Review article
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Efficacy of platelet-rich plasma in the treatment of pain syndrome in knee osteoarthritis: a meta-analysis of the studies with a 6-month follow-up

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Abstract

Introduction The scientific literature database contains numerous studies comparing the efficacy of platelet-rich plasma (PRP) and hyaluronic acid (HA) preparations in knee osteoarthritis, but the results are contradictory due to methodological limitations and high heterogeneity of treatment protocols.

Purpose To compare the data from scientific studies on the effectiveness of using PRP and medium molecular weight HA preparations in the treatment of patients with knee osteoarthritis.

Materials and methods A search of randomized controlled trials was conducted in PubMed, Embase, and the Cochrane Library published in the period 2017–2024 using the following keywords: osteoarthritis, knee joint, intra-articular injections, platelet-rich plasma, hyaluronic acid, WOMAC, and meta-analysis. Studies that examined patients diagnosed with knee osteoarthritis of any severity who received intra-articular injections of PRP or HA and assessed pain using the WOMAC were reviewed. After rigorous selection, four studies with identical treatment protocols were included.

Results The meta-analysis included 4 studies involving 333 patients (164 in the PRP group and 169 in the HA group). The mean WOMAC pain score at 6 months after the start of treatment was 4.52 (SD = 1.59) in the PRP group and 4.95 (SD = 2.07) in the HA group. The effect size of Hedges' g was 0.26 (95 % CI: –0.61 to 1.14; $p = 0.336$). Egger's test did not reveal a statistically significant publication bias ($p = 0.06$).

Discussion Our study revealed no significant differences between the use of PRP and HA, which contradicts several previous meta-analyses. This may be due to the use of more stringent inclusion criteria in our analysis and the evaluation of HA preparations with only medium molecular weight.

Conclusion This meta-analysis was aimed to compare the effectiveness of using PRP and medium molecular weight HA in the treatment of patients with knee osteoarthritis and did not reveal statistically significant differences between the groups in severity of pain using the WOMAC system six months after the start of treatment, which indicates comparable effectiveness of these therapy methods.

Keywords: hyaluronic acid, platelet-rich plasma, injections, intra-articular, osteoarthritis, knee, pain measurement, treatment outcome, meta analysis

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INTRODUCTION

Osteoarthritis (OA) of the knee joint is a degenerative disease characterized by progressive destruction of the articular cartilage, damage to the subchondral bone, synovium, and ligaments, and is one of the leading causes of chronic pain and disability among the adult population worldwide [1]. The issues of large joint OA diagnosis and treatment is socially significant, since the disease leads to a significant decrease in quality of life, limitation of daily activities, and loss of ability to work. According to epidemiological studies, the prevalence of OA of the knee joint among the adult population varies from 10 to 30%, and the incidence is more common in women and the elderly [2]. The main symptoms of OA are pain, joint stiffness, lameness, and limited mobility, which significantly reduces the quality of life of patients.

Currently, both conservative and surgical methods are used to treat patients with OA. Conservative treatment is aimed at reducing pain, improving joint function, and slowing disease progression. Conservative methods include drug therapy, including the use of nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and slow-release symptomatic medications, as well as physiotherapy, exercise therapy, orthotics, and intra-articular injections [3, 4]. Current surgical techniques, such as high corrective osteotomies and total joint arthroplasty, are effective in late-stage patients with joint deformities, significant mobility limitations, and severe pain. However, surgical intervention is associated with risks such as infectious complications, thromboembolism, and implant instability. The postoperative rehabilitation period does not always lead to full restoration of joint function.

Conservative treatment is preferred in the early stages of the disease. Currently, intra-articular injections of hyaluronic acid (HA) are widely used in conservative treatment. HA is a natural component of synovial fluid and provides lubrication, cushioning, and nutrition to the articular cartilage. The introduction of exogenous HA can improve the viscoelastic properties of synovial fluid and stimulate natural repair processes, promoting cartilage regeneration and maintaining synovial homeostasis [5, 6]. HA relieves pain, reduces inflammation, and improves joint mobility. However, the effect of HA injections is temporary, lasting from several weeks to several months.

In recent years, platelet-rich plasma (PRP), an autologous biological product obtained from the patient's own blood by centrifugation, has been used in the treatment of patients with knee OA. PRP contains a high concentration of platelets, which, when activated, release a variety of growth factors that stimulate cartilage regeneration [7, 8]. PRP injections can relieve pain, improve joint function, and slow the progression of degenerative changes. Clinical studies by Raeissadat et al. and Filardo et al. showed that PRP injections significantly relieve pain and improve joint mobility compared to control groups, with the effect persisting for 6–12 months after treatment [9, 10].

The scientific literature contains numerous studies comparing the efficacy of PRP (PRP therapy) and HA preparations in knee OA. However, the results of the studies remain contradictory due to methodological limitations such as the lack of standardized protocols, small sample sizes, insufficient blinding, and short-term follow-up [11–13]. Moreover, high heterogeneity in PRP preparation protocols has been revealed, as well as differences in platelet concentrations, activation methods, and intra-articular administration algorithms, as well as in the frequency and duration of treatment courses. These factors significantly complicate the comparison of study results and are the main sources of controversy when comparing the efficacy of PRP and HA used for knee OA [14]. We suppose that the results of our study could help determine which method provides more efficient and long-lasting pain relief in knee OA, which is critical for choosing the optimal treatment strategy.

The **purpose** of the study was to compare the data from scientific studies on the effectiveness of using PRP and medium molecular weight HA preparations in the treatment of patients with knee osteoarthritis.

MATERIAL AND METHODS

Our meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study protocol was registered in the PROSPERO international registry. A literature search was conducted in three major electronic databases: PubMed, Embase, and the Cochrane Library for the period from January 2018 to December 2024. The search strategy included a combination of the following MeSH terms and keywords: osteoarthritis, knee joint, intra-articular injections, platelet-rich plasma, hyaluronic acid, WOMAC, and meta-analysis. Terms were combined using Boolean operators AND/OR to create an optimal search string. A manual search of the reference lists of the selected articles was additionally conducted. Pain severity in the analyzed studies was assessed using the WOMAC scale six months after the start of intra-articular injections for knee OA.

Inclusion and exclusion criteria

Criteria for inclusion of articles in the study: patients with a confirmed diagnosis of knee joint osteoarthritis of any severity; interventions — PRP injections (for the treatment group) and HA injections (control group); main outcomes: assessment of pain severity using the WOMAC after six months; secondary outcomes were based on the IKDC, Lekken and VAS. Only randomized controlled clinical trials were selected for analysis.

Exclusion criteria: studies of patients with bilateral knee osteoarthritis, non-randomized studies and publications from which data could not be extracted for analysis.

Selection of studies had four phases:

1. Identification: 192 literature sources were found in electronic databases; four additional publications from other sources were identified; the total number of identified studies was 196.
2. Screening: At this stage, two independent researchers conducted an initial screening of the titles and abstracts of the identified articles to exclude irrelevant publications based on the following criteria: lack of data on targeted interventions, population not relevant to the study topic, results not related to the objectives of the analysis. After removing duplicates, 170 publications remained. All publications were screened based on titles and abstracts. 11 full-text articles met the inclusion criteria; 159 publications were excluded from the study at the screening stage.
3. Final selection: full texts of the articles that passed the initial selection were analyzed for compliance with inclusion and exclusion criteria. In case of disagreement between researchers, the issue was resolved through discussion, and if necessary, a third researcher was involved to make a final decision.

Publications were excluded due to the following reasons: missing WOMAC data at six-month follow-up (n = 2); missing data on total WOMAC score (n = 1); lack of a control group in the study design (n = 2); review articles without original data (n = 2).

4. Outcome: Four studies met all inclusion criteria and were used for quantitative synthesis (meta-analysis).

The study selection process is schematically presented in a PRISMA diagram (Fig. 1).

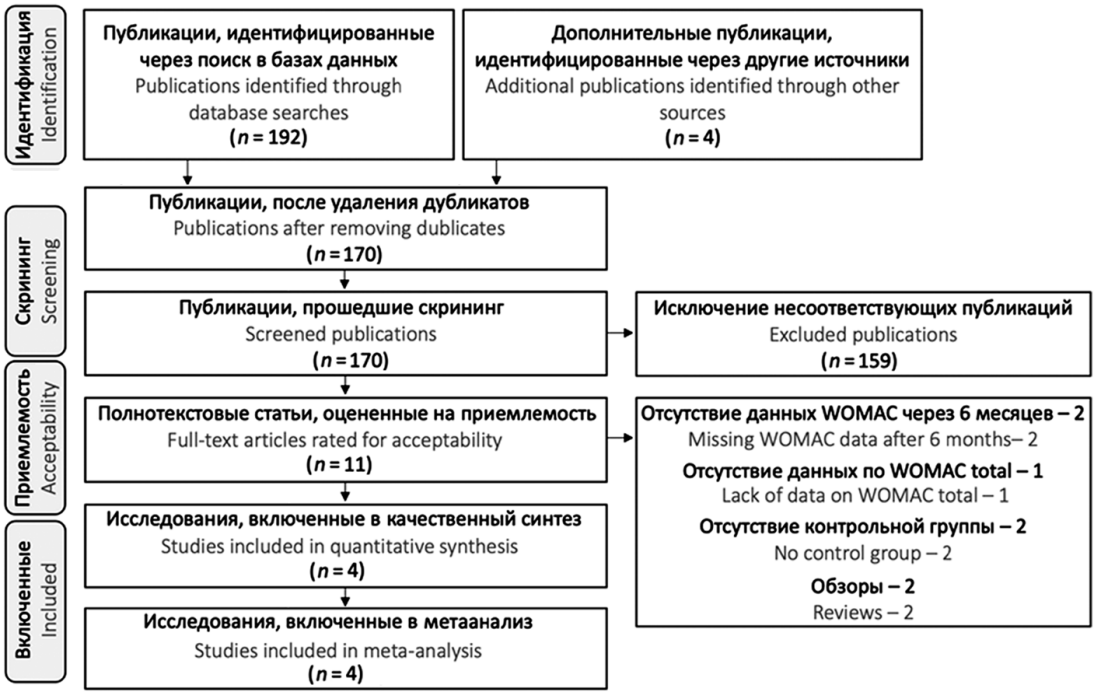

Fig. 1 PRISMA flowchart of the selection process of studies for inclusion in a meta-analysis on the effectiveness of intra-articular injections for knee osteoarthritis management

Data extraction

Data were extracted by two independent investigators using a standardized form including the following data: author, year of publication, country, number of participants in the study, age, gender, body mass index (BMI), classification, duration of follow-up, dosage and number of injections. The WOMAC index was chosen to evaluate the effectiveness of treatment because it is a generally accepted comprehensive indicator that covers data on pain and functional limitations in OA patients. If the study did not provide absolute values, but relative ones (difference in WOMAC values between the study baseline and six months follow-up), the data were recalculated into absolute values to unify the results and ensure their correct generalization. In particular, such an action was performed with the data of the study by Raeissadat et al [9]. Also, to unify the results, all time values measured in months or days are converted to weeks. Other information, such as demographic characteristics and dosages, was necessary to control potential confounding factors and to assess the homogeneity of the study groups.

Risk of bias assessment

Risk of bias assessment was performed independently by two investigators using the Cochrane Risk of Bias Tool. Aspects such as random sequence generation, concealed allocation, blinding of participants and personnel, incomplete outcome data, and publication selectivity were considered. This approach allowed us to minimize bias and increase the reliability of the data obtained.

Statistical analysis

Stata 12.0 (StataCorp., College Station, TX, USA) was used for data analysis. The primary outcomes (pain and function according to the WOMAC) were calculated using the standard mean difference (SMD) with a 95% confidence interval. The SMD was chosen to account for differences in measurement scales between studies, making it the preferred method for meta-analyzing the data from sources that used different assessment scales. Heterogeneity was assessed using the I^2 statistic, with values of 25 %, 50 %, and 75 % interpreted as low, moderate, and high levels of heterogeneity, respectively.

The random-effects method was used for the meta-analysis, which accounts for potential heterogeneity between studies and allows for more general conclusions. A p value of < 0.05 was considered statistically significant, providing sufficient confidence in the analytical results.

RESULTS

The studies included in the meta-analysis covered data on 333 patients treated for knee OA: 164 patients in the PRP group and 169 patients in the HA group.

The meta-analysis showed no statistically significant difference in the baseline pain levels between the PRP and HA groups (Hedges' g = 0.25, standard error = 0.20, 95 % CI: –0.38 – 0.88; p = 0.205). The mean baseline pain level varied due to distorted pain perception depending on the baseline disease stage, as well as on concomitant aggravating pathological conditions. Thus, some publications either did not provide data on the severity of the underlying disease or provided only partial data. Baseline data on the WOMAC pain score for each study are presented in Table 1.

Table 1

Comparison of mean values on the WOMAC pain index before the start of therapy

Author, year, reference number	PRP			HA			Study weight, %	Proportion of cases (95 % CI)
	M	SD	Total of patients	M	SD	Total of patients		
Duymus et al, 2017 [20]	15.40	2	33	16.6	1.10	34	23.15	0.74 [0.25;1.25]
Raeissadat et al, 2021 [9]	9.69	1.30	52	9.44	1.60	49	27.25	0.00 [–0.39;0.39]
Su et al, 2018 [21]	9.57	1.45	25	9.60	1.19	30	21.86	–0.17 [–0.71;0.37]
Wang et al, 2022 [22]	4.2	0.42	54	4.38	0.43	56	27.75	0.42 [0.04;0.80]

Note: M — mean value; SD — standard deviation; CI — confidence interval

Six months after the start of treatment, the mean WOMAC pain score decreased in both the PRP and HA groups. The mean pain score was 4.52 (SD = 1.59) in the PRP group and 4.95 (SD = 2.07) in the HA group. However, the difference in pain score between the groups at six months did not reach statistical significance (p = 0.336). The Hedges'g effect size was 0.26 (95 % CI: -0.61 to 1.14). The results for each study included in the meta-analysis are presented in Table 2.

Table 2

Comparison of mean values on the WOMAC pain index six months after the start of therapy

Author, year, reference number	PRP			HA			Study weight, %	Proportion of cases (95 % CI)
	M	SD	Total of patients	M	SD	Total of patients		
Duymus et al, 2017 [20]	9.4	1.70	33	9.7	1.60	34	24.43	0.18 [–0.30;0.67]
Raeissadat et al, 2021 [9]	4.69	0.90	52	5.64	0.70	49	26.44	0.12 [–0.27;0.51]
Su et al, 2018 [21]	4.7	0.70	25	5.56	0.82	30	22.35	1.10 [0.54;1.70]
Wang et al, 2022 [22]	2.87	0.35	54	2.79	0.38	56	26.78	–0.22 [–0.60;0.16]

Note: M — mean value; SD — standard deviation; CI — confidence interval

The analysis of the results reported in the study by Raeissadat et al revealed that the system for quantitatively assessing treatment effectiveness presented changes in WOMAC pain as negative values relative to the baseline, thus necessitating the use of a data standardization method to ensure comparability of the results [9].

A meta-analysis showed that six months after the start of treatment, the Hedges' effect size for the total WOMAC score increased to 0.79 compared to baseline. However, this effect was not statistically significant ($p = 0.282$).

Egger's test was used to assess potential publication bias, the results of which are presented in Table 3.

Table 3

Egger's test results

Parameter	Value	Standard error	95 % CI
Intercept	11.14	3.48	0.05–22.23
Slope	–2.26	0.77	–4.70–0.18

Note: t-criterion = 3.20; *p*-value = 0.086

Egger's test did not reveal statistically significant publication bias ($p = 0.086$), which is graphically confirmed in Figure 2.

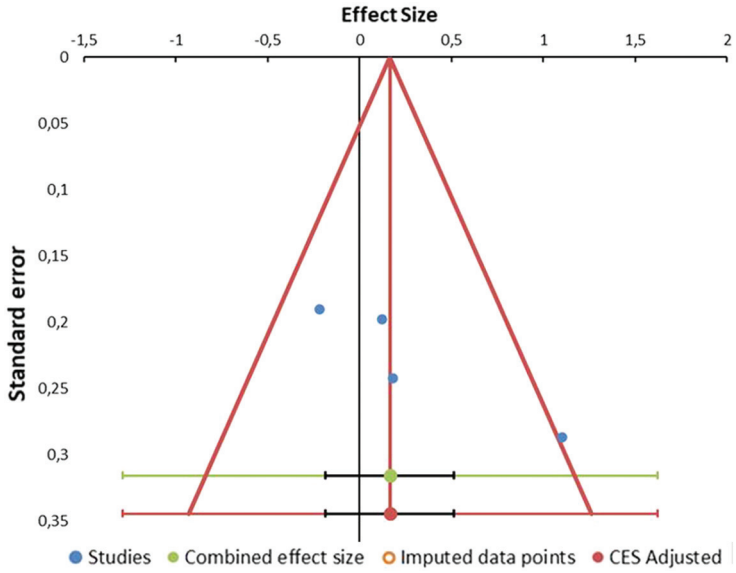

Fig. 2 Funnel chart

A funnel chart is a graphical method for assessing publication bias. Ideally, when there is no publication bias, the points on the graph should be distributed symmetrically around a vertical line through the summary effect size. Funnel plot asymmetry may indicate publication bias. In the present meta-analysis, the funnel plot appears relatively symmetrical, which may indicate the absence of publication bias and correlates with the results of the Egger's test.

DISCUSSION

The objective of this meta-analysis was to evaluate the efficacy of PRP compared with HA in reducing knee OA pain six months after treatment initiation. The findings of 333 patients included into the study from four randomized controlled trials revealed no statistically significant differences between the two methods in the WOMAC pain score, highlighting the need for a more in-depth analysis of factors influencing treatment outcomes. It is possible that factors such as patient characteristics and methodological differences in approaches may have influenced the results, confounding potential differences.

The efficacy of PRP and HA may depend on OA severity: patients with early-stage disease often respond equally well to both treatments, while in advanced stages of OA, the response to PRP and HA injections may differ. Including information on patients with varying degrees of OA severity

in the meta-analysis could have resulted in differences in the efficacy of PRP and HA being obscured. Thus, studies involving patients with early-stage osteoarthritis showed that HA injections are less effective in patients with more severe stages of the disease [15–22].

Individual patient's characteristics such as age, gender, genetic predisposition, comorbidities, lifestyle, and physical activity level can also influence the outcome of PRP and HA [23–28]. Elderly patients often have lower regenerative potential, which decreases the effectiveness of PRP. Men and women respond differently to treatment due to differences in hormonal levels. Genetic predisposition also affects tissue regeneration. Patients with comorbidities such as diabetes may have increased inflammatory responses, which impairs treatment outcomes. Lifestyle, including physical activity level, is also critical: active patients may respond better to therapy due to improved circulation and metabolism, while patients with obesity or diabetes may respond worse due to greater joint inflammation.

The authors of the studies under presented review did not always considered genetic predisposition and individual differences in regenerative potential, which could have impacted the accuracy of the results. It is important to conduct studies with similar patients' characteristics to determine which patients may benefit most from PRP or HA therapy and how treatment can be personalized [29, 30].

The lack of standardization of PRP preparation and administration protocols is also an important factor affecting treatment outcomes. To standardize protocols, it is necessary to determine the optimal centrifugation parameters, platelet concentration, and leukocyte content, as well as uniform methods of PRP administration. The introduction of standardized instructions would reduce variability and improve the comparability of results between studies. The reviewed publications used different methods of PRP preparation and centrifugation, with different platelet and leukocyte concentrations [29–32]. Su et al. [21] used PRP without leukocytes, while other researchers used PRP with different leukocyte contents, which could affect the results, since leukocytes contribute to the development of inflammatory reactions [26]. Also, differences in PRP administration methods (volume and number of injections, intervals between them) could affect the degree of treatment effectiveness [32–34]. The use of different anticoagulants could also affect the biological activity of PRP [19, 24, 36].

The quality of plasma obtained for PRP can vary depending on the equipment and methods used in laboratories. Even small changes in centrifugation speed or time can significantly alter the composition of the final product, which directly impacts treatment efficacy [37]. It is important to standardize not only the primary steps of PRP preparation but also ancillary processes, such as sample collection and processing. The introduction of standardized recommendations for patient preparation can also reduce variability in results. Thus, the use of anticoagulants or other medications prior to the procedure can alter platelet reactivity and thereby affect treatment outcome [38–40].

PRP administration methods depend on the physician's technique, the injection site (intra-articular or periarticular), and even the depth of injection [41]. This is another aspect requiring standardization. The development of detailed recommendations for injection technique could minimize these differences and contribute to increased reproducibility of treatment outcomes. Thus, the need for standardization covers the entire process from plasma preparation to patient interaction and procedure execution, requiring a comprehensive approach and the participation of specialists from various fields such as clinicians, researchers, and rehabilitation specialists.

A limitation of this meta-analysis is a small number of included studies (only four), which lowers statistical power and increases the risk of random errors. The small number of studies increases the likelihood that the results may be due to chance and not reflect the true picture of the effectiveness of treatment methods. To improve statistical reliability, it is necessary to conduct larger studies to ensure a sample sufficient for reliable conclusions. High heterogeneity (I^2 = 79.74 %) indicates significant differences in study design, patient characteristics, and treatment methods used [32, 35–39, 42]: age of participants, OA stage, presence of comorbidities, level of physical activity. Differences in the methods of PRP preparation and administration could also aggravate the heterogeneity of the data. Different approaches to patient selection also contributed: some studies included patients with minimal symptoms, while others included patients with severe osteoarthritis [40–47].

Some studies showed a significant influence on the overall effect [21, 22], likely due to differences in methodology and disease stage of the participants. This highlights the need for sensitivity analyses to identify sources of heterogeneity and their contribution to the meta-analysis results. Heterogeneity may also be related to the methods of assessing treatment effectiveness; the use of different scales for assessing pain and functionality makes it difficult to compare results [48–51]. To address these shortcomings, large, well-designed studies with more homogeneous participant characteristics and standardized treatment protocols are needed.

Potential publication bias should also be considered, as results with positive outcomes are published more often than neutral or negative ones. This leads to a distorted view of the effectiveness of interventions. Registered study protocols and study transparency can help reduce the risk of publication bias and improve the quality of meta-analyses [52]. To increase statistical power and the reliability of results, large multicenter studies are needed to collect more data and provide more reliable conclusions [37, 53–55].

This meta-analysis assessed the treatment effect six months after the start of injection therapy, but longer follow-up (12 months or more) is required to identify more consistent differences between groups. Long-term follow-up would allow us to detect delayed effects that are not evident in the short term, as well as to evaluate the stability of the achieved improvements and potential long-term changes in the cartilage tissue condition. The studies showed that the effect of PRP can last longer than that of HA, especially when followed for more than six months [56–58]. Such studies will help to evaluate possible delayed side effects and changes in cartilage tissue structure and determine whether the beneficial effects can accumulate with repeated injections [38, 47, 58–62].

Repeated courses of therapy can enhance the regenerative effect and improve clinical outcomes. Long-term studies will help better understand how individual factors, such as genetic predisposition and physical activity level, influence the duration and stability of the treatment effect [63–66]. In addition to pain, changes in the cartilage tissue, improvements in joint mobility, and overall quality of life should also be assessed.

To assess potential publication bias in the meta-analysis, the Egger and Begg & Mazumdar tests were used, which revealed no statistically significant bias (p = 0.06 for the Egger test). Trim and Fill analysis also confirmed the stability of the results. However, it is important to remember that these methods have limitations, and their interpretation should be done with caution [41]. Additional approaches are necessary to minimize bias and ensure maximum reliability and robustness of the findings.

Further research should focus on several key aspects. First, it is necessary to examine the impact of osteoarthritis severity on the efficacy of PRP and HA, stratifying patients by severity to develop

more targeted treatment strategies. Second, individual factors (age, gender, body mass index, comorbidities, lifestyle, and genetic predisposition) should be considered to develop personalized treatment approaches [44, 67, 68].

Standardized protocols for PRP preparation and administration are needed to reduce data heterogeneity and more accurately in assessing treatment efficacy. It is important to standardize all steps of the process—from blood collection and processing to centrifugation parameters and administration methods [16]. Standardization should include monitoring of plasma quality, platelet concentration, white blood cell count, and the use of anticoagulants. Recommendations for patient preparation before the procedure can also improve the reproducibility of results.

Finally, large, multicenter studies with long-term follow-up are needed to evaluate the long-term effects of PRP and HA, as well as their impact on functional outcomes and patient quality of life [69–71]. Such studies should aim to identify the benefits of combination therapy and examine the impact of repeated courses of therapy.

Thus, the primary goal of conservative treatment in OA is to stabilize degenerative and inflammatory processes in the joint, which can help prolong joint function and delay the need for total joint arthroplasty [72]. In this regard, multicenter studies will help improve our understanding of the mechanisms of action of PRP and HA and contribute to the development of recommendations aimed at increasing treatment effectiveness and improving the quality of life in knee OA patients.

CONCLUSION

The meta-analysis aimed at a comparative assessment of the effectiveness of PRP and HA of average molecular weight in the treatment of Knee OA patients did not reveal statistically significant differences between the groups of patients in the severity of pain measured with the WOMAC score six months after the start of treatment, which indicates comparable effectiveness of these methods of therapy.

However, it is necessary to consider the limited number of studies included in the analysis, high heterogeneity between them and the lack of standardized protocols for the preparation and administration of PRP. For a more accurate comparative assessment of the effectiveness of PRP and HA, future large and well-designed studies with a long follow-up due to the severity of the disease, patient characteristics and standardized methods for the preparation and administration of PRP are needed.

Conflict of interest *The authors declare no obvious or potential conflicts of interest.*

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Ethical statement *Not required for this type of study*

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