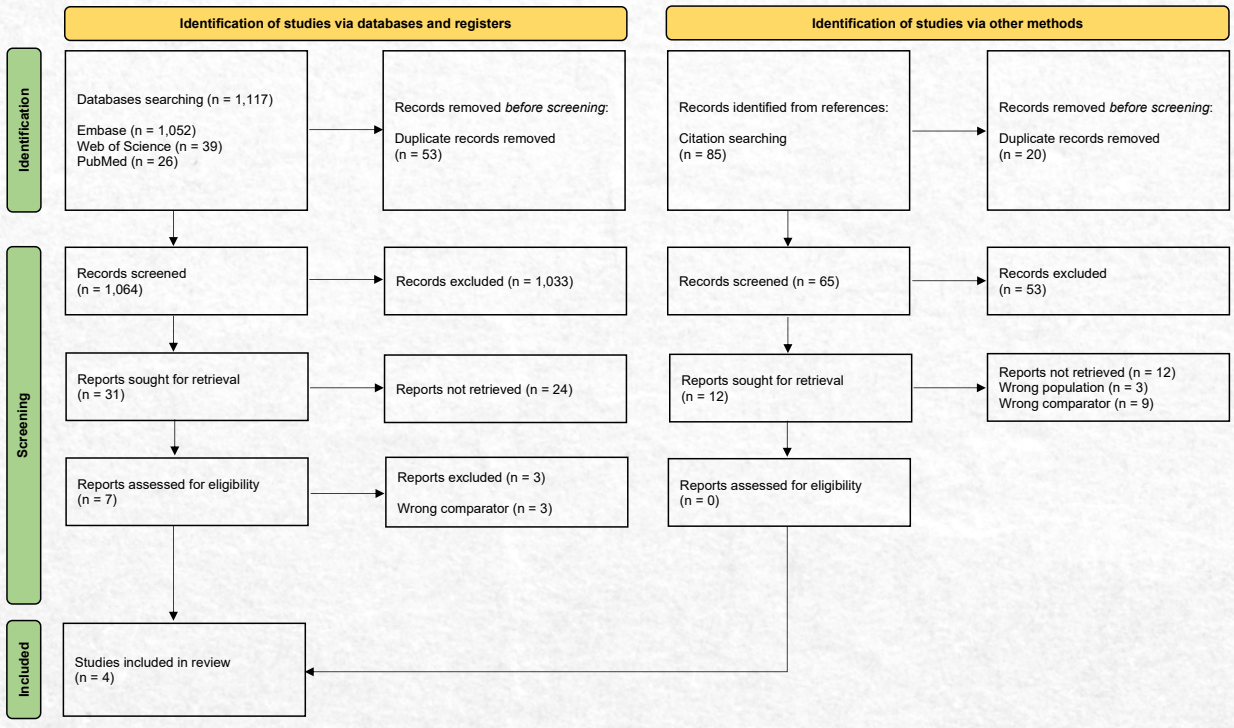

Figure 1. Flowchart of Article Selection, According to PRISMA Guidelines.

Study Characteristics

All selected studies employed animal models.[7] used 30 C57BL6J mice,[8] used 42 C57BL6J mice,[22] used 30 rabbits, and[13] used 40 New Zealand rabbits. Table 1 presents the characteristics of the four articles.

OA induction methods varied across studies, including anterior cruciate ligament transection [7], anterior and posterior cruciate ligament transection [13], lateral parapatellar skin incision[22], and non-invasive axial tibial loading[8] All studies used the knee joint as the model of interest.

Regarding treatment protocols, PRP preparation, and outcome assessment, substantial heterogeneity was observed.[22] administered three weekly injections of 0.3 mL of PRP and HA, [13] administered five weekly injections of 0.5 mL of PRP and 0.2 mL of sodium HA, and[8] administered three injections of 15 L of PRP and HYADD-4G. [7] did not specify the treatment protocol.

The preparation of platelet-rich plasma lacked standardization across the studies. While two studies did not specify the protocol used [13-7] one study employed the double centrifugation method[8] and another employed the Landesburg protocol[22] Centrifugation speeds, duration, and supplementation varied, highlighting the heterogeneous nature of PRP protocols.[8-22] performed two centrifugations. Centrifugation speed in the first round ranged from 200 to 2,000 g, with duration ranging from ten to 20 minutes. Speed in the second round also ranged from 200 to 2,000g, with duration of ten minutes. [7-13] described only one centrifugation, with speed ranging from 3,000 2,000 rpm and duration from six to 15 minutes. With regards to supplementation, anticoagulants such as 1 mL of sodium citrate and heparin were used in two studies[22-8], whereas the other two studies did not provide information on anticoagulant usage[7-13] Calcium chloride was used as an activator in two studies[22-13], with quantities ranging from unspecified to 0.02 mL. [8-7] Did not specify activator usage. Platelet counting was reported in only one study[22], with a significantly higher platelet concentration in PRP compared to peripheral whole blood. The remaining studies did not provide cell count information[8-13-7].

The outcomes were divided into the inflammatory process and histopathological analysis. Two studies [22-13], measured the inflammatory process and performed enzyme-linked immunosorbent assay (ELISA) to estimate inflammatory marker levels. [22] Found that the level of interleukin 1β in the joint fluid was lower in animal models treated with PRP compared to HA. [13] Found no significant differences in levels of IL-1, IL-6, or TNF-α between PRP and HA treatments. Histopathological analysis was conducted in three studies[22-8-7]. But assessment methods and results were heterogeneous, limiting direct comparison.

[22-8] Measured cartilage histology, with one study employing the Mankin Score and finding that PRP outperformed HA[22] while the other study used the assessment tool of the Osteoarthritis Research Society International and found no difference between groups [8] Synovial histology was assessed using the Synovitis Score method, which revealed no difference between PRP and HA treatments[7-8]. [7] Measured matrix metalloproteinase-1 using immunostaining and found no difference between treatments. This information is synthesized in Table 1.

Table 2 summarizes the characteristics of hyaluronic acid (HA) and platelet-rich plasma (PRP) used in the studies included in this review. Considerable heterogeneity was observed in both the types of HA and the PRP preparation protocols.

Regarding HA, some studies used generic hyaluronic acid or sodium hyaluronate without reported molecular weight[22-13], while others employed specific commercial formulations, such as HYADD® 4-G (500–730 kDa) or low molecular weight HA (50–120 kDa)[8-7] respectively. This variability may influence the rheological properties, viscosity, and therapeutic potential of HA in formulations combined with PRP.

Concerning PRP, preparation protocols showed substantial variability.[22-7] Applied double-spin methods with different times and speeds, whereas [13-7] used single-spin centrifugation, reflecting differences in platelet enrichment and growth factor content. Growth factor concentrations also varied widely among studies, with TGF-β, PDGF, and bFGF ranging from 0.077 to 135.19 ng/mL, indicating inconsistency in PRP composition.

Furthermore, none of the studies reported platelet or leukocyte counts in the prepared PRPs. Differences were also observed in anticoagulants used (sodium citrate, heparin, citrate glucose) and activation methods ($CaCl_2$ or bovine thrombin), further highlighting the lack of standardization in PRP protocols.

Study	Population		Comparation groups	Intervention			Outcomes inflammation and histopathologic analysis			
	Animal model strain, sex, weight, age	OA induction	(number)	PRP dosage	HA dosage	Treatment protocol	Variable	Tool	Statistical results	p value
Liu et al. (2014)	Rabbit N/A N/A 6–8 mo.	Lateral parapatellar skin incision	CG (10) PRP Group (10) HA Group (10)	0.3 mL	0.3 mL	1x/Wk for 3 Wk	Inflammatory marker (IL-1β) Cartilage histology	ELISA Mankin Score	+ +	p < 0.01 p < 0.05
Heng-dong et al. (2015)	Rabbit New Zealand ♂ and ♀ 2.25 ± 0.50 kg 5–8 mo.	Anterior and posterior cruciate ligament transection	CG (8) Model Grup (8) PRP Group (8) HA Group (8) HA + PRP Group (8)	0.5 mL	0.2 mL	1x/Wk for 5 Wk	Inflammatory marker (IL-1) Inflammatory marker (IL-6) Inflammatory marker (TNF-α)	ELISA ELISA ELISA	= = =	p > 0.05 p > 0.05 p > 0.05
Duan et al. (2017)	Mouse C57BL|6J N/A N/A 10 wk.	Non-invasive axial tibial loading	CG (8) PRP Group (8) HA Group 8 mg|mL (10) HA Group 15 mg|mL (8) PRP Group + HA (8)	15 µL	15 µL	3x/Wk for 1 Wk	Cartilage histology Synovial histology	OARSI Score Synovitis Score	= =	p > 0.05 p > 0.05
Chiou et al. (2018)	Mouse C57BL|6J ♀ N/A 8 wk.	Anterior cruciate ligament transection	CG (6) Sham Group (6) PRP Group (6) HA Group (6) HA + PRP Group (6)	N/A	N/A	N/A	Molecular marker (MMP-1)	Immunostaining	=	p > 0.05

Abbreviations: (♀) Female; (♂) Male; (CG) Control group; (ELISA) Enzyme-Linked Immunosorbent Assay; (HA) Hyaluronic acid; (HA Group) Intervention group treated with HA; (HA + PRP Group) Intervention group treated with HA and PRP; (IL-1) Interleukin 1; (IL-1β) Interleukin 1β; (IL-6) Interleukin 6; (MMP-1) Matrix metalloproteinase-1 (Mo.) Months; (N/A) Not available; (OARSI) Osteoarthritis Research Society International; (PRP) Platelet-rich plasma; (PRP Group) Intervention group treated with PRP; (TNF-α) Tumor necrosis factor alpha; (Wk.) Week.

Table 1. Summary of descriptive characteristics of the included studies.

	HA		Platelet-rich plasma						
Study	Type	MW (kDa)	Preparation protocol	1st spin		2nd spin		Growth factors (ng/mL)	Supplementation	
				Time	Speed	Time	Speed		Anticoagulant	Activation
Liu et al.	Hyaluronate acid	N/A	Double-spin	10 min	200 g	10 min	200 g	TGF- β (135.19 ± 16.8) PDGF (31.22 ± 4.3) bFGF (0.077 ± 0.021)	Sodium citrate (2.5%)	$CaCl_2$ (1/10 P-PRP volume)
Heng-Dong et al.	Sodium hyaluronate	N/A	Single-spin	15 min	2000 rpm	N/A	N/A	N/A	Citrate glucose (0.4 mL)	$CaCl_2$ (0.02 mL)
Duan et al.	HYADD® 4-G	500–730	Double-spin	20 min	200 g	10 min	2000 g	TGF-β (46.87) PDGF (2.68)	Heparin	N/A
Chiou et al.	Hyaluronic acid	50-120	Single-spin	6 min	3000 rpm	N/A	N/A	N/A	N/A	Bovine thrombin (100 IU/150 mL PRP)

Table 2. Characteristics of HA and PRP used in the included studies.

Risk of Bias Appraisal

Risk of bias was appraised using the SYRCLE tool. Table 3 presents the results for each study. Criteria 1, 5, and 6 were not addressed in any article, indicating Unclear risk of bias regarding the generation of the allocation sequence, random outcome assessment, and blinding of the handlers to intervention allocation during the experiment. Only Criterion 9, which addresses the absence of selective outcome reporting, received affirmative responses across all studies.

Author	Year	Selection			Performance		Detection		Atrittion	Reporting	Other	Results
		1	2	3	4	5	6	7	8	9	10	
Liu et al.	2014	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Yes	5/10
Heng-dong et al.	2015	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear	5/10
Duan et al.	2017	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	5/10
Chiou et al.	2018	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	2/10

Note: "Yes" responses indicated low risk of bias, "No" responses indicated high risk of bias, and "Unclear" responses indicated that the degree of bias could not be attributed. Criteria used for publication bias analysis: (1) Was the allocation sequence adequately generated and applied? (2) Were groups similar for baseline characteristics or adjusted for confounding factors in the analysis? (3) Was allocation adequately concealed? (4) Were animals housed randomly during the experiment? (5) Did caregivers and/or investigators not know which intervention each animal received during the experiment? (6) Were animals randomly selected for outcome assessment? (7) Was the outcome assessor blinded? (8) Were incomplete outcome data adequately addressed? (9) Are study reports free from selective outcome reporting? (10) Was the study apparently free from other problems that could result in high risk of bias?

Table 3. SYRCLE Tool Criteria for Risk of Bias Assessment.

Discussion

The aim of this systematic review was to investigate the effect of the intra-articular injection of platelet-rich plasma (PRP) compared to hyaluronic acid (HA) on the inflammatory process and histopathological characteristics of cartilage and the synovium in animal models of OA. A key observation was the lack of standardization in PRP preparation, treatment dosage, and assessment protocols, which may explain the divergent results among studies. Differences in growth factors concentration, activation methods, injection frequency, and animal models likely contributed to variability in outcomes. Moreover, the diversity in outcome measures (including different inflammatory markers, histological scoring systems, and timing of assessments) further complicates direct comparisons.

Among the four studies included, three [13-8-7] found no differences between treatments with regards to cartilage and synovial histology or levels of IL-1, IL-6, TNF-α, and matrix metalloproteinase-1 (MMP-1), whereas one study [22] reported that PRP treatment yielded superior results compared to HA in terms of cartilage histology and IL-1β levels. These findings indicate that PRP may provide anti-inflammatory and chondroprotective benefits under certain conditions. Nonetheless, the observed discrepancies are likely attributable to variations in OA induction methods, animal species and strains, and differences in PRP dosage, concentration, and preparation protocols. Such heterogeneity highlights the difficulty of comparing results across studies and emphasizes the need for standardized protocols in both preclinical and clinical research. Establishing consensus guidelines for PRP preparation, characterization, and administration in animal models would enhance reproducibility and enable a more accurate assessment of its therapeutic potential [11].

Regarding the inflammatory evaluation, [22] measured the level of IL-1β in the joint fluid, while [13] examined levels of IL-6, IL-1, and TNF-α. Both studies detected the concentration of inflammatory factors using enzyme-linked immunosorbent assays (ELISA) and obtained divergent results. [13] Demonstrated that the group receiving intra-articular PRP injection had a lower concentration of IL-1 in the joint fluid compared to the group that received HA, whereas[13] found no significant difference in the concentration levels of inflammatory markers between the two treatments. Although both studies used the same animal model, [13] administered five applications at a frequency of once per week of 0.5 mL of PRP and 0.2 mL of HA, while [22]used a dose of 0.3 mL of PRP and HA, administered three times at a frequency of once per week.

Three studies assessed histopathological outcomes [22-8-7]. Histological analysis of cartilage was conducted in two studies [22-8] but the intervention method, outcome assessment tool, and results differed. [8] Used mice as the animal model, induced OA through non-invasive axial tibial loading, administered three applications

with a dose of 15 L of PRP and HA, and employed the Osteoarthritis Research Society International (OARSI) Score for outcome assessment, reporting no significant difference between the two groups (PRP vs. HA). In contrast,[22] induced OA in rabbits by performing a lateral parapatellar skin incision, used a dose of 0.3 mL of PRP and HA, administered three applications once per week, and employed the Mankin Score for outcome assessment, reporting a significant difference favoring PRP over HA. A study conducted by [28] compared the Mankin Score and OARSI for the assessment of human knee joints in all stages of osteoarthritis development and concluded that both systems are complex and time-consuming and have variability; as the measures depend on an assessor and involve a semi-quantitative scoring system, the analyses are subjective [28].[8-22] Obtained heterogeneous results but did not follow the same standard with regards to the methods or assessment system employed. Synovial histology was measured in only one study [8] and no significant difference was found between treatment groups. [7] Conducted histopathological analysis using MMP-1 as a molecular marker and found no significant difference between PRP and HA treatments, although the intervention methods were not reported clearly.

We retrieved three articles that did not find differences between treatment with PRP compared to HA [13-8-7] and one article that reported PRP to be superior to HA [22]. Our findings partially diverge from those reported by [10], who conducted a systematic review and found PRP to be superior to HA in terms of pain and stiffness in patients with knee OA, with a clinically significant difference after six to 12 months of follow-up, although the improvement was only partial and the strength of the evidence was low.

Systematic review studies are highly recommended for assessing methodological quality in research and determining the effectiveness of treatments. Thus, the design of the present study occupies the highest level in the hierarchy of scientific evidence [8-2]. In this review, risk of bias was appraised using the SYRCLE RoB tool. Among the ten items on this scale, the criteria with the highest risk of bias were Item 1 (adequate allocation sequence), Item 5 (blinding of investigators), and Item 6 (randomization of animal selection for outcome assessment). None of the studies included in this review satisfied these three items.

Strengths and Limitations of Study

This is the first systematic review to compare the effects of PRP versus HA on the inflammatory process and histological characteristics of cartilage and the synovium in animals with OA. Strengths include adherence to PRISMA and Cochrane recommendations. However, methodological heterogeneity, regarding OA induction, PRP preparation, dosage, treatment protocol, and outcome assessment, limits direct comparisons. The four studies did not apply the same method for inducing OA and the PRP preparation method, HA dosage, PRP dosage, and treatment protocol were also heterogeneous, with some studies lacking information on these aspects. Additionally, the studies measured different characteristics and different assessment tools were used in the analysis of cartilage histology, which was conducted in two studies [22-8]. It is hoped that this review will be of some assistance in designing high-quality preclinical studies in the future.

Conclusion

The results revealed no difference between treatment with PRP and HA in terms of synovitis, MMP-1 concentration, and the concentration of the pro-inflammatory markers IL-6, IL-1, and TNF-α. Divergent results in cartilage histology suggest that PRP may have potential benefits in specific contexts, but variability in OA induction methods, PRP preparation, dosage, and assessment tools limits comparability. These findings highlight the importance of standardized protocols and methodologically rigorous preclinical studies to enhance reproducibility and provide a more reliable foundation for future clinical research.

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