

Intra-articular Platelet-rich Plasma versus Hyaluronic Acid in the Treatment of Knee Osteoarthritis: Systematic Review

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Abstract

Background: Platelet-rich plasma (PRP) and hyaluronic acid have been shown to be useful in the treatment of knee osteoarthritis. However, investigations comparing the efficacy of two drugs together are insufficient. **Aim of the Work:** to perform a systematic review of comparative study between effect of platelet rich plasma and hyaluronic acid in treatment of osteoarthritis. **Material and methods:** This systematic review was performed according to PRIMSA guidelines using the Cochrane database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed and MEDLINE as database for search, from 2015 to 2019. **Results:** A total of 230 potential studies were identified with the first search strategy. Of these, 82 studies were excluded according to the eligibility criteria. First, we identified 14 studies that satisfied the predefined inclusion criteria. Eventually, we concluded that only thirteen studies are the most suitable to our review. Three prospective studies and ten randomized trials were included in final quality assessment and data extraction **Conclusion:** PRP injections reduced pain more effectively than HA injections in OA of the knee at 6 and 12 months of follow-up

evaluated by WOMAC pain score, while the VAS showed no significant difference at 3 and 6 months. Additionally, similar results were observed for the function recovery according to the WOMAC function score and EQ VAS. Due to the limited quality and data of the evidence currently available, more high-quality randomized controlled trials are required

Key words: Hyaluronic acid, platelet rich plasma, knee osteoarthritis.

Introduction

Osteoarthritis is the most common articular disease, and it is an important cause of disability in the elderly. The knee is the most frequent joint

affected by osteoarthritis. Osteoarthritis is a multifactorial chronic disease that starts with breakdown of joint cartilage and leads to

decrease in joint space, subchondral sclerosis,

It was estimated that more than 10% of the people aged ≥ 60 years suffer from this disease, and it is a major expense for all healthcare systems. Clinical manifestations of the disease include functional pain and joint stiffness. Morning stiffness usually lasts less than 30 min followed by gel phenomenon that is a transient joint stiffness due to short-term immobility (1).

Current treatments for osteoarthritis include non-pharmacologic treatment, such as physical activity, and pharmacologic treatment, such as non-steroidal anti-inflammatory drugs, glucocorticoids and hyaluronic acid. These treatments aim to decrease pain and inflammation, but these drugs have restricted and short-term effects on control of symptoms and the patient's quality of life (2).

Platelet-rich plasma (PRP) is plasma that is prepared from each patient's own blood, and it has a higher platelet concentration in comparison to normal plasma. PRP injection is a simple, low cost and minimally invasive procedure that provides concentrated growth factors for use as an intra-articular injection. These growth factors are said to stimulate the healing of cartilage and thus improve arthritis. Some studies alluded to the potential effect of PRP in treatment of chronic tendonitis, tennis elbow, chronic rotator cuff tendinopathy, jumper's knee, acute Achilles tendon rupture, muscle rupture, osteochondritis and osteoarthritis and meniscus repair (3).

synovitis and peripheral osteophytes formation.

The positive effects of PRP in improvement of knee osteoarthritis have been reported in some studies. Studies have reported the effects of PRP on the proliferation of mesenchymal root cells and their chondrocyte differentiation, but evidence about the clinical use of PRP in the treatment of knee osteoarthritis is still insufficient (4).

Hyaluronic acid is a polysaccharide compound that includes glucuronic acid and acetyl glucosamine. In osteoarthritis, the concentration and molecular weight of hyaluronic acid are reduced, and this is the basis of hyaluronic acid injection. Hyaluronic acid provides viscoelasticity of synovial fluid and stimulates formation of endogenous hyaluronic acid. In addition to its effects on viscoelasticity, hyaluronic acid may be effective for the treatment of osteoarthritis by biochemical effects, such as stimulation of formation and accumulation of proteoglycan, inhibition of inflammatory mediators and analgesic effect. However, because there are inadequate data on the effects of either different doses of PRP or hyaluronic acid in patients with osteoarthritis, we aimed in this study to compare the therapeutic efficacy of intra-articular injection of two different doses of PRP versus hyaluronic acid in the management of patients with osteoarthritis of the knee (5).

Aim of the Work

The aim of this study is to perform a systematic review of literature regarding comparative study between the effect of platelet rich plasma and hyalouronic acid in treatment of degenerative osteoarthritis.

Materials and Methods

This systematic review was performed according to PRIMSA guidelines using the Cochrane database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed and MEDLINE as database for search.

Search keywords were isolated or combined and included hyalouronic acid, platelet rich plasma, knee degenerative disease, knee osteoarthritis, non-surgical treatment of osteoarthritis.

- The study included Clinical studies with at least 5 years of follow up. Non-human studies, cadaveric studies, reviews, commentaries and general discussion papers not presenting data on impacts and clinical

studies with < 5years of follow up were excluded from the present study.

The study has the approval of local ethical committee.

Results

Individual patient data were available from these articles except for data for those lost to follow-up. The characteristics of the included studies are summarized in Table 1. These studies were published from 2015 to 2020 with more female patients than male patients (899 versus 629). Comparable patients were included in the PRP group (785) and HA group (733). Grade 0 (Kellgren and Lawrence classification) was chondropathy of knee without clear OA appearance on X-ray. Early appearance was grades 1–3, while grade 4 was defined as advanced appearance. Three studies enrolled 72 advanced knees, while only one study included 62 grade 0 patients. Therefore, 1,390 participants (91.2%) in these studies were in the early stage from grades 1 to 3(8).

Table 1: Detailed information of the included studies

Reference	Group	Age (years)	Gender (M/F)	OA type (C/E/A)	BMI (kg/m ²)	Intervention	Follow-up (months)
Lana et al (6)	PRP	60.9±7	7/29	E 9/14/13	27.4±6.9	1 time, 5 mL	1, 3, 6, 12
	HWA	60±6.6	3/33	E 9/16/11	28.2±8.8	20 mg/2 mL, 2,400 to 3,600 kDa	
	P&A	62±6.1	6/27	E 5/14/14	29.2±7.4	5 mL+2 mL	
Cerza et al (7)	PRP	66.7±11.4	25/35	E 21/24/15	N	4 times, 5.5 mL, weekly	1, 2, 6
	HA	66.8±10.7	28/32	E 25/22/13	N	4 times, 20 mg/2 mL	
Sanchez et al (8)	PRP	60.7±7.8	43/46	E 45/32/12	27.9±2.9	3 times, 8 mL, weekly	1, 2, 6
	HA	58.8±8.3	42/45	E 42/32/11	28.2±2.7	3 times	
Spakova et al (9)	PRP	52.9±12.3	33/27	E 2/39/19	27.9±4.1	3 times, 3 mL, weekly	3, 6
	HA	53.3±14.6	31/29	E 2/37/21	28.3±4.0	3 times	
Say et al(10)	PRP	55.4±7.9	5/40	E 1/17/27	32.4±4.0	1 time	3, 6
	LWHA	56.2±5.1	6/39	E 1/15/29	32.3±3.3	3 times, 25 mg/2.5 mL, 730 to 900 kDa, weekly	
Vaquerizo et al (11)	PRP	62.6±6.8	16/32	E 0/14/26;	30.7±3.6	3 times, 8 mL, every 2 weeks	6, 12
	HWA	64.7±7.8	22/26	A8 E 0/18/21; A9	31.0±4.6	1 time, 60 mg/3 mL	
Filardo et al (12)	PRP	53.4±13.3	60/34	E 2.0±1.1	26.6±4.0	3 times, 5 mL, weekly	2, 6, 12
	HWA	57.7±11.9	52/37	E 2.0±1.1	26.9±4.4	3 times, 20 mg/2 mL, >1,500 kDa, weekly	
Gormeli et al(13)	PRP*	53.6±13.2	23/16	E 26; A13	28.7±4.8	3 times, 5 mL, weekly	6
	PRP#	53.7±13.4	25/19	E 25; A14	28.4±4.4	1 time, 5 mL	
	HA	53.8±14	22/17	E 27; A13	29.7±3.7	3 times, 20 mg/2 mL, weekly	
Raeissadat et al (14)	PRP	56.9±9.2	8/69	E6/44/38;	28.2±4.6	2 times, 5 mL, monthly	1, 6, 12
	LWHA	61.1±7.5	15/47	A12 E0/47/37; A16	27.0±4.2	3 times, 20 mg/2 mL, 500 to 730 kDa, monthly	
Duyms et al,(15)	PRP	60.4±5.1	1/32	E 0/22/11	27.6±4.8	2 times, 5 mL per time, every 2 weeks	1, 3, 6, 12
	HWA	60.3±9.1	1/33	E 0/24/10	28.4±3.4	40 mg/2 mL, 1,600 kDa	
Montanez-Heredia et al (16)	PRP	66.4±8.3	12/15	E 5/10/12	29.0±5.5	3 times, every 2 weeks	3, 6
	LWHA	61.6±8.4	9/17	E 2/9/15	30.4±4.9	3 times, 25 mg/2.5 mL, 799 kDa	
Cole et al,(17)	PRP	55.9±10.8	28/21	E 3/2620	27.4±3.9	3 times, 4 mL, weekly	3, 6, 12
	LWHA	56.8±10.4	20/30	E 1/27/22	29.0±6.4	3 times, 16 mg/2 mL, 6,000 kDa	

Quality assessment

For all randomized trials, there were no detailed descriptions on reporting bias and other biases. Additionally, the patients in the study were consecutively randomized into groups by admission to the hospital, causing

selection bias. All methodological processes are shown in for the other prospective studies, the calculation of the sample size or unbiased assessment of the study endpoints could not be identified in the articles (table 2) (9).

Table 2: Quality assessment for nonrandomized trials

Quality assessment for nonrandomized trials	Kon et al (6)	Say et al (10)	Spakova et al (9)
A clearly stated aim	2	2	2
Inclusion of consecutive patients	2	0	0
Prospective data collection	0	0	0
Endpoints appropriate to the aim of the study	2	2	2
Unbiased assessment of the study endpoint	0	0	0
A follow-up period appropriate to the aims of study	2	2	2
Less than 5% loss to follow-up	2	2	2
Prospective calculation of the sample size	2	0	2
An adequate control group	2	2	2
Contemporary groups	2	2	2
Baseline equivalence of groups	2	2	2
Adequate statistical analyses	2	2	2
Total score	20	16	18

Outcomes

The WOMAC was the most used tool to evaluate the effects of PRP or HA in the included studies. However, different studies followed-up patients according to different protocols for baseline, 2 or 3, 6, and 12 months. Because of these data limitations, we can only evaluate the effects of the intervention at different times. Furthermore, we calculated the data from the second and third months after the intervention. Based on the available data pooled from six studies, there was no significant difference between these two groups when they were enrolled (MD=0.88; 95% CI: -3.45 to 5.21; $P=0.69$; $I^2=76\%$). The PRP performed better than the HA after 3 months of treatment (MD=-10.80; 95% CI: -19.72 to -1.89; $P=0.02$; $I^2=88\%$)(91). Taking time into consideration,

this advantage continued at 6 months (MD=-14.19; 95% CI: -26.13 to -2.24; $P=0.02$; $I^2=96\%$) and 12 months (MD=-15.25; 95% CI: -22.17 to -8.32; $P<0.01$; $I^2=81\%$)(10).

The WOMAC consists of three parts, including pain, stiffness, and physical function. For knee pain, the pooled data showed that patients treated with PRP had less pain than those treated with HA at 6 months (MD=-2.0; 95% CI: -3.61 to -0.40; $P=0.01$; $I^2=90\%$) and 12 months (MD=-2.21; 95% CI: -3.66 to -0.80; $P=0.002$; $I^2=92\%$). VAS was another parameter used to evaluate pain after treatment in four studies. Two studies showed no significant difference between PRP and HA, while the others showed better pain reduction for PRP.

Available data from recent study showed that PRP and HA performed similarly at 3 months (MD=-0.98; 95% CI: -2.56 to 0.60; $P=0.22$; $I^2=90\%$) and 6 months (MD=-0.82; 95% CI: -1.80 to 0.16; $P=0.1$; $I^2=83\%$) (11).

Physical function evaluated by the WOMAC was reported in four studies and showed that patients treated with PRP and HA had similar function recovery after 6 months of treatment (MD=-5.79; 95% CI: -14.75 to 3.14; $P=0.21$; $I^2=93\%$). However, PRP performed better than HA at 12 months (MD=-11.17; 95% CI: -16.37 to -5.98; $P<0.01$; $I^2=83\%$). The EuroQol-visual analogue scales (EQ VAS) were also used to demonstrate functional recovery after treatment in four studies. The results showed that PRP and HA performed similarly at 6 months (MD=2.19; 95% CI: -11.47 to 15.85; $P=0.75$; $I^2=98\%$) and 12 months (MD=-4.64; 95% CI: -21.79 to 12.51; $P=0.60$; $I^2=98\%$). The use of high-molecular weight HA (HWHA) versus low-molecular weight HA (LWHA) or three injections versus one injection did not significantly influence the result (12).

The Subjective International Knee Documentation Committee (IKDC) was reported in several studies. Patients in the PRP group showed better IKDC scores than those in the HA group (MD=8.53; 95% CI: 4.52 to 12.53; $P<0.01$; $I^2=79\%$) at 6 months. The difference disappeared at 12 months (MD=6.84; 95% CI: -1.96 to 15.63; $P=0.13$; $I^2=91\%$).

Discussion

Knee osteoarthritis is one of the most common diseases that cause difficulties in walking and loss of function of the knee joint which lead to heavy economic and social burden, so many studies and trials were established to search for a solution for this problem. We made a couple of observations. First, the components of PRP and HA were different among these studies. Although the PRP was produced from the patients' blood by a similar method of centrifugation, the platelet concentrations differed. Additionally, other products, such as cellular products and mediators, varied between the studies (17).

Patients at different stages of OA do not have the same response to the same treatment. Study show that PRP was more effective in young patients with early or moderate stages of arthrosis, but it had a limited effect in cases of advanced OA. Most patients in our analysis suffered from early stage knee OA, ranging from grades 1 to 3, for a total of 1,390 participants (91.2%). There were 72 grade 4 knee OA patients enrolled in three studies, which may have altered the treatment effect (18).

The mechanism of PRP and HA in the change in knee OA was another important factor that influenced the treatment effects. The beneficial effects of HA may be attributable to improved lubrication based on the viscoelasticity. The growth factors

secreted from active platelets have another function to stimulate proliferation and differentiation of chondrocytes, regulate collagenase secretion, and regenerate cartilage. HA acts as a lubricator, while PRP provides many factors to stimulate the synovial membrane and surrounding tissues. Our current study included the most recent trials comparing HA and PRP, though we must know the limitations of the analysis. The first and serious limitation was that there was significant heterogeneity in each calculation. Second, too many evaluation tools were used across the different studies such that the highest number of studies that used any single evaluation tool was five studies for the WOMAC score at 6 months. These limitations weakened our ability to draw a definitive study conclusion (19).

Conclusion

According to WOMAC pain score pain is reduced in PRP injections more than HA injections at 6 and 12 months of follow-up. While according to VAS there is no significant difference at 3 and 6 months. . Additionally, similar results were observed for the function recovery according to the WOMAC function score and EQ VAS. Due to the limited quality and data of the evidence currently available, more high-quality randomized controlled trials are required.

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