



## HOPE, HYPE, HURDLES AND FUTURE PERSPECTIVE FOR PRP, PRP VERSUS HYALURONIC ACID INJECTION IN OSTEOARTHRITIS OF THE KNEE

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### ABSTRACT

#### Background

Comparative studies of platelet-rich plasma (PRP) and hyaluronic acid show variable results.

#### Purpose

A review was conducted to understand the current role of PRP and its efficacy *versus* hyaluronic acid in osteoarthritis (OA) of the knee joint.

#### Methods

Out of 170 identified studies, 14 studies involving 1575 patients with 637 males and 938 females were selected based on PRISMA flow chart guidelines and were analyzed for the study.

#### Results

A standard PRP regimen consisting of 2–3 intra-articular injections (IA) of 4–6 mL of leucocyte poor PRP at 1–2 weekly intervals provides a better result than HA during the first 3–6 months, and which may continue up to one year. PRP and HA may have synergistic effect; pain and swelling are the two most common complications with PRP, the incidence is more with leucocyte rich PRP (LP-PRP) and intra-osseous PRP treatment.

#### Conclusion

PRP provides hope and is more effective than hyaluronic acid in pain relief and improving the quality of life in mild to moderate osteoarthritis of the knee joint. However, hype, that is effective in all, irrespective of grades of OA, mal-aligned or stiff knee, ligamentous laxity, and can avoid joint replacement is a big hindrance in establishing it as a preferred treatment in OA knee. The author follows the above-mentioned PRP regimen; and recommends to combine leucocyte poor PRP with HA for IA injections & with LP-PRP injections along with the two most common painful points (medial collateral ligament, pesaniserius) in a highly painful OA knee. PRP may not address extra-articular causes of knee pain (mal-alignment, muscle wasting, tendinosis), should be corrected for optimum outcome. Contact sports, running, exercises putting pressure on knee and NSAID should be avoided during PRP treatment. Also, more randomized controlled trials are required to further standardize the PRP preparation, administration, injection interval & proper documentation of efficacy and complications in the regenerative registry.

**Keywords:** Osteoarthritis, Knee, Hyaluronic acid, Platelet-Rich Plasma, Hope, Hype, Hurdles, Future Perspective.

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## BACKGROUND

Platelet-rich plasma (PRP) has been advocated as a more effective treatment than hyaluronic acid in osteoarthritis of the knee joint. However, literature comparing the results of PRP and hyaluronic acid is debatable and conflicting. Some studies report PRP as better<sup>1</sup> treatment while another report as having the same effect<sup>2</sup> or worse<sup>3</sup> than hyaluronic acid in relieving the pain of osteoarthritis of the knee. It is also not clear whether both the above-mentioned treatment is providing relief in all grades<sup>4</sup> of osteoarthritis of the knee and how long (months to one year only) these two treatments provide symptomatic relief.<sup>5</sup> Because of this conflicting literature, many orthopedic surgeons<sup>3</sup> do not believe in the role of PRP in osteoarthritis of the knee. Also, health insurance companies do not cover the cost of PRP, as they believe it to be an experimental treatment.<sup>6</sup> The situation is further compounded due to the strict regulation of PRP and stem cell use in many different countries.<sup>6</sup> PRP therapy is more expensive than hyaluronic acid and needs a proper set up for preparing PRP for intra-articular injections.<sup>6</sup> Due to these reasons, only a few treatment facilities provide PRP to cash-paying groups of patients or on the subsidized rate at government hospitals across the globe. On the other hand, Hyaluronic acid injections are freely available, less expensive, do not require any preparation and can be given in outpatient clinics.

## MATERIALS AND METHODS

A review was conducted in 2018 to determine the efficacy and role of PRP over hyaluronic in osteoarthritis of the knee joint. A thorough search was done to identify all the studies (in English -language, until June 2018) comparing the results of intra-articular PRP with hyaluronic acid in osteoarthritis of the knee joint, from Pubmed, Cochrane library, Google scholar databases, and Sage platform. The search included keywords like “Platelet-rich plasma”, “PRP”, “hyaluronic acid”, “osteoarthritis”, “knee joint”, “hyaluronic acid Vs platelet-rich plasma”, “PRP Vs HA” and “PRP with hyaluronic acid”. A hand search was also done from the reference list of retrieved studies, from the archive of the American Academy of Orthopaedic Surgeons and SICOT (International

Society of Orthopaedic Surgery & Traumatology) to find the additional potentially relevant studies. This search strategy had a limitation as it included only English- language studies, also it is not possible to access all the relevant published studies on all the databases/platform site due to financial and time constraints. Again, authors were not contacted for any clarification on methodology or any other ambiguity in the studies due to financial and time constraints. Preferred Reporting Items<sup>7,8</sup> for Systemic Reviews guideline (Figure 1. PRISMA Flowchart) were followed to identify & screen these studies and to finally determine their eligibility for inclusion in this review.

## INCLUSION AND EXCLUSION CRITERIA

Randomized and nonrandomized controlled studies comparing the results of PRP with hyaluronic acid injections in patients having osteoarthritis of the knee were included in the study. Studies involving other arthritis, poly-osteoarthritis, not comparing PRP with hyaluronic acid, duplicated studies, not following standard treatment protocol or ethical guidelines were excluded from the study.

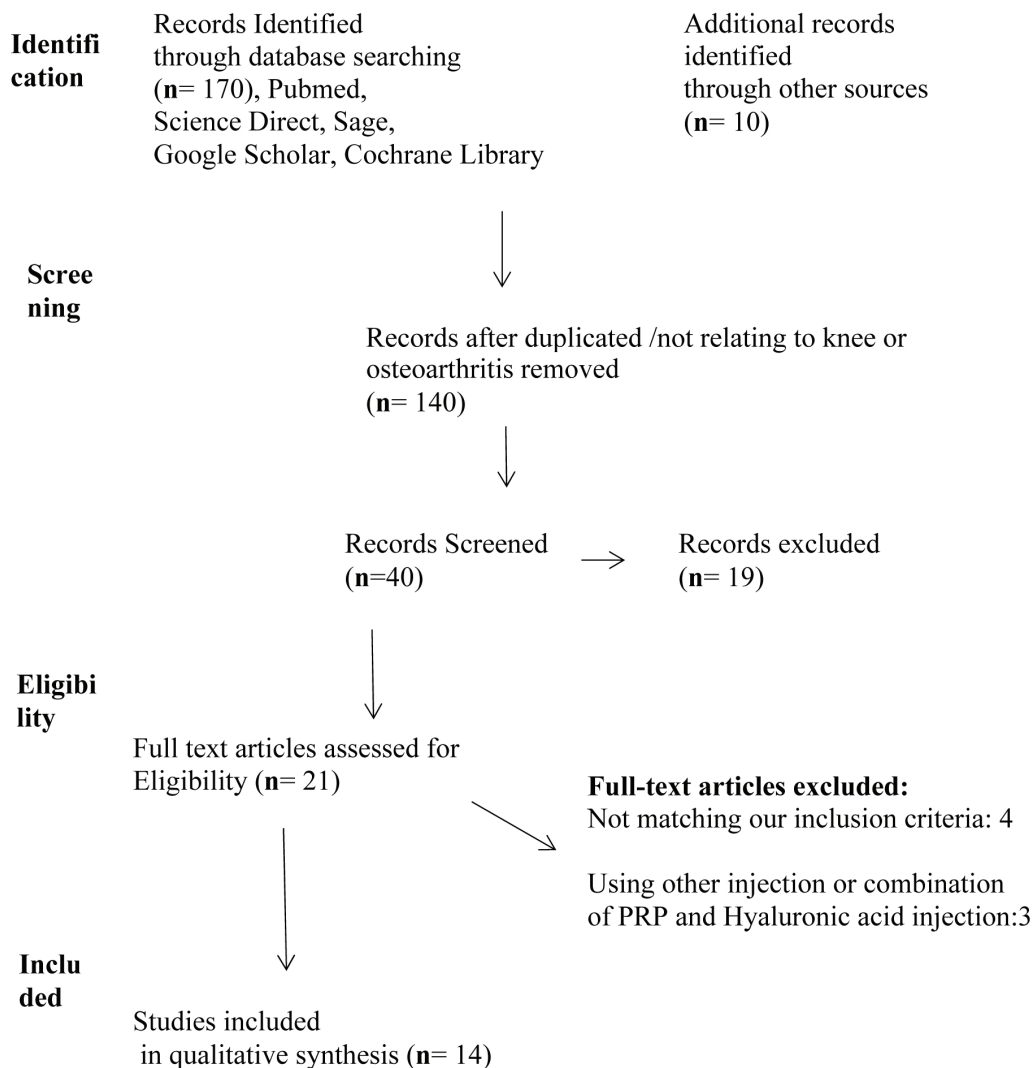
## STUDIES IDENTIFICATION AND SELECTION

By using the PRISMA flow diagram (see Figure 1), a total of 170 records were identified from the search of databases and platforms. An additional 10 records were retrieved by a hand search of the cross-references, books, and websites. 140 studies not related to osteoarthritis of the knee and duplicated studies were excluded from the screening. Remaining 40 studies were screened and 19 more studies were found to be ineligible for assessment. So, eligibility of a total of 21 studies having full-text articles was assessed for inclusion in the study; out of these 4 were excluded not matching our inclusion criteria and 3 were excluded for using other combinations of injections, finally, only 14 studies were selected in this systemic review.

## QUALITY ASSESSMENT OF STUDIES

Quality assessment of randomized studies was done by the Oxford Quality Scoring system.<sup>9</sup> Quality assessment of non-randomized studies was done by using the Cochrane risk of bias assessment tool.<sup>10</sup>

**FIG. 1** Flowcharts of the study selection process.<sup>7</sup>



**RESULTS**

Fourteen studies (Table 1) published until June 2018, comparing the effect of PRP over hyaluronic acid were included in this review. There were nine randomized controlled studies and five prospective comparative studies. One study<sup>1</sup> belonged to Level IV; while the rest of the studies were Level I studies. These 14 studies included 1575 patients; 637 were males; 938 were females and the average age was 59.82 years (range 50.67 to 66.5). A standard PRP regimen consisting of 2–3 intra-articular injections of 4–6 mL of leucocyte poor PRP at 1–2 weekly

intervals provided a better result than HA during 3–6 months, and which may continue up to one year.<sup>11–16</sup> Two studies showed that PRP and HA may have a synergistic effect<sup>22,23</sup>; pain and swelling are the two most common complications with PRP, the incidence was more with leucocyte rich PRP and intra-osseous PRP treatment.<sup>11–16</sup>

**DISCUSSION AND CONCLUSION**

**Osteoarthritis of Knee and Treatment Options**

Primary osteoarthritis is a degenerative process resulting from decreased anabolic and increased

**TABLE 1** Showing Studies, Patient Number, Diagnosis, Treatment Group, Complications, and Results

	S.N/Authors	T/T; Patients no	Interval of injection & Follow-up period (months)	Complications	Grade /Classification	Conclusion (Effectiveness)
1	Cerza F et al, 2012 [1]	PRP: 60  HA: 60	4, weekly  4, weekly FU: 1,2,6	None	KL: 1(21), 2(24), 3(15) KL: 1(25), 2(22), 3(13)	PRP>HA HA not effective in Grade 3 OA
2	Cole BJ et al, 2017 [2]	PRP-LP: 49  HA: 50	3, weekly  3, weekly FU: 3,6,12	Not reported	KL:1(3), 2(26), 3(20) KL: 1(0), 2(27), 3(22)	PRP>HA
3	Filardo et al, 2015 [3]	PRP: 94  HA: 89	3, weekly  3, weekly FU: 2,6,12	Pain/mild effusion PRP>HA	KL: Mean score: 2 ± 1.1 KL: Mean Score: 2 ± 1.1	PRP is not superior to HA
4	Kilincoglu V et al, 2015 [11]	PRP: 61  HA: 57	3, weekly  3, weekly FU: 3,6	Mild swelling: 3 (PRP)	KL: Stage 1, 2	PRP > HA
5	Montanez- Heredia et al, 2016 [12]	PRP: 27  HA: 26	3, every 2 week  3 every 2 week  FU): 3,6	Pain, mild swelling in one	KL:1(5), 2(10), 3(12) KL: 1(2), 2(9), 3(15)	PRP> HA
6	Spakova et al, 2012 [13]	PRP: 60  HA: 60	3, weekly  3, weekly FU: 3,6	None	E: 2, 39,19  E: 2, 37, 21	PRP>HA
7	Kon et al, 2011 [14]	PRP: 50  HA: 50 LWHA: 50	3, every 2 week  One One  FU: 2,6	None	CD: 22; KL: EOA: 20, LOA:8 CD: 19, KL: EOA:22; LOA:9	PRP> HA Better in a young patient, low degeneration/ OA
8	Say et al, 2013 [15]	PRP:45  HA:45	One time  3, weekly FU: 3,6	None	KL: 1(1), 2(17), 3(27) KL: 1(1), 2(15), 3(29)	PRP > HA

(continued)

**TABLE 1** Showing Studies, Patient Number, Diagnosis, Treatment Group, Complications, and Results (continued)

<b>9</b>	Su Ke et al, 2018 [16]	<b>PRP</b> (IO/IA): 28  <b>PRP</b> (IA): 26  <b>HA</b> (IA): 32	2, at two weekly  2, at two weekly  2, two weekly 5, weekly <b>FU</b> :1,3,6,12,18	2 Pain  3 Pain, swelling 2 Pain, swelling	<b>KL</b> 2(16), 3(11)  <b>KL</b> 2(13), 3(12) <b>KL</b> 2(14), 3(16)	PRP(IO/IA)> PRP (IA)/HA
<b>10</b>	Sanchez et al, 2012 [17]	<b>PRP</b> : 89  <b>HA</b> : 87	3, weekly  3, weekly <b>FU</b> : 1,2,6	Mild PRP=HA	-	PRP> HA
<b>11</b>	Vaquerizo et al, 2013 [18]	<b>PRP</b> : 48 <b>HA</b> : 48	3 times every 2 weeks One time <b>FU</b> : 6,12	Pain at the site of injection	-	PRP> HA
<b>12</b>	Raeissadat et al, 2015 [19]	<b>PRP</b> : 77  <b>HA</b> :62	2, monthly  3, monthly  <b>FU</b> : 1,6,12	None	<b>KL</b> : 1(6), 2(44), 3(38),4(12) <b>KL</b> : 1(0), 2(47),3(37),4(16)	PRP>HA
<b>13</b>	Duymus et al. 2017 [20]	<b>PRP</b> : 33  <b>HA</b> : 33	2, two weekly  2, two weekly  <b>FU</b> : 1,3,6,12	Not Reported	<b>KL</b> :2(22), 3(11)  <b>KL</b> :2(24), 3(10)	PRP > HA / Ozone
<b>14</b>	Gormeli et al, 2017 [21]	<b>PRP</b> : 39  <b>PRP</b> : 39  <b>HA</b>  <b>Saline</b>	3, weekly  One  One One  <b>FU</b> : 6	Not Reported	<b>KL</b> : EOA: 26, AOA: 13 <b>EOA</b> : 30, AOA: 14 <b>EOA</b> : 25, AOA: 14 <b>EOA</b> : 27, AOA: 13	1. Both PRP/HA is effective 2. Multiple injections do not significantly improve AOA

CD = chondrogenic disorder; EOA = early osteoarthritis; PRP = platelet-rich plasma; FU = follow-up; hyaluronic acid; HA = hyaluronic acid; KL = Kellgren grade of osteoarthritis; LWHA = low weight hyaluronic acid; LP = leucocyte poor; LOA = late osteoarthritis; OA = osteoarthritis.

catabolic activities in articular cartilage and synovial membrane of joints. It usually presents as pain, swelling, stiffness, and joint deformity after the age of 50 years and is more common in women and after mal-united intra-articular fracture around the knee joint.<sup>24,25</sup>

Conventional treatment of mild osteoarthritis of knee involves analgesic, lifestyle modification, weight reduction, joint support with physiotherapy. Treatment options of advanced osteoarthritis with joint stiffness or deformity include corrective osteotomy, partial or total knee replacement. For moderate and highly painful early osteoarthritis, hyaluronic acid has been an important adjuvant in the treatment over the last few decades.<sup>25</sup>

**Hyaluronic Acid and Hyaluronic Injection Treatment**

Hyaluronic acid is a non-sulfated glycosaminoglycan in the extracellular matrix of the articular cartilage; it helps in maintaining the chondrocyte function and viscoelastic properties of synovial fluid.<sup>25,26</sup> The hyaluronic acid injection is believed to increase the endogenous production of hyaluronic acid,<sup>27</sup> stimulate

cartilage matrix synthesis and metabolism. It gives pain relief in osteoarthritis by inhibiting enzymes degrading cartilage and the inflammatory process.<sup>28</sup> It is generally a safe treatment but mild pain and redness may occur at the site of injection in some patients. Effects of intra-articular hyaluronic acid injections are short-lasting and need repeat injections at 3–6 month intervals.<sup>29</sup>

**Platelet, Platelet Granules, and Growth Factors (Table 2)**

Platelet-rich plasma (PRP) has become a very popular treatment for osteoarthritis during the current decade. Buffy coat is the most commonly used standard method for PRP preparation by centrifuging blood at high speed.

**PLATELET CLASSIFICATIONS**

Sports medicine classification and PAW classification are the two most widely used PRP Classification. Mishra et al<sup>50</sup> gave Sports Medicine Classification and classified PRP based on the leucocyte (presence or absence) and platelet counts; also on platelet activation. Type 1 is non-activated leucocyte rich PRP; Type 2 is

**TABLE 2** Showing Basics Science of Platelet, Granules, Activation, and Functions of Different Growth Factors

Platelet:	Platelet Granules
<p>Circulated inactivated platelets are biconvex discoid cells of 2–3 µm in diameter and have an average life span of 8–9 days. Platelets retain their viability and function for 5 days stored at 22 centigrade of temperature.<sup>30,31</sup></p> <p><b>Platelet Activation:</b> Degranulation of the alpha granules and fibrinogen breakdown to initiate matrix formation. Activation causes growth factor release in 10 minutes and &gt; 90% preformed factors release is complete within one hour.<sup>32</sup> The secretion of growth factors continues for 5–7 days.<sup>32</sup></p> <p><b>Endogenous:</b> Best method; in contact with tissue (collagen) and prolong the release of platelet granules.<sup>33</sup></p> <p><b>Exogenous:</b></p> <ul style="list-style-type: none"> <li>• Addition of Calcium Chloride, Calcium Gluconate or thrombin</li> <li>• Freeze-Thaw cycle (only degranulation)</li> </ul>	<p><b>Dense Granule:</b></p> <ul style="list-style-type: none"> <li>• Serotonin, ADP, Polyphosphate</li> <li>• It helps in degranulation.</li> </ul> <p><b>Alpha Granules:</b> One platelet<sup>23</sup> contains 50–80 alpha granules of variable sizes (200–500 nm).</p> <ul style="list-style-type: none"> <li>• <b>Growth factors:</b> PDGF, SDF1a, bFGF, EGF, IGF-1, TGB-1.</li> <li>• <b>Angiogenic Factor:</b> VEGF, FGF, PDGF, EGF, HGF, IGF, Angiogenin.</li> <li>• <b>Necrotic Factors:</b> α TNE, β TNE.</li> <li>• <b>Proteases:</b> MMP2, MMP9, IL1.</li> <li>• <b>Anti-angiogenic Factors:</b></li> <li>• Angiostatin, PF4.</li> <li>• <b>Homeostatic Factors:</b> Factor V, VWF, fibrinogen.<sup>34–36</sup></li> </ul>

ADP = adenosine diphosphate; EGF = epidermal growth factor; FGF = fibroblast growth factor; IGF = insulin growth factor; IL1 = interleukin 1; MMP = matrix metalloproteinase; PDGF = platelet-derived growth factor; PF4 = platelet factor 4; SDF = stromal cell-derived factor 1; VWF = Von Willebrand factor.

**TABLE 3** PRP: Definition, Functions, and Types

Platelet-Rich Plasma (PRP)	PRP: Functions	Platelet-Poor Plasma (PPP)
<p><b>PRP term was given in 1970</b>  <b>Definition:</b> Autologous blood fraction with a platelet count above the baseline (1,50000-350000/<math>\mu</math>L) or one million platelets/<math>\mu</math>L, or 3–5 times above the whole blood.<sup>32,36</sup></p> <p><b>Content:</b> PRP contains around 1100 proteins, 1500 proteins based bioactive factors.<sup>37</sup></p> <p><b>Autologous PRP:</b> No risk of disease transmission, cross-contamination, and rejection.<sup>38</sup></p> <p><b>Types of PRP:</b></p> <ul style="list-style-type: none"> <li>• Leucocyte Rich PRP</li> <li>• Leucocyte Poor PRP</li> <li>• Activated/Non-activated PRP</li> </ul>	<ul style="list-style-type: none"> <li>• Angiogenic: See at 1.5 million / microliter.<sup>39-41</sup></li> <li>• Improve the synthesis of collagen II and prostaglandin.<sup>42</sup></li> <li>• Improve chondrocyte proliferation with increased matrix production.<sup>43,44</sup></li> <li>• Improve cartilage remodeling.<sup>43,44</sup> Increased hyaluronic acid production by synoviocytes.<sup>43,44</sup></li> <li>• Reduced interleukin-1 directed increased level of matrix metalloproteinase.<sup>45</sup></li> <li>• Tissue sealant.<sup>46</sup></li> <li>• Limited antimicrobial properties.<sup>47</sup></li> <li>• It helps in stem cell proliferation, differentiation, migration, homing.<sup>48</sup></li> </ul>	<p><b>PPP Gel/Fibrin glue/Fibrin Sealant:</b>                  This is platelet-poor plasma (&lt; 10,000 microliters) having all the clotting factor and forms a fibrin matrix once get activated by calcium chloride. It acts as a scaffold promoting cell migration and matrix formation. It is angiogenic (VEGF R2, CD34).</p> <p><b>PRP Gel:</b> Platelet-rich fibrin matrix or platelet-rich fibrin membrane; provides structural support.<sup>49</sup></p>

VEGF = vascular endothelial growth factor.

activated leukocyte rich PRP; Type 3 is non-activated leukocyte poor PRP; Type 4 is activated leukocyte poor PRP. Each type is subdivided into A (>5 times of platelet concentration) or B (<5 times of platelet concentration).

DeLong et al<sup>51</sup> gave PAW (Platelet Activation White blood cells); Platelet concentration  $\leq$  of baseline (P1), baseline - 150,000 (P2), 750000 - 1250000 (P3), > 1250000 (P4); White blood count above baseline (A), below baseline (B), *Neutrophil count* above baseline ( $\alpha$ ), below baseline ( $\beta$ ); Activation method: Endogenous or exogenous (X).

**PRP: HOPES, HYPE, HURDLES, FUTURE PERSPECTIVE**

**Hope**

PRP has been hailed as a new biological treatment providing pain relief, improving range of motions, knee functions and quality of life. It is also hoped that it might provide long term benefits, avoid the arthroscopic and joint reconstructive procedure, and can enhance performance in elite athletes by promoting early healing and return to sports activities.

**Hype**

PRP also brings a hype created by over-enthusiasm, incomplete or wrong information & commercial interest. It is claimed that PRP and regenerative treatment is effective in all grades of osteoarthritis or chondral injuries of the knee joint. Furthermore, different available commercial kits claim to have pure platelet concentrate and better result one over the other.

**Hurdles**

Insurance companies do not cover PRP and other biological treatments for OA knee as they believe it as an experimental treatment due to non-standardized PRP preparations, administration, and variable results. For cash-paying patients, health providers are forced to charge high prices for PRP to cover their cost due to expensive lab setup as per regulatory requirement, pre-injection screening blood test and expensive commercial PRP kits. It is also very difficult to validate the effectiveness, results and complications of different PRP kits and regimens due to lack of proper registry. Although many patients have high expectations with PRP treatment due to hyped market and incomplete information; still some physicians and patients are

skeptical due to variable results, multiple injections, and safety issues.

### **PRP: Future/Proposal**

The insurance company has to be reassured that despite variable results of PRP with different PRP preparation/administration, it consistently shows pain relief and good quality of life lasting for 6 months to 1 year. This symptom-free interval will reduce the cost involved in pain killers, numbers of physiotherapy and hyaluronic acid injections, paid sick leaves and finally improve the other co-morbidity due to better mobility and avoid knee surgeries in many patients. National and local Orthopaedic, *Physician & Allied Medical Services* associations needs to meet regulatory authorities to convince them with PRP results to issue more flexible regulatory guidelines for practitioner and insurance companies, to provide more support to train the practitioners and lab personnel to improve the quality of PRP treatment. Patients need to be informed about the exact indications, benefits, problems and need for multiple injections. Extra-articular sources of pain (mal-alignment, muscle wasting or imbalance, tendinopathy) must be addressed to avoid failed PRP treatment. PRP should be supported with other adjuvants (short term rest to knee joint after the injection, physiotherapy, knee support, prolotherapy, redesigned exercises/workout) as like any other medical or surgical treatment.

### **PRP VERSUS HYALURONIC ACID**

This review was done to see whether PRP is more effective in the treatment of osteoarthritis of the knee joint. Studies were identified, screened, matched with our inclusion/exclusion criteria and finally selected by using the PRISMA flow diagram. All the randomized studies (see Table 1) showed a Jadad score of 3; two nonrandomized studies<sup>16,17</sup> showed selection and performance bias. Two studies<sup>18,19</sup> did not mention the date of the enrolment of patients. Conflict of interest was not declared by two studies.<sup>3,18</sup> Three studies<sup>1,19,20</sup> showed detection and performance bias. In the majority of the studies, injections were given in grade 1–3 osteoarthritis of the knee, only two studies<sup>19,21</sup> used in grade 4 OA knee. Except for one study<sup>16</sup> which gave both intra-articular and intra-osseous, patients

in all other studies (13 studies, 92.85%) received intra-articular injections. Su Ke et al<sup>16</sup> reported that combined intraosseous<sup>21</sup> and intra-articular injections provide better relief than only intra-articular hyaluronic injection. However, it requires drilling or Jamshidi needle to introduce PRP into the subchondral area under fluoroscopic guidance. It also requires sedation and weight-bearing may be painful for a few days due to more pain & swelling than intra-articular injection.

The majority of the studies (see Table 1 ) showed multiple injections (2–3) given at weekly (8 studies), or every two weeks (5 studies) provide effective pain relief. Only one study<sup>19</sup> gave monthly injections and reported multiple injections do not cause a significant improvement in advanced osteoarthritis of the knee joint. Studies used different follow-up protocols at 1, 2, 3, 6, 12, and 18 months. But all of them have done at least one assessment at 6 months. So, an attempt was made to see the effect of intervention at six months in all the studies. Except for two studies, which evaluated the first effect at 6 months<sup>18,21</sup> data was co-calculated for all other 12 studies for the 2<sup>nd</sup> and 3<sup>rd</sup> months after the intervention. The outcome score used by these studies showed that PRP was more effective than hyaluronic acid at 3 months. This beneficial effect continued until 6 months in all the studies and up to one year in 3 other studies.<sup>16,19,20</sup> Subgroup analysis of all the studies except one<sup>3</sup> showed that there is a statistically significant improvement in pain relief (VAS score and as a subcomponent of WOMAC score) at 3 months and 6 months after PRP treatment than hyaluronic acid. But no statistically significant difference in the functional score (WOMAC, International Knee Documentation Committee score) was seen in PRP over hyaluronic acid. Pain and swelling were the two most common complications observed in these studies It was not possible to calculate the overall rate of complications as three studies<sup>2,20,21</sup> did not mention complications and 3 other studies<sup>3,17,18</sup> did not specify the exact number of patients having complications. The majority of studies (12 studies, 85.714%) reported PRP is more effective than HA and one<sup>21</sup> study (7.142%) showed that both are effective.

But this effectiveness in all other studies was more evident in early to moderate osteoarthritis and a good outcome was not seen in grade 4 OA (advanced



osteoarthritis). There are few systemic reviews available on understanding the role of PRP in osteoarthritis of knee joints. One systemic review<sup>52</sup> included only randomized controlled trials and left all other studies (case-controlled, prospective studies, nonrandomized trial), this reduced the sample size and prevented the assessment of regression and publication bias. We need to review all the available literature to conclude the exact role of PRP and hyaluronic acid in osteoarthritis of the knee joint. Three other recent systematic reviews done by<sup>53-55</sup> included studies comparing PRP with all other intra-articular treatment methods (corticosteroid, placebo, hyaluronic acid, ozone). They concluded PRP is better than placebo treatment and corticosteroid injections. But we want to see whether PRP is better than hyaluronic acid and to understand the exact role of these two in terms of WOMAC score (pain, stiffness, function), several injections for treatment, duration of pain relief and complications. One systematic review<sup>53</sup> included follow-up of WOMAC, Pain sub scores, physical function subscores and total scores at 3, 6, and 12 months after treatment were recorded. We don't know when does the PRP starts working and the course of effect with time. So to only include studies, which matches these predefined, follow-up intervals and excluding those who do not match is not justified. It has been shown that HA and PRP could have a synergistic effect by suppressing the cytokines and chemokines induced inflammation and degeneration in osteoarthritis.<sup>22,23</sup>

#### THE WEAKNESS OF THIS REVIEW

A proper review needs access to a broad range of databases and peer-reviewed journals but there is always a possibility of missing one or more important research studies due to time and financial constraints. Despite careful selection of studies based on PRISMA guidelines<sup>7,8</sup> for this review proposal, it might contain studies with minor ethical insufficiency or might contain studies whose informed consent or methodology might not be valid by the time this proposed systemic review is completed.

#### CONCLUSION

PRP provides hope & is more effective than hyaluronic acid in pain relief and improving the quality of life in mild to moderate osteoarthritis of the knee joint.<sup>11-16</sup> However, hype, that is effective in all, irrespective of grades of OA, maligned or stiff knee, ligamentous laxity, and can prevent the need for

joint replacement is a big hindrance in establishing it as a preferred treatment in OA knee. A standard PRP regimen consisting of 2-3 intra-articular injections of 4-6 mL of leucocyte poor PRP at 1-2 weekly intervals provides a better result than HA during 3-6 months, and which may continue up to one year.<sup>11-16</sup> PRP and HA may have a synergistic effect,<sup>22,23</sup> pain and swelling are the two most common complications with PRP, the incidence is more with leucocyte rich PRP and intra-osseous PRP treatment. The author follows the above-mentioned PRP regimen; and recommends to combine leucocyte poor PRP with HA for IA injections and with LP-PRP injections along with the two most common painful points (MCL, Pesanisernius) in a highly painful OA knee. PRP may not address extra-articular causes of knee pain (mal-alignment, muscle wasting, tendinosis), should be corrected for optimum outcome. Contact sports, running, exercises putting pressure on knee and NSAID should be avoided during PRP treatment. Also, a more randomized controlled trial is required to further standardize the PRP preparation, administration, injection interval and proper documentation of efficacy and complications in the regenerative registry.

#### AUTHOR CONTRIBUTIONS

**Conception and design:** Ashok Kumar

**Provision of study materials:** Anikait Ghosh Kadamb, Ashok Kumar

**Collection and assembly of data:** Anikait Ghosh Kadamb, Ashok Kumar

**Data analysis and interpretation:** Ashok Kumar

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#### DISCLOSURE

IRB Approval: No IRB required for this study as no human or animal were involved for this review and information is available in public domain.

The authors have **not received any funding** for this study; has **no commercial** interest with any PRP or regenerative product. The data and material used for this study are available in the public domain and

is accessible. All the authors agree with writing of this paper and approve the current final form of this paper and has no conflict of interest regarding the content or authorship of this paper.

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