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Evaluating the Effectiveness of Intra-articular Platelet Rich Plasma Injections for the Treatment of Knee Osteoarthritis: A Systematic Review

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Abstract

Introduction: Osteoarthritis (OA) is the most frequently presented joint disorder, and its treatment is often challenging. Current literature has controversial results regarding the efficacy of Platelet Rich Plasma therapy (PRP) when compared to placebo injections. This systematic review investigates the role of intra-articular PRP injections as a recommended treatment option for knee OA with the potential to establish appropriate guidelines for treating physicians.

Method: This review used PUBMED, Cochrane and CINHAL database. A thorough review of literature examining PRP injections as treatment options for knee OA was performed. Two independent reviewers evaluated the studies against inclusion and exclusion criterias. The WOMAC stiffness score, VAS Score, and KOOS score were used to assess efficacy of PRP treatment. Twelve articles met the criteria for inclusion and were analysed in this study.

Results: PRP injections caused a significantly better improvement in WOMAC stiffness score (25.5%), VAS Score (31.7%), and KOOS score (6.2%) after six months of treatment.

Conclusion: This review demonstrated significant improvement in pain relief and stiffness levels in patients with knee OA receiving intra-articular PPR when compared to placebo. Further research is required to establish the optimum dose and duration of treatment with PRP injections for knee OA.

Keywords: *Osteoarthritis (OA), Platelet Rich Plasma therapy (PRP), Knee osteoarthritis (KOA),*
Total knee arthroplasty (TKA)

Summary

What is known about the use of Platelet Rich Plasma and its use in Osteoarthritis?

- Platelet Rich Plasma (PRP) is a concentrate of one's own platelets that is currently being researched for its effect in various fields of medicine.

- Research has found that it can promote and accelerate healing processes as well as relieve pain.

- Knee Osteoarthritis is the inflammation caused by wear and tear causing the cartilage to become rough and the protective surface between the joint to decrease.

What are the new findings in this field?

- Extensive literature has been produced on the role of PRP in treatment of Osteoarthritis. Findings have varied significantly where some studies show improvement in pain reported by patients, increase in range of motion and halting disease progression, while others failed to highlight any significant findings. Further research is required to provide conclusive evidence on the beneficial role of PRP in the management of knee osteoarthritis. This systematic review aims to compile results of available studies looking at the role of PRP in treatment of knee osteoarthritis.

Introduction

Osteoarthritis (OA), also known as Degenerative Joint disease, is one of the most common forms of arthritis (1). The prevalence of symptomatic knee osteoarthritis (KOA) is approximately 10% in men and 13% in women aged 60 years or older (2). Over 30 million people in the USA are affected, accounting for nearly 23% of the adult population (3,4). OA also has significant financial impact, ranking second amongst the most expensive conditions treated in US hospitals in 2013 (5). It is also the most common cause for total hip and knee replacements (6). Obesity, female gender, old age, knee injury, bone density, repetitive joint use, muscle weakness, and joint laxity, significantly contribute to the development of osteoarthritis, particularly in weight-bearing joints (1). Pain secondary to OA is a critical factor when deciding to seek medical attention and is an important antecedent to disability (7). The progressive rise of this disease indicates that OA will have an increasing impact on health care and the economy.

Treatment of KOA is challenging due to the absence of vascular and neural supply in the adult knee cartilage. This causes limited regenerative potential with minimal healing possibility for the joint. The pathophysiology involves a complex mixture of mechanical, molecular, and biochemical interactions. Current treatment aims to reduce pain and slow the disease progression. Overall, treatment goals for KOA target activity adjustments, alleviating pain, and stiffness, improving function, addressing deformities, and delaying or avoiding the need for total knee arthroplasty (TKA).

Platelet-rich plasma (PRP), an autologous mixture of highly concentrated platelets, growth factors and other bioactive compounds, has emerged as a promising treatment option for KOA. The use of PRP was first described in 1997 and ever since, has commonly been used in orthopedic and sports medicine to treat tendon, bone, and ligament injuries (8). The growth factors released by PRP have shown to promote proliferation, enhance cell recruitment, and angiogenesis. This leads to the reduction of critical regulators in the inflammatory process and decreases inflammatory enzyme expression (9–13).

In OA, PRP is seen to affect local and infiltrating cells, especially synovial and endothelial cells, cartilage, and bone cellular components (14,15). The combinatorial effects of PRP make it a relevant choice for the treatment of KOA, especially as a primary analgesic (16). This is due to its ability to enhance the proliferation of osteoblasts, tenocytes and mesenchymal stem cells resulting in reduced pain levels postoperatively (17). Some studies evaluating the effectiveness of intra-articular PRP injections in KOA have shown promising results in terms of improvement of clinical symptoms (17). Another study reflected similar findings in terms of pain, where PRP injections were found to reduce pain in early KOA when compared to normal saline (18). However, other studies have concluded no significant difference in the use of intra-articular PRP versus normal saline when assessing symptoms or structural changes in KOA (19). These discrepancies in literature highlight the mixed views supporting the use of PRP in the treatment of KOA.

Despite the increasing amount of research in this field, vital issues such as evidence on efficacy and standardized dose remain unanswered. This review aims to analyze the role of intra-articular PRP injections as an effective treatment option for management of KOA. The results will help provide conclusive evidence on the use of PRP in KOA while also guiding treatment guidelines and encouraging further research in this discipline.

Methods

We used PUBMED, Cochrane, and CINHAL to identify randomized control trials (RCT) that compare intra articular PRP injections with placebo in the treatment of KOA. Keywords include: PRP, Platelet-Rich Plasma, Plasma therapy, Autologous conditioned plasma, Knee arthritis, Osteoarthritis, Degenerative arthritis, Degenerative joint disease. The inclusion and exclusion criteria are illustrated in Table 1.

The outcome parameters chosen for this review were the Western Ontario and McMaster Universities Arthritis Index (WOMAC) stiffness score, Visual Analogue Scale (VAS) score, and the Knee injury and Osteoarthritis Outcome Score (KOOS) score at 6 months after the initial injection. The WOMAC stiffness score is a scale ranging from 0 to 8, assessing the severity of knee stiffness in the morning and later during the day. Higher scores signify increased joint stiffness (20). The VAS score is a self-reported measurement of acute and chronic pain. Subjects indicate their pain levels on a 10 cm scale ranging from "no pain" at the left end (0 cm) and the "worst pain" at the right end (10 cm) (21). The KOOS score is a 42-item questionnaire assessing the patient's subjective reflection about the health, functionality, and symptoms of their knee. This score consists of 5 subscales that measure pain, symptoms, activities of daily living, sport & recreation, and quality of life. The minimum score is 0 indicating severe knee impairment and the maximum score is 100 which indicates no knee problem (22). The two grading systems are used to assess the severity of KOA; Kellgren-Lawrence and Ahlbäck, however, these were not taken into consideration during our evaluation (23,24).

Table 1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. RCTs looking at the effectiveness of PRP vs placebo injections in treating/managing KOA as the primary aim of the study and only PRP injections are being used. 2. RCT published in last the 10 years (2012-2022). 3. Studies published in English that are free full texts and full texts.	1. Studies where the effectiveness of PRP injections is not primary outcome. 2. Studies looking at PRP injections in conjunction with other treatment modalities (oral medications, steroid injections). 3. Studies that are not RCT. 4. Studies that do not fit the study period (2012-2022). 5. Studies that are unpublished. 6. Published non-English research. 7. Studies evaluating the effectiveness of PRP in joints other than the knee.

The screening process for this review is depicted in Figure 1. The initial screening involved a total of 5707 studies; PUBMED (3424 studies), Cochrane (2245 studies), and CINHAL (38 studies) exported as an endnote format and downloaded into a shared drive. These studies were then exported to Covidence, a primary research screening and extraction software tool that enables extraction of studies based on inclusion and exclusion criteria. All three reviewers voted on the exclusion and inclusion criteria for the study. Duplicate studies were removed, leaving 5501 studies to be screened. Two reviewers independently filtered the literature based on the criteria. Studies with conflicting votes were assigned to a third, independent reviewer for a final decision. Of the 5501 studies, 5299 were excluded leaving 179 studies for full text review. During the second screening cycle, 167 studies were excluded due to irrelevance to the inclusion/exclusion criteria. The screening process yielded a total of 11 studies that were analysed in this review.

The results obtained were evaluated using the Weighted Mean Outcome (WMO) of the included studies. The statistical analyses were conducted by RevMan 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and the results obtained were deemed statistically significant at 2-sided P values <0.05 (25).
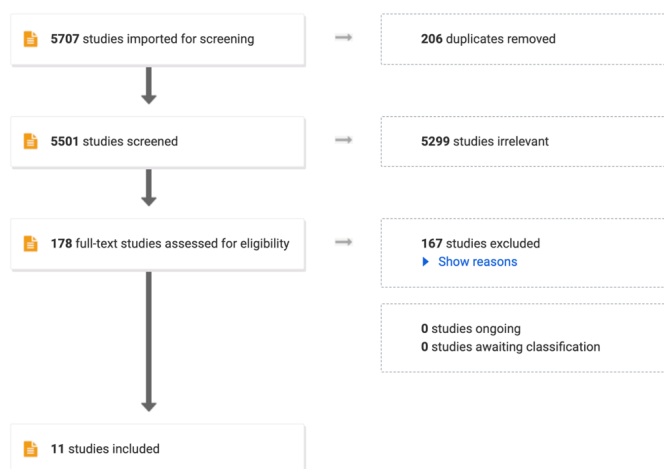
Figure 1: PRISMA diagram.

Patient and Public Involvement

No patient involved

Results

Characteristics of included studies (refer to Table 2)

Studies spanned different countries, with two articles each from India (18,26), Taiwan (27,28) and Australia (19,29). One article each was retrieved from the USA (30), Turkey (31), Pakistan (32), Brazil (33), Spain (34), and China (35).

Males accounted for 38.7 % and females for 61.2%. The sample size varied greatly from 40 to 644 participants. The mean age variation in the sample ranged from 24 to 66.4. BMI of patients varied between 23.98 to 68. The duration of follow up varied between studies, however for the purpose of the review, we analyzed the results at the 6 month follow up. PRP protocols used in the various studies differed in terms of their preparation, centrifugation and injection regime of dosage and intervals. Normal saline was the most common control that was used in most of the included studies except for one study that used corticosteroids as control (34). Ten out of the 14 studies used the Kellgren and Lawrence staging to assess the grade of KOA. Three studies used the Ahlbäck staging.

VAS was the most used outcome in eight of these studies (18,26,29,31–35). In total, the number of patients evaluated in the studies that we reviewed were 1859.

Table 2: Baseline characteristics of patients in the trials included in this systematic review.

Study	Country	Treatment regimen	No. of patients	Male/female	Age (SD)	BMI	Grade of OA (K-L) (I/II/III/IV)
Bennell. K (19)	Australia	PRP	144	59/85	62.2 (6.3)	29 (3.7)	0/69/75/0
		Saline	144	60/84	61.6 (6.6)	29.6 (4.5)	0/72/72/0
Chu.J (35)	China	PRP	322	123/185	53.9 (5.0)	27.5 (3.2)	89/136/83/0
		Saline	322	127,175	54.5 (5.3)	27.9 (3.6)	95/129/78/0
Dório.M (33)	Brazil	PRP	20	1/19	66.4 (5.6)	28.3 (4.1)	0/13/7/0
		Plasma	21	2/19	66.1 (7.5)	28 (3.1)	0/13/8/0
		Saline	21	2/19	62.5 (8.1)	27.6 (3.8)	0/14/7/0
Elik. H (31)	Turkey	PRP	30	1/29	61.30 (7.9)	30.37 (4.47)	2/14/14/0
		Saline	27	3/24	60.19 (6.80)	30.70 (3.97)	3/13/11/0
Ghai.B (26)	India	PRP	20	5/15	49.8 (9.42)	67 (9.56)	Grade 1 and 2
		Saline	20				
Wu. Y (28)	Taiwan	PRP	20	5/15	63.25 (6.84)	24.14 (2.93)	14/6/0/0*
		Saline	20	5/15			14/6/0/0*
Patel. S (18)	India	Single PRP	27	11/16	53.11 (11.5)	26.28 (3.23)	37/11/2/0*
		2 PRP	25	5/20	51.64 (9.22)	25.81 (3.31)	36/10/2/0*
		Saline	23	6/17	53.65 (8.17)	26.21 (2.93)	25/18/3/0*

Jubert. N (34)	Spain	PRP	35	12/23	65.56 (8.6)	31.20 (4.36)	0/0/10/25
		Saline	30	6/24	68 (7.17)	30.98 (4.16)	0/0/17/13
Lewis. E (29)	Australia	Single PRP	47	20/27	55.1 (12.6)	29.3 (6.7)	11/23/0/0
		Multiple PRP	27	9/18	59.4 (8.9)	29.7 (6.1)	8/13/0/0
		Saline	28	12/16	60.1 (9.3)	29.9 (5.5)	8/17/0/0
Qamar. A (32)	Pakistan	PRP	50	17/33	60.03 (4.7)	82.12 (7.6)	0/13/18/19
		Saline	50	20/20	58.7 (3.9)	79.6 (6.7)	0/9/26/15
Smith. P (30)	United stated of America	PRP	30	5/10	53.53 (8.22)	29.53 (6.89)	0/8/7/0
		Saline	15	6/9	46.60 (9.37)	27.47 (4.78)	0/10/5/0

* Ahlbäck score

The weighted mean outcome for each scoring system was calculated using the following formula which was implemented in Microsoft excel (Table 3).

$$A_s = \frac{\sum_{i=1}^{t} m_i \, x \, n_i}{\sum_{i=1}^{t} n_i}$$

- s = the scoring system ϵ {VAS, KOOS, WOMAC}
- A = the weighted average of the s scoring system.
- t = number of studies per score
- i = the study number.
- m = mean score of a single study.
- n= Number of participants per study.

$$A_{KOOS} = \frac{52.9 \, x \, 144 + 32.3 \, x \, 35 + 48.7 \, x \, 47}{144 + 35 + 47} = 48.84$$

E.g., For the PRP pre injection KOOS score:

Table 3: Analysis of results comparing PRP versus the control group (normal saline).

Mean Score	Pre-injection mean score		Post-injection mean score		Mean change in scores		Mean percentage change	
	PRP	Saline	PRP	Saline	PRP	Saline	PRP	Saline
WOMAC (stiffnes)	3.98	3.82	1.94	3.38	2.04	0.44	25.5%	5.5%
VAS	5.02	5.08	1.85	4.16	3.17	0.92	31.7	9.2%
KOOS	48.84	61.35	54.62	62.31	6.22	-0.96	6.2%	1.0%

Mean Change in Score = Pre-injection Score - Post-injection score

$$Percentage\ Change = \frac{Mean\ Change\ in\ Score}{Maximum\ Score} \times 100$$

Wherein the maximum score for the WOMAC is 8, VAS is 10 and KOOS is 100.

The results demonstrated that PRP injections caused significantly better improvement in the WOMAC stiffness score, VAS score, and KOOS scores when compared to the placebo injection after 6 months of treatment. This suggests that knee PRP injections are superior to placebo injections in the treatment of KOA.

Western Ontario and McMaster Universities Arthritis Index

A total of seven studies reported the data using the WOMAC stiffness score (18,26,28,30,31,33,35). The mean WOMAC stiffness score for the PRP groups decreased by 2.04, whereas a decrease of 0.44 is seen in the placebo groups. This equates to a 25.5% improvement in knee stiffness in the PRP groups compared to the saline groups, which saw a 5.5% improvement in knee stiffness. Most notably Smith. P and Elik. H demonstrated a significant decrease in WOMAC stiffness score in their PRP groups by 3 and 2.7 respectively. (Figure 2)
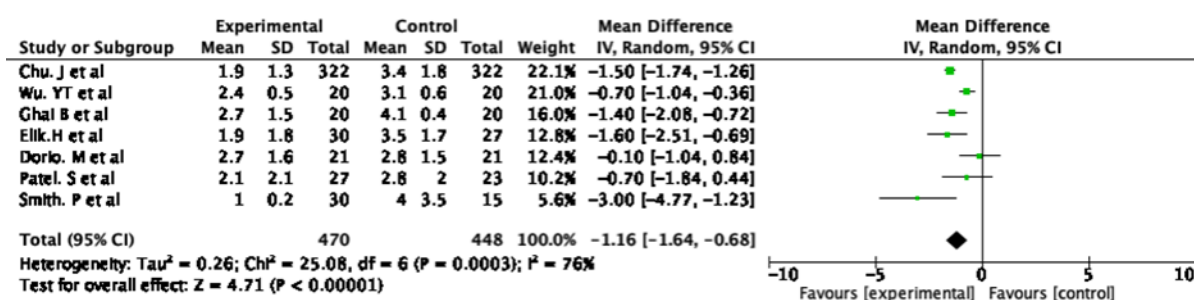

Figure 2: *Forest plots evaluating pain relief pre and post the PRP injection. WOMAC score.*

Visual Analog Scale (VAS) score

A total of eight studies reported the VAS Score (18,26,29,31–35). The mean VAS score for the PRP groups decreased by 3.17, whereas a decrease of 0.92 is seen in the placebo groups. This equates to a 31.7% reduction in knee pain in the PRP groups, compared to the saline groups which saw a 9.2% reduction in knee pain. Most notably Jubert. N, Chu. J, and Ghai demonstrated the most profound improvements in pain in their PRP groups with a decrease in VAS score of 3.7, 3.5, and 3.5 respectively. (Figure 3)
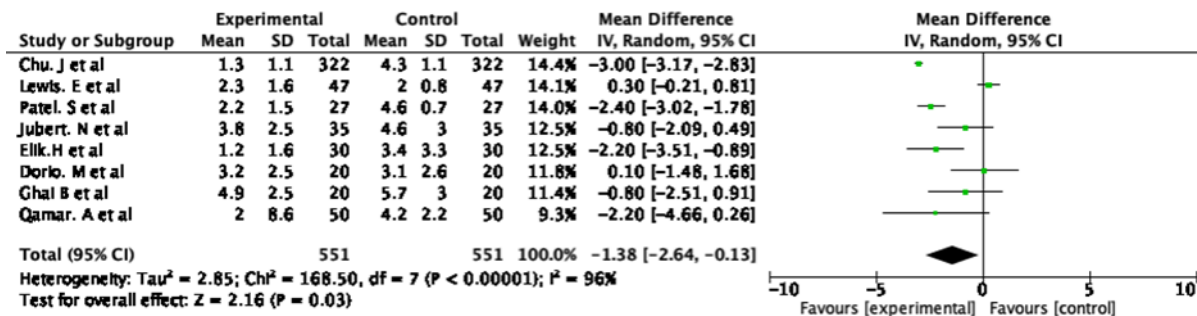
Figure 3: *Forest plots evaluating pain relief pre and post the PRP injection. (VAS score)*

Knee Injury and Osteoarthritis Outcome Score (KOOS)

A total of three studies reported the KOOS score (19,29,34). The mean KOOS score for the PRP group increased by 6.2, whereas a decrease of 0.96 was observed in the saline group, equating to a 6.2% net improvement in treatment outcome in the PRP group, compared to the saline group which saw a 1% net improvement in treatment outcome. Most notably Jubert. N et al demonstrated the most significant net improvement in knee functionality in his PRP group with an increase of 22.6 in KOOS score. However, as this study had the lowest sample size, it had the least weighted impact on the KOOS score. This will be addressed further in the discussion section. (Figure 4)
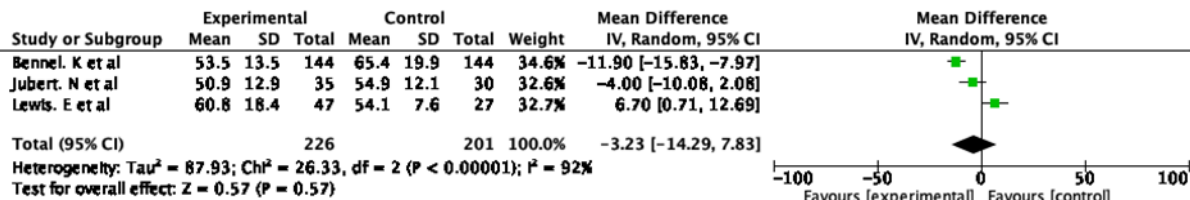

Figure 4: *Forest plots evaluating pain relief pre and post the PRP injection. (KOOS score)*

Risk of bias

In order to evaluate the methodological quality of the analyzed RCTs, the modified Jaded scales were used. The scales consisted of four domains: randomization, concealment of allocation, double blind, attrition rates and dropouts. The scale has a score of 0 (very poor) to 7 (rigorous), where higher scores reflect better quality studies. To reduce selection bias, two separate authors independently reviewed the studies and a third reviewer resolved any generated conflicts. The results are demonstrated in (Figure 5 and Figure 6).
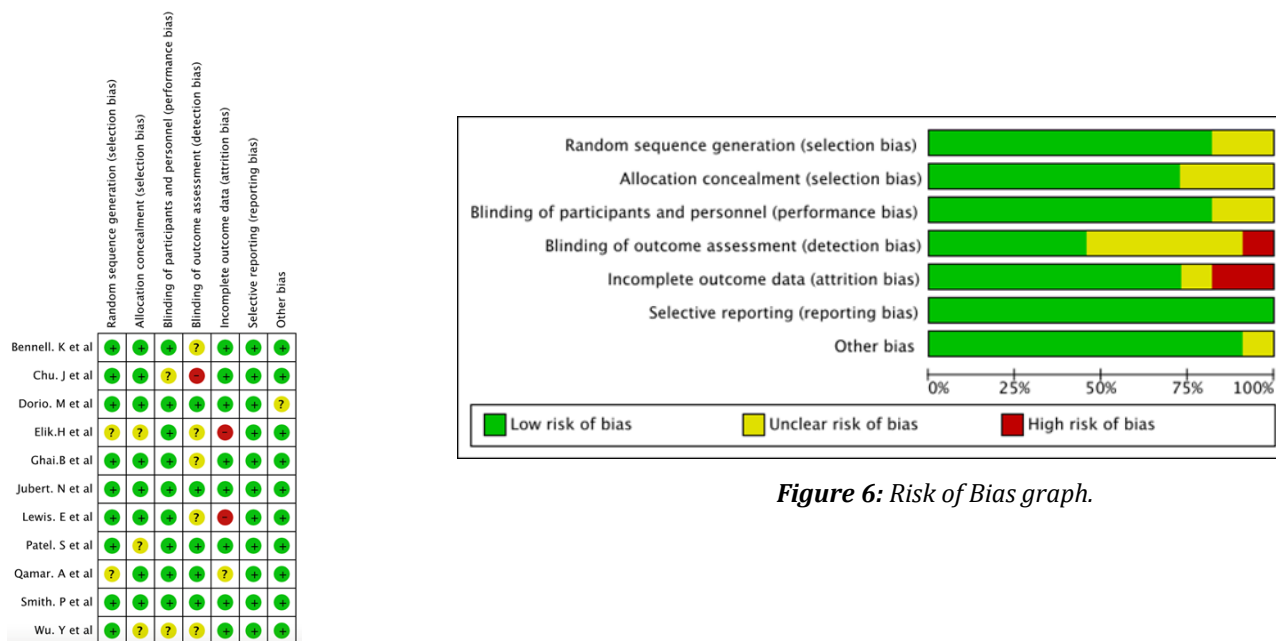

Figure 6: *Risk of Bias graph.*

Figure 5: *Results of the quality evaluation. Green (criterion satisfied), Yellow (unclear satisfaction of criterion), Red (criterion not met). Risk of bias summary.*

Discussion

The utility of PRP has gradually become common practice across various fields in medicine but its role in the treatment of OA is most widely reported. This systematic review investigated the effects of intra-articular PRP injections in the treatment of KOA. The summarized data clearly indicated a significant improvement in the VAS scores, WOMAC scores and KOOS scores compared to the use of normal saline.

Our review highlighted, maintained effectiveness at 6 months after a single injection. The WOMAC score indicated that there was a better outcome with PRP in six (18,26,30,31,33,35) out of the seven studies that used this scale for evaluation of stiffness. The VAS scores had a better outcome with PRP in eight out of the nine studies. All the studies that used the KOOS scoring system indicated a better overall improvement with PRP (19,29,34).

Prior studies have indicated that PRP demonstrates a preferred line of treatment for OA (27,36,37). However, a review of other studies does not demonstrate improved clinical outcomes of PRP; thereby indicating that the use of PRP in the treatment of KOA remains disputed (19,38). A RCT by Kim. B et al, reported that the overall change in pain and stiffness at 12 months was not significant as compared to the saline placebo (19). Another significant clinical trial carried out by Moretti. L et al concluded that although there was noteworthy pain reduction in people who were diagnosed with KOA, there were no radiographic changes reflected (39). Recent studies have also indicated an increased efficacy of PRP in Ahlbäck grades I and II as compared to more severe OA (40).

The review highlighted a significant variation across gender distribution, where women accounted for a greater proportion of the sample size in each RCT. This distribution reflects common findings reflected in current literature where OA is more common in women (41–43). Some studies have even highlighted a variation in pathophysiology of OA in women, where different parts of the knees are affected disproportionately (44,45). Additionally, women present in advanced stages, have varying patterns of gait and report increased pain and associated dysfunction in daily activities (44–49). These findings may alter the reproducibility of PRP intervention in cases of male patients. However further evidence is required to support this claim.

This study includes a holistic review of clinical trials performed by two independent reviewers. The strengths of this study include analysis of prospective trials using evidence-based techniques and validated quality assessment tools. The use of standard outcome measurements such the WOMAC, VAS and KOOS across studies was suited for evaluation and comparison. These scoring scales allowed for effective evaluation various treatment outcomes from predominantly subjective perspectives. The WOMAC score allowed for assessment the role of PRP intervention when assessing joint stiffness, a valuable factor when predicting quality of life (20). The VAS score helped assessment of acuity and chronicity of subjective pain (21). The KOOS scale provided broader outcomes for assessment (22). Collectively, these three grading scales provided a holistic view of the overall improvement of KOA when using intra-articular PRP. Additionally, strict adherence to rigorous methodology, Covidence and PRISMA guidelines allowed the results to be both reliable, accurate and reproducible.

Although the systematic review yielded significant findings, our study was met with limitations. The RCTs evaluated varied in terms of the duration of KOA diagnosis as well as patient age. The preparation, centrifugation, leukocyte concentration and dosage of PRP may also have potentially considerable effects on efficacy and outcomes in treating KOA. Furthermore, this review evaluated symptoms at the 6 months interval. A shorter interval between follow-ups would have provided more accurate assessment of treatment progression, while long term analysis would have enabled us to establish the overall prognosis of each intervention. None of the studies reviewed collected radiographic data at follow-up. This data would have been useful in objective assessment of the pathological response. Moreover, the included studies did not indicate the aggregate of patients who did not benefit from PRP and subsequently required a TKA. Mean age, BMI and comorbidities were not accounted for during analysis. Our review evaluated the effects of PRP compared to normal saline, a physiological solution with minimal, if any, treatment benefits. Corticosteroids or hyaluronic acid serve as more clinically relevant comparisons that may offer more competitive treatment outcomes. Although our results correlate with earlier studies (50,51), a direct comparison cannot be established due to variation in PRP dosage and follow up intervals. Additionally, a few of the included studies (19,35) had large sample sizes, skewing the overall results.

PRP is a new field in regenerative medicine and therefore warrants further research to assess its clinical efficacy in arthritis associated conditions. Studies should evaluate the effect of different PRP formulations and establish the optimum dosage to improve the prognosis of KOA. Moreover, greater emphasis should be placed on research that establishes more reliable criteria to enhance the prognosis of KOA in clinical practice.

Conclusion

This systematic review concluded that when comparing intra-articular PRP to placebo in treatment of KOA, significant reduction in pain and decrease in stiffness levels were illustrated when using the WOMAC, VAS and KOOS scores.

Contributorship statement

- Joanna Thomas – Evaluating eligibility of studies, writing of original draft, review, analysis of results and editing.

- Jayaditya Patil - Evaluating eligibility of studies, writing of original draft, review, and editing.

- Wessam Dallal - Evaluating eligibility of studies, writing of original draft, review, editing, analysis and interpretation of results.

- Anastasia Athanasiou - Evaluating eligibility of studies, review, editing, and interpretation of results.

All authors reviewed the results and approved the final version of the manuscript.

Competing interests

The authors declare that there are no conflicts of interest.

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Data sharing statement

This material is the authors' own original work, which has not been previously submitted for publication elsewhere.

Ethical approval statement

This research is a systematic review that did not require ethics approval as it did not use human or animal subjects.

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