Effectiveness of Different Types of Intraarticular Injections for the Knee Osteoarthritis; a Systemic Review

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Abstract

Background: Osteoarthritis (OA) is most prevalent type of arthritis, which significantly affects the patient's mobility complex. **The aim to** evaluate the evidence from the literature regarding the superiority of platelet-rich plasma (PRP), hyaluronic acid (HA), or corticosteroids (CS) over each other's. **Methods**: An electronic search was conducted between January 2010 to March 2021 in different databases; PubMed, SCOPUS, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). The articles included were the randomized, nonrandomized trials that were published in English with full text available. **Results**: From a total 6912 screened citations, thirty studies met our inclusion criteria with a total 3303 cases. Most on included studies (N=13) compared platelet-rich plasma to hyaluronic acid and six studies compared hyaluronic acid to cortico-steroids, four studies compared hyaluronic acid to hyaluronic acid + cortico-steroids , one study compared platelet-rich plasma to cortico-steroids and another study compared platelet-rich plasma to hyaluronic acid, cortico-steroids. Regarding platelet-rich plasma compared to hyaluronic acid, evidence favored platelet-rich plasma over hyaluronic acid in majority of studies, the effect of platelet-rich plasma lasted longer up to 12 months, and it might be extended to 18 months if intra-osseous injection would be considered. On the other hand, hyaluronic acid should moderate efficacy over cortico-steroids injection but its effects survived only up to six months. **Conclusion;** platelet-rich plasma is most effective type on the long term and it provides pain relief up to 12 months especially in cases with low grades osteoarthritis and young age patients.

Keywords: Intraarticular; Injections; Knee; Osteoarthritis

Introduction

Pharmacological treatments are widely recommended in orthopedic international guidelines for management of osteoarthritis. However, the use of intra-articular therapies of diverse active drugs remains controversial (1).

Osteoarthritis is a complex "whole joint" disease pursued by inflammatory mediators, rather than purely a process of "wear and tear". Probably a polygenic disease may be affected by environmental factors (2).

Old age, female gender, overweight and obesity, repeated knee injuries, repetitive use of knee, bone density, muscle weakness, and joint laxity are associated with the progression of osteoarthritis (3).

Multifactorial etiopathogenesis that is characterized by the gradual loss of articular cartilage, osteophyte formation, subchondral bone remodeling, and inflammation of the joint. Besides cartilage degradation, synovitis, subchondral bone remodeling, degeneration of ligaments and menisci, and hypertrophy of the joint capsule take parts in the pathogenesis. Pain is the hallmark symptom of osteoarthritis (2). Osteoarthritis is a major source of disability owing to pain and loss of function. It is the most common form of joint disease and among the top 10 causes of disability worldwide. For the knee osteoarthritis, various conservative treatment modalities are recommended by clinical guidelines (2).

The non-pharmacological modalities of treatment are patient education and self-management, exercises, weight reduction, walking supports (crutches), bracing, shoe and insoles modification, local cooling/heating, acupuncture, and electromagnetic therapy (3).

Pharmacologic therapies can be summarized as paracetamol, non-steroidal anti-inflammatory drugs, opioids, and slow-acting drugs (glucosamine and chondroitin sulfate). If orally administered drugs are ineffective, intraarticular injection (corticosteroids, viscosupplements, and blood-derived products is the last non-operative modality that can be preferred (1).

Intra-articular corticosteroid injections provide short-term reduction in osteoarthritis pain and can be considered as an adjunct to core treatment for the relief of moderate to severe pain in people with osteoarthritis (4).

Intra-articular hyaluronic acid injections might have efficacy and might provide pain

reduction in mild osteoarthritis of knee up to 24 wk. However, for hyaluronic injections, the cost-effectiveness is an important concern that patients must be informed about the efficacy of these preparations. Although more high-quality evidence is needed, recent studies indicate that intra-articular platelet rich plasma (PRP) injections are promising for relieving pain, improving knee function and quality of life, especially in younger patients, and in moderate to severe osteoarthritis cases. The major contraindication for intra-articular injections is septic arthritis. In addition, in the presence of overlying soft tissue infection (5).

The purpose of this work was to conduct a systematic review study from former available studies to compare between effectiveness of different methods of intra-articular injections (cortico-steroids – hyaluronic acids – Platelet rich plasma) for knee osteoarthritis.

Materials and methods

This systematic review was prepared with a careful following of the Cochrane Handbook for Systematic Reviews of Interventions. This review also adhered to The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines during the design of our study.

Literature search

A literature search was conducted between January 2010 till March 2021 using PubMed, Scopus, Web of Science, and Cochrane Library. A search was performed for all published articles that evaluated different types of Intra-articular injections for the knee osteoarthritis.

- Search done for article title, abstract, keywords using the following keywords:
- “Knee osteoarthritis” , “osteoarthritis” , “knee” , “hyaluronic acid" , "HA” , “platelet-rich plasma" , "PRP” , "corticosteroids" , "steroids" , "CS".
- These keywords was used along with “OR” and “AND” operators as following: (“Knee osteoarthritis” OR “osteoarthritis” OR “knee”) AND (“hyaluronic acid" OR "HA” OR “platelet-rich plasma" OR "PRP” OR "corticosteroids" OR "steroids" OR "CS")

The "related articles" function was used to expand the search from each relevant study identified. Bibliographies of retrieved papers were further screened for any additional

eligible studies. Search was done for articles that were included in previous related systematic reviews. The identified citations were retrieved using Endnote X8 software package (Thompson Reuter, USA).

Eligibility criteria

Included studies that met following inclusion criteria:

1. **Population**: patients with knee osteoarthritis.
2. **Intervention**: Platelet-rich plasma
3. **Comparator**: Hyaluronic acid , Corticosteroids
4. **Outcome parameters**: safety and efficacy outcomes.
5. **Study design**: This search was limited to randomized clinical trials (RCTs) as they are the gold standard in assessment of evidence form the literature.

Animal studies, reviews, book chapters, thesis, editorial letters and papers with overlapped dataset, were excluded. Eligibility screening was conducted in a two step-wise manner (title/abstract screening and full-text screening). Two reviewers independently according to the predetermined criteria did each step.

There were no restrictions on language, race, sex, or age. The duplicated articles were removed primarily using Endnote X8 program (Thompson Reuter, USA) and manually using titles and abstracts screening

Data extraction

Data were extracted by two independent authors and revised by another two independent authors. Extracted the characteristics of each study as following: first author, Number of patients, gender, and mean age, BMI, grade of osteoarthritis and mean follow-up, Additionally extracted the following scores; Western Ontario and McMaster Universities Arthritis Index C (WOMAC), Visual analogue scale (VAS), Knee injury and Osteoarthritis Outcome Score (KOOS), Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society (OMERAT-OSARSI responders) and Lequesne index .

Results

We obtained 4,403 articles from PubMed, 3,334 articles from Scopus, 1,976 articles from Cochrane library and 4,126 from web of science. 8393 duplicated articles were removed using Endnote X8 program (Thompson Reuter, USA), 5,446 articles manually underwent titles and abstracts

screening and 398 articled underwent full-text review as shown **(Figure 1)**. Twenty-six studies finally met with inclusion criteria.

Characteristics of included studies

Twenty-six studies were identified that evaluated different types of Intra-articular injections for the knee osteoarthritis with a total 3303 cases. Mean age of patients across the studies ranged between 50 and 70 years. Thirteen studies compared Platelet-rich plasma to Hyaluronic acid , six studies compared Hyaluronic acid to Corticosteroids , four studies compared Hyaluronic to Hyaluronic acid plus Corticosteroids , one study compared Platelet-rich plasma to Corticosteroids and another study compared Platelet-rich plasma to Hyaluronic acid , Corticosteroids**..**

Outcomes

Western Ontario and McMaster Universities Arthritis Index C (WOMAC)

Pain subscale: six studies compared platelet-rich plasma to Hyaluronic acid, two studies compared Hyaluronic acid to cortico-steroids and three studies compared Hyaluronic acid to cortico-steroids + Hyaluronic acid. Three studies showed platelet-rich plasma had significantly lower pain score than Hyaluronic acid**.** while the other three showed there was no significant difference between platelet-rich plasma and Hyaluronic acid. One study showed that Hyaluronic acid had better pain control than cortico-steroids, while the other study showed there was no significant difference between them**.** All three studies were consistent that there was no significant difference between Hyaluronic acid and cortico-steroids + Hyaluronic acid. **Table 1.**

Stiffness subscale: five studies compared PRP to HA, two studies compared HA to CS and one study compared HA to CS+HA. Three studies showed PRP had significantly lower stiffness score than HA, while the other two showed there was no significant difference between PRP and HA. One study showed that HA lowered knee stiffness than CS, while the other study showed there was no significant difference between them, There was no significant difference between HA and CS+HA**, Table 2.**

Physical Function subscale: five studies compared PRP to HA, two studies compared HA to CS and one study compared HA to CS+HA. Three studies showed there was

significant difference between PRP and HA regarding physical function, while the other two showed there was no significant difference. One study showed that HA had favorable physical function knee than CS, while the other study showed there was no significant difference between them **.** There was no significant difference between HA and CS+HA **, Table 3.**

Total score: five studies compared PRP to HA, two studies compared HA to CS and two studies compared HA to CS+HA. Three studies showed PRP had lower WOMAC score than HA, while the other two showed there was no significant difference **.** One study showed that HA had more decrease in WOMAC score CS **,** while the other study showed there was no significant difference between them **.** There was no significant difference between HA and CS+HA. **Table 4.**

Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society and Health Assessment (OMERAT-OSARSI responders)

Two studies compared PRP to HA, one study compared HA to CS and one study compared HA to CS+HA. One study reported higher responders in PRP than HA **,** while the other study showed there was no significant difference between PRP and HA. Similarly, one study reported higher responders in HA than CS, while the other study showed there was no significant difference between them **.** There was no significant difference between HA and CS+HA**. Table 5**.

Lequesne index

Two studies compared PRP to HA, one study compared HA to CS+HA. One study reported lower lequesne index in PRP than HA, while the other study showed there was no significant difference between PRP and HA**.** There was no significant difference between HA and CS+HA**. Table 6.**

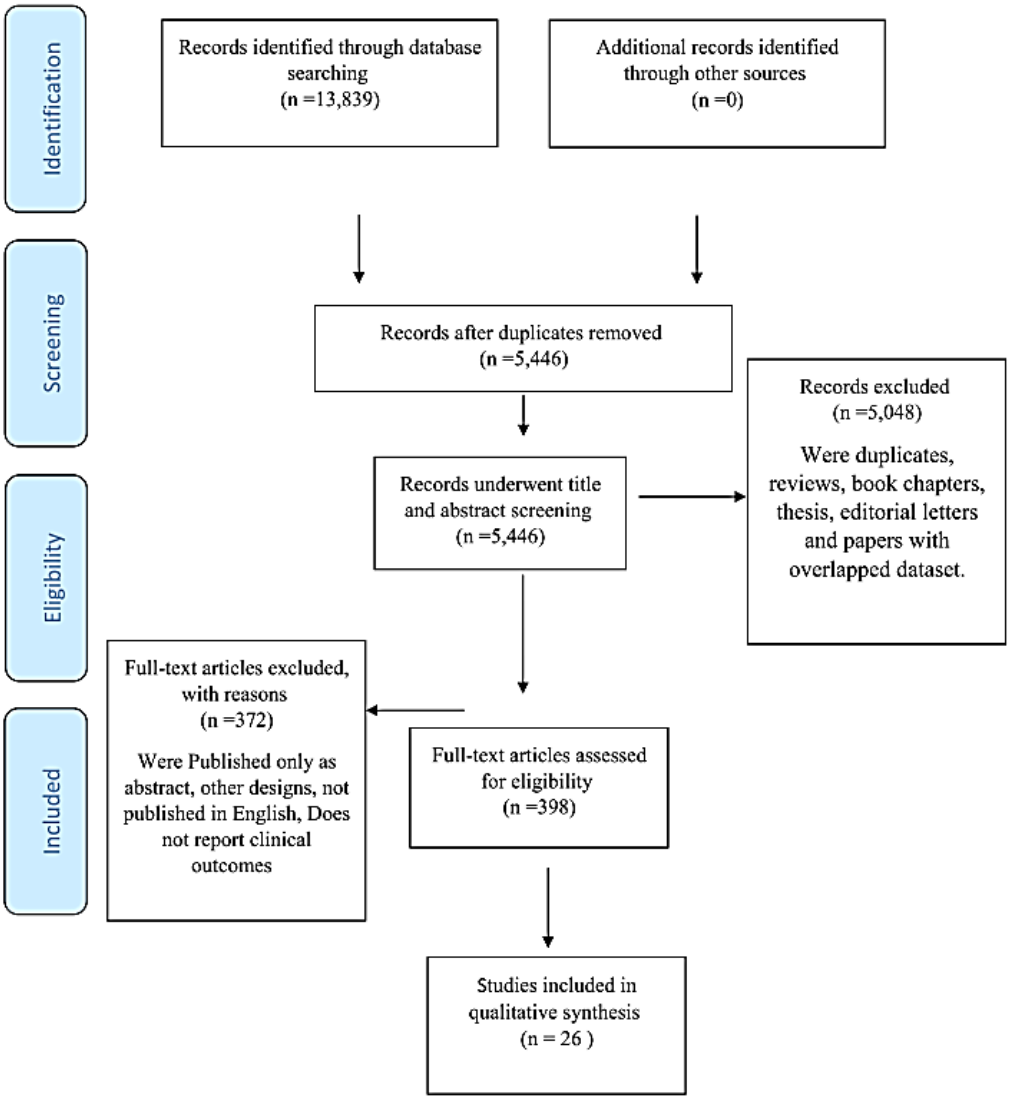

Figure 1: PRISMA flow diagram showing process of studies selection

Table 1: WOMAC outcome (Pain subscale).

Study ID	Baseline			Follow up		
	PRP	HA	P value	PRP	HA	P value
Raeissadat et al.,(10)	8.46 (4.17)	6.91 (3.82)	0.03	4.03 (3.36)	5.08 (3.71)	0.0001
Sánchez et al., (11)	40.4 16	38.4 5.6	0.417	24.1 (15.5)	26.9(15.8)	0.265
Duymus et al., (12)	15.4 ± 2.0	16.6 ± 1.1	N.S	11.4 ± 2.4	14.2 ± 1.1	<0.001
Vaquerizo et al., (13)	9.6 (2.5)	10.2 (3.5)	0.373	6.3 (3.3)	10.7 (3.7)	<0 .001
Cole et al., (14)	7.00 ± 0.53	7.52 ± 0.58	N.S	3.02 ± 0.48	4.00 ± 0.60	N.S
Su et al., (15)	9.57 ± 1.45	9.60 ± 1.19	N.S	8.57 ± 0.50	8.32 ± 0.63	N.S
Study ID	CS	HA	P value	CS	HA	P value
Leighton et al., (7)				favored HA over CS		
Askari et al., (6)	13.21 (3.56)	13.9 (4.37)	0.332	12.6 (3.69)	13.11 (4.24)	0.471
Study ID	HA	CS+HA	P value	HA	CS+HA	P value
Ertürk et al., (16)	12.9 ± 1.0	13.0 ± 1.5	N.S	9.9 ± 1.6	9.5 ± 1.2	N.S
Hangody et al., (17)	61.0 ± 11.7	58.9 ± 12.3	0.22	42.4 ± 18.7	39.5 ± 22.8	0.22
Petrella et al., (18)	68.1	69.4	N.S	38	35	N.S

WOMAC: Western Ontario and McMaster Universities Arthritis Index C, PRP: Platelet-rich plasma, HA: Hyaluronic acid , CS: Corticosteroids , n.s : not significant.

Table 2: WOMAC outcome (Stiffness subscale).

Study ID	**Basaline**			**Follow up**		
	PRP	**HA**	**P value**	**PRP**	**HA**	**P value**
Raeissadat et al.,(6)	2.2 (1.76)	1.88 (1.72)	0.179	1.19 (1.4)	2.14 (1.66)	0.0001
Sánchez et al., (7)	41.8 17.3	38.5 18.3	0.233	25.2(15.4)	25.5(17.9)	0.901
Duymus et al., (8)	6.1 ± 0.9	6.0 ± 0.8	N.S	4.7 ± 1.2	5.4 ± 0.7	<0.001
Vaquerizo et al., (9)	3.7 (1.7)	4 (2)	0.102	2.6 (1.4)	4.7 (2)	< .001
Su et al., (11)	4.63 ± 0.56	4.72 ± 0.79	N.S	4.07 ± 0.69	4.24 ± 0.66	N.S
Study ID	CS	HA	P value	CS	HA	P value
Leighton et al., (12)				favoured HA over CS		
Askari et al., (13)	4.35 (2.69)	4.71 (2.9)	0.475	4.44 (2.63)	4.29 (2.88)	0.762
Study ID	HA	CS+HA	P value	HA	CS+HA	P value
Petrella et al., (18)	70.5	70.3	N.S	46	41	N.S

WOMAC: Western Ontario and McMaster Universities Arthritis Index C, PRP: Platelet-rich plasma, HA: Hyaluronic acid, CS: Corticosteroids , n.s : not significant.

Table 3: WOMAC outcome (Physical Function subscale).

Study ID	Baseline			Follow up		
	PRP	**HA**	**P value**	**PRP**	**HA**	**P value**
Raeissadat et al.,(6)	28.91 (12.63)	19.88 (12.32)	0.001	13.19 (10.39)	19.51 (11.9)	0.0001
Sánchez et al., (7)	39.6 16.3	38.8 17.4	0.755	24.8(15.9)	25.9(17.2)	0.682
Duymus et al., (8)	54.5 ± 6.7	54.3 ± 1.8	N.S	38.6 ± 7.7	49.6 ± 3.3	<0.001
Vaquerizo et al., (9)	32.6 (9.9)	36.7 (13.7)	0.382	21.9 (11.3)	38.9 (14.2)	< .001
Su et al., (11)	36.30 ± 1.26	35.56 ± 1.71	N.S	33.63 ± 2.75	35.84 ± 2.90	N.S
Study ID	CS	HA	P value	CS	HA	P value
Leighton et al., (12)				favoured HA over CS		
Askari et al., (13)	35.98 (11.36)	35.9 (12.38)	0.97	33.29 (11.03)	33.54 (12.69)	0.907
Study ID	HA	CS+HA	P value	HA	CS+HA	P value
Petrella et al., (18)	66.2	65.1	N.S	33	35	N.S

WOMAC: Western Ontario and McMaster Universities Arthritis Index C, PRP: Platelet-rich plasma, HA: Hyaluronic acid , CS: Corticosteroids, n.s : not significant.

Table 4: WOMAC outcome (Total scale).

Study ID	Baseline			Follow up		
	PRP	**HA**	**P value**	**PRP**	**HA**	**P value**
Raeissadat et al.,(6)	76.9 (9.5)	75.4 (10.7).	0.557	36.5 (17.9)	65.1 (10.6)	<0.001
Sánchez et al., (7)	121.8 44.4	115.6 45.1	0.378	74(42.7)	78.3(48.1)	0.561
Duymus et al., (8)	76.1 ± 9.4	77.0 ± 2.5	N.S	54.9±10.8	69.3±4.3	<0.001
Vaquerizo et al., (9)	45.9 (12.7)	50.8 (18.4)	0.137	30.8 (15.5)	54.2 (19.2)	< .001
Su et al., (11)	50.17 ± 1.60	49.88 ± 1.54	N.S	48.07 ± 1.9	46.88 ± 3.8	N.S
Study ID	CS	HA	P value	CS	HA	P value
Bisicchia et al., (19)	45.0 ± 10.1	41.4 ± 15.1	0.14	42.3 ± 7.5	39.6 ± 17.9	0.28
Tammachote et al., (8)	39 ± 16	43 ± 16	<0.0001	21 ± 19	21 ± 15	<0.0001
Study ID	HA	CS+HA	P value	HA	CS+HA	P value
Campos et al., (20)	50 (16)	55 (18)	S	37 (19)	38 (17)	N.S
Ertürk et al., (16)	60.1 ± 6.3	62.0 ± 6.1	N.S	44.5 ± 7.4	43.0 ± 5.9	N.S

WOMAC: Western Ontario and McMaster Universities Arthritis Index C, PRP: Platelet-rich plasma, HA: Hyaluronic acid, CS: Corticosteroids n.s : not significant

Table 5: OMERAT-OSARSI responders N (%).

Study ID	PRP	HA	P value
Sánchez et al., (11)	47 (52.8%)	43 (49.4%)	0.653
Vaquerizo et al., (13)	40 (83%)	13 (27%)	< .001
Study ID	CS	HA	P value
Housman et al., (21)	66 (50%)	73 (57%)	N.S
Leighton et al., (7)	52%	62.8%	0.02
Study ID	HA	CS+HA	P value
Petrella et al., (18)	22 (69%)	22 (65%)	N.S

OMERAT-OSARSI : Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society and Health Assessment

Table (6): Lequesne index.

Study ID	**Basaline**			**Follow up**		
	PRP	**HA**	**P value**	**PRP**	**HA**	**P value**
Sánchez et al., (11)	9.5 3.0	9.1 3.2	0.408	5.2(3.4)	5.4(3.3)	0.714
Vaquerizo et al., (13)	12.8 (3.8)	13.1 (38)	0.738	8.9 (3.7)	14.4 (3.8)	< 0.001
Study ID	HA	CS+HA	P value	HA	CS+HA	P value
Campos et al., (20)	13 (3.8)	14 (4.1)	N.S.	10 (4.2)	11 (3.7)	N.S.

PRP: Platelet-rich plasma, HA: Hyaluronic acid, CS: Corticosteroids, N.S: not significant

Discussion

The current study was conducted to comprehensively evaluate the evidence from the literature regarding whether is one of the intra-articular injections is superior to other types in order to allow the surgeon to take a decision what is the best injection could be used.

In this study, cortico-steroids was compared to Hyaluronic acid in six studies. Despite that majority of studies reported similar efficacy for both Hyaluronic acid and cortico-steroids, Hyaluronic acid seems to have additional benefits over cortico-steroids.

It was reported that patients 3 injection of Hyaluronic acid compared two injection of cortico-steroids in order to achieve similar outcome (6). Leighton et al reported decline in the effect of cortico-steroids after 6 months while Hyaluronic acid maintained its effect (7). Though, both cortico-steroids and Hyaluronic acid were not able to sustain their effect after one year.

Similarly**,** it was reported cortico-steroids had better pain control in the first two weeks following injection (8). This may due to authors used lidocaine with cortico-steroids, which might increase the early pain-relieving effect.

The reason for superior results in hyaluronic acid group may be due to that, patients whom were recruited in the studies have less pain and dysfunction at baseline**.** Hyaluronic acid injection therapy may have protective effects on the articular cartilage by increasing the Hyaluronic acid concentration in synovial fluid, as well as inhibitory effects on the catabolism of articular cartilage by reducing the MMP-9 concentration. (9).

Conclusion

It seems that platelet-rich plasma is most effective type on the long term and it provides pain relief up to 12 months especially in cases with low grades osteoarthritis and young age patients. Additionally, hyaluronic acid and cortico-steroids had comparable results but cortico-steroids was effective in achieving short term pain relief while hyaluronic acid had prolonged effect than cortico-steroids, with high molecular weight better than low molecular weight in low grade osteoarthritis. More evidence is needed regarding the superiority of platelet-rich plasma over cortico-steroids and hyaluronic acid to validate our findings.

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