Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review

Carlos J. Meheux, M.D., Patrick C. McCulloch, M.D., David M. Lintner, M.D., Kevin E. Varner, M.D., and Joshua D. Harris, M.D.

Purpose: To determine (1) whether platelet-rich plasma (PRP) injection significantly improves validated patient-reported outcomes in patients with symptomatic knee osteoarthritis (OA) at 6 and 12 months postinjection, (2) differences in outcomes between PRP and corticosteroid injections or viscosupplementation or placebo injections at 6 and 12 months post-injection, and (3) similarities and differences in outcomes based on the PRP formulations used in the analyzed studies.

Methods: PubMed, Cochrane Central Register of Controlled Trials, SCOPUS, and Sport Discus were searched for English-language, level I evidence, human in vivo studies on the treatment of symptomatic knee OA with intra-articular PRP compared with other options, with a minimum of 6 months of follow-up. A quality assessment of all articles was performed using the Modified Coleman Methodology Score (average, 83.3/100), and outcomes were analyzed using 2-proportion z-tests.

Results: Six articles (739 patients, 817 knees, 39% males, mean age of 59.9 years, with 38 weeks average follow-up) were analyzed. All studies met minimal clinical important difference criteria and showed significant improvements in statistical and clinical outcomes, including pain, physical function, and stiffness, with PRP. All but one study showed significant differences in clinical outcomes between PRP and hyaluronic acid (HA) or PRP and placebo in pain and function. Average pretreatment Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were 52.36 and 52.05 for the PRP and HA groups, respectively (P = .420). Mean post-treatment WOMAC scores for PRP were significantly better than for HA at 3 to 6 months (28.5 and 43.4, respectively; P = .0008) and at 6 to 12 months (22.8 and 38.1, respectively; P = .0062). None of the included studies used corticosteroids. Conclusions: In patients with symptomatic knee OA, PRP injection results in significant clinical improvements up to 12 months postinjection. Clinical outcomes and WOMAC scores are significantly better after PRP versus HA at 3 to 12 months postinjection. There is limited evidence for comparing leukocyte-rich versus leukocyte-poor PRP or PRP versus steroids in this study. Level of Evidence: Level I, systematic review of Level I studies.

Osteoarthritis (OA) of the knee is a common condition associated with pain and morbidity. The increasing number of patients with symptomatic OA will continue to place an increasingly large economic burden on global health care systems. Knee arthroplasty is a reliable and successful surgical treatment to address end-stage OA. Unfortunately, the cost of and time delay to knee replacement is potentially prohibitive in some countries. In the United States, potential overutilization of arthroplasty is being met with increasing scrutiny of preoperative nonsurgical treatment. This includes both nonpharmacological and pharmacological approaches. Intra-articular corticosteroid and viscosupplementation injections have successful, albeit short-term, benefits.

Recent American Academy of Orthopaedic Surgeons clinical practice guidelines have demonstrated...
Table 1. Effects of Platelet-Rich Plasma on Inflammation and Metabolism

<table>
<thead>
<tr>
<th>Increases Anti-inflammatory Markers</th>
<th>Decreases Proinflammatory Markers</th>
<th>Anabolic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>AggreCan</td>
<td>Cyclooxygenases</td>
<td>Proteoglycan synthesis</td>
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<tr>
<td>Metalloproteinases</td>
<td>Proteoglycan synthesis Cartilage regeneration</td>
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<td>Disintegrins</td>
<td>Tumor necrosis factor alpha</td>
<td>Interferon gamma</td>
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<td>Tumor necrosis factor alpha</td>
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<tr>
<td>Selectins</td>
<td>Interleukin-1</td>
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</tbody>
</table>

inconclusive evidence to recommend for or against corticosteroid and strong evidence against hyaluronic acid (HA) viscosupplementation injections for patients with symptomatic knee OA. This has led to the emergence of other injectable options for symptom relief and functional improvement in these patients.

Platelet-rich plasma (PRP) is an autologous derivative of whole blood that contains high concentrations of growth factors including transforming growth factor-β, insulin-like growth factor, platelet-derived growth factor, basic fibroblast growth factor, and vascular endothelial growth factor, as well as bioactive proteins that influence the healing of tendon, ligament, muscle, and bone. As a result, it has been studied for its efficacy in management of various pathologies including but not limited to OA, lateral epicondylitis, rotator cuff disease, Achilles and patella tendinopathy, hamstring injuries, and degenerative spine disease. Through the effects of the various growth factors, PRP has been shown to have a positive effect on chondrogenesis and mesenchymal stem cell proliferation. PRP has also been shown to increase anti-inflammatory and decrease proinflammatory mediators (Table 1). Evidence has shown a reduction in the transactivation of nuclear factor-kappa B, the critical regulator of the inflammatory process. PRP also decreases the expression of inflammatory enzymes cyclooxygenase 2 and 4, metalloproteinases, and disintegrins. These combined effects of PRP make it a potential injectable option for management of OA.

Clinically, the comparative efficacy and effectiveness of intra-articular injections of PRP, HA, and corticosteroid in the treatment of knee OA are unclear and controversial. There are limited studies comparing these options, and there are variations in the treatment approach including subject-, knee-, and outcome-specific variables including PRP preparation techniques, platelet count, severity of OA, number of injections, and molecular weight of HA. There have been numerous studies investigating the effects of PRP or HA in the treatment of knee OA, but most do not compare these 2 or use a control group.

The purpose of this systematic review was (1) to determine whether PRP injection is able to significantly improve validated patient-reported outcomes in patients with OA of the knee at 6 and 12 months postinjection, (2) to determine whether there is a significant difference in outcomes between PRP and viscosupplementation or PRP and placebo injections at 6 and 12 months postinjection; and (3) to determine the similarities and differences between the variety of PRP formulations used in the analyzed studies. It was hypothesized that (1) PRP injections will significantly improve validated patient-reported outcomes in patients with OA of the knee at 6 to 12 months postinjection, (2) there will be a significant difference in outcomes between PRP and viscosupplementation or PRP and placebo at 6 and 12 months postinjection, and (3) different preparations of PRP will yield significantly different results.

Methods

A systematic review was registered on PROSPERO on August 12, 2014 (registration ID: CRD42014013032). Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. English-language original research therapeutic level I evidence (based on Oxford Centre for Evidence Based Medicine) randomized comparative trials were eligible for inclusion. The studies that were sought compared the use of autologous PRP with HA viscosupplementation, corticosteroid, placebo, or other intra-articular injections for the treatment of symptomatic knee OA in humans with a minimum follow-up of 6 months. Basic science ex vivo and in vitro studies, levels II, III, IV, or V evidence, letters to the editor, nonknee OA, asymptomatic OA, and PRP compared with surgical options were excluded.

Separate electronic searches of the following databases were conducted: PubMed, Cochrane Central Register of Controlled Trials, SCOPUS, and Sport Discus. The searches were performed on February 12, 2015. The search terms used including “platelet-rich plasma knee osteoarthritis”, “platelet rich plasma gonarthritis”, and “platelet rich plasma knee degenerative joint disease” were entered as medical subject headings for searches in all the databases used. The search results were reviewed for duplicates and the inclusion criteria to determine articles that were included in the final analysis (Fig 1).

Two authors (C.J.M. and J.D.H.) independently reviewed all articles using the methodology recommended by Harris et al. The study type and design, methods, level of evidence, and populations enrolled were first identified. Primary and secondary outcomes were analyzed. This information was used to reach a consensus based on the conclusions made by the authors of the original studies.

Because of the heterogeneity of outcome measures, a best-evidence synthesis was used instead of a
meta-analysis. The results of the quality assessments of the individual studies were used to classify the level of evidence. This qualitative analysis was performed with 5 levels of evidence based on the quality and results of the included studies. In addition, study methodological quality was analyzed using the Modified Coleman Methodology Score (MCMS). Descriptive statistics were calculated using the mean ± standard deviation for quantitative continuous data and frequencies with percentages for qualitative categorical data. Comparisons in outcome scores at pre- and post-injection time points and between PRP and HA groups were made using the 2-proportion z-test calculator using alpha 0.05 because of the difference in sample sizes between compared groups.

**Results**

Six articles (739 patients, 817 knees) were analyzed (Table 2). There were 39% males and 61% females with a mean age of 59.9 years per patient and 59.2 years per knee and mean follow-up of 38 weeks per patient and 37 weeks per knee. Radiographically, the Kellgren-Lawrence grading system was used to determine severity of knee OA. Two studies used the Ahlback classification system and showed that 58.2% were grade I, 32.4% were grade II, and 9.4% were grade III. Four studies used the Kellgren-Lawrence classification and showed that 8.7% were grade I, 40.7% were grade II, 37.9% were grade III, and 12.6% were grade IV. The Filardo et al. study only reported average Kellgren-Lawrence grades for HA and PRP groups (2.1 and 2.2, respectively) and therefore was not included in the grade-percentage stratification above. According to the MCMS, 3 articles were excellent (with scores of 85 or greater), and 3 were good (scores between 70 and 84), with a mean score of 83.3/100. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was the most frequently used outcome score (5 of 6 studies), however, one of 6 used International Knee Documentation Committee (IKDC), one of 6 used Knee Injury and Osteoarthritis Outcome Score (KOOS), one of 6 used Short Form-36, one of 8 used Tegner, 2 of 6 used the visual analog scale (VAS), and 2 of 6 used Lequesne.

PRP significantly improved validated patient-reported outcomes, according to WOMAC and IKDC scores, in patients with OA of the knee at 6 and 12 months post-injection (Table 3). PRP was also shown to be better than HA at improving patient outcomes. The outcomes evaluated included pain, physical function, and stiffness. According to 2-proportion z-tests, the average pretreatment WOMAC scores for PRP and HA were 52.36 and 52.05, respectively (P = .420), among studies that
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<tr>
<td>Subject enrollment date</td>
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<td>Not recorded</td>
<td>January 2008-October 2009</td>
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<td>Italy, Europe</td>
<td>India, Asia</td>
<td>Spain, Europe</td>
<td>Spain, Europe</td>
<td>Iran, Asia</td>
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<td>Conflict of interest</td>
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<td>None</td>
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<td>None</td>
<td>Not mentioned</td>
<td>None</td>
</tr>
<tr>
<td>No. of subject (knees)</td>
<td>120 (120)</td>
<td>109 (109)</td>
<td>78 (156)</td>
<td>176 (176)</td>
<td>96 (96)</td>
<td>160 (160)</td>
</tr>
<tr>
<td>Gender: male, female</td>
<td>53, 67</td>
<td>68, 41</td>
<td>22, 53</td>
<td>85, 91</td>
<td>38, 58</td>
<td>23, 116</td>
</tr>
<tr>
<td>Mean age</td>
<td>66.4</td>
<td>56.5</td>
<td>52.8</td>
<td>59.8</td>
<td>63.6</td>
<td>58.8</td>
</tr>
<tr>
<td>Bilateral v unilateral knee injections</td>
<td>Unilateral</td>
<td>Unilateral</td>
<td>Bilateral</td>
<td>Unilateral</td>
<td>Unilateral</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Right v left</td>
<td>91 right, 29 left</td>
<td>Not recorded</td>
<td>78 left, 78 right</td>
<td>Not recorded</td>
<td>Not recorded</td>
<td>Not recorded</td>
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</table>

**Study Group 1**
- 60 patients received 4 weekly intra-articular injections of PRP
- 54 patients received 3 weekly intra-articular injections of PRP
- 26 patients (52 knees) received a single injection of PRP and 25 patients (50 knees) received 2 injections of PRP 3 weeks apart
- 87 patients received 3 weekly intra-articular PRGF-Endoret
- 48 patients received 3 biweekly intra-articular injections of PRP
- 87 patients received 2 intra-articular injections of PRP

**Study Group 2**
- 60 patients received 4 weekly intra-articular injections of HA
- 55 patients received 3 weekly intra-articular injections of HA
- 23 patients (46 knees) received a single injection of normal saline (8 mL)
- 89 patients received 3 weekly intra-articular HA
- 48 patients who received 1 intra-articular HA

**Radiographic classification**
- Kellgren-Lawrence Grade I: 25
- Kellgren-Lawrence Grade II: 22
- Kellgren-Lawrence Grade III: 13
- Average of Grade 2.2 for PRP group and Grade 2.1 for HA group
- Kellgren-Lawrence Grade I: 98
- Kellgren-Lawrence Grade II: 39
- Kellgren-Lawrence Grade III: 23
- Kellgren-Lawrence Grade I: 87
- Kellgren-Lawrence Grade II: 64
- Kellgren-Lawrence Grade III: 47
- Kellgren-Lawrence Grade IV: 17
- Kellgren-Lawrence Grade I: 87
- Kellgren-Lawrence Grade II: 64
- Kellgren-Lawrence Grade III: 47
- Kellgren-Lawrence Grade IV: 17

**Length of follow up**
- 24 weeks
- 12 months
- 6 months
- 24 weeks
- 48 weeks
- 52 weeks

**Outcome scores used**
- WOMAC
- IKDC, TEGNER, KOOS, EQ-VAS
- WOMAC, VAS
- WOMAC, Lequesne
- WOMAC, Lequesne, OMERACT-OARSI
- WOMAC, SF-36

**Prior surgeries**
- No
- 63 subjects
- Not recorded
- Not recorded
- Not recorded

**Prior Injections**
- No
- 63 subjects
- Not recorded
- Not recorded
- Not recorded

**Prior physical therapy**
- Yes
- Not recorded
- Not recorded
- Not recorded
- Not recorded

**Post injection treatments**
- None
- None
- None
- None
- None

**Use of NSAIDs (few days pre injection and immediate post-injection)**
- No
- No
- Not recorded
- Not recorded
- Not recorded

**Use of cryotherapy post-injection**
- No
- Yes
- No
- No
- No

**Injection approach**
- Superolateral
- Superolateral
- Superolateral
- Superolateral
- Anteromedial or Lateral midpatellar
compared both treatment modalities. At 12 to 26 weeks, the average WOMAC scores for PRP and HA treatments were 28.5 and 43.4, respectively, with a significant difference ($P = .0008$) favoring PRP over HA. At 26 to 52 weeks, the average WOMAC scores for PRP and HA treatments were 22.8 and 38.1, respectively, with a significant difference ($P = .0062$) favoring PRP over HA.

There was a significant difference between pre-PRP and 4 to 6 weeks ($P = .047$), 6 to 12 weeks ($P = .006$), 12 to 26 weeks ($P < .001$), and 26 to 52 weeks ($P < .001$). There was no significant difference between 4 to 6 weeks and 6 to 12 weeks ($P = .52$); 6 to 12 weeks and 12 to 26 weeks ($P = .26$); and 12 to 26 weeks and 26 to 52 weeks ($P = .21$). WOMAC was most frequently used outcome score (5/6 studies). All post-PRP time points up to 12 months were significantly better than preinjection in WOMAC score. The distribution-based method using the standard error of measurement was used to determine the minimal clinical important difference (MCID). A difference in WOMAC and IKDC scores of at least one standard error of measurement was considered the criterion for achieving MCID.24 The WOMAC and IKDC scores analyzed in this review revealed true MCID in outcomes.

All studies showed significant clinical and statistical improvements in outcomes at 3 to 12 months of follow-up, including pain, physical function, and stiffness, with the use of PRP in treating knee OA according to WOMAC and IKDC scores. All but one study showed significant differences between PRP and HA or PRP and placebo in clinical outcomes of improvement of pain and function for at least 6 to 12 months. One study compared PRP to saline (placebo), and no studies compared PRP to corticosteroid injection.

No study compared leukocyte-poor PRP to leukocyte-rich PRP. However, all studies except Filardo et al. used leukocyte-poor PRP, and all studies except Filardo et al. showed significant clinical and statistical improvements on WOMAC scores between HA and PRP or HA and placebo groups. The studies used different PRP preparations with 3 of 6 using calcium chloride activator, one of 6 used leukocyte-rich PRP, 4 of 6 using the single spin approach, and 2 of 6 using the double spin approach (Table 4). The different PRP systems used were also classified using the PAW classification system, a classification system for PRP that looks at platelet concentration, activation method, and white blood cell (WBC) count.25

Owing to the fact that the only outcomes that were able to be compared were those of WOMAC scores as indicated above, the best-evidence synthesis is moderate and the summary of recommendation taxonomy is "B" for this review.22,26

**Discussion**

It was determined that intra-articular PRP injections significantly improve the clinical outcomes in
Table 3. Summary of Results Including WOMAC, VAS, Tegner, Lequesne, IKDC, and SF-36 Scores from the Various Studies

<table>
<thead>
<tr>
<th>Articles</th>
<th>Pretreatment</th>
<th>Early (4-6 Weeks)</th>
<th>Mid (6-12 Weeks)</th>
<th>Late (12-26 Weeks)</th>
<th>Extended (26-52 Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerza et al.27</td>
<td>ACP: WOMAC</td>
<td>76.9 ± 9.5</td>
<td>ACP: WOMAC</td>
<td>49.6 ± 17.7</td>
<td>ACP: WOMAC</td>
</tr>
<tr>
<td></td>
<td>HA: WOMAC</td>
<td>75.4 ± 10.7</td>
<td>HA: WOMAC</td>
<td>55.2 ± 12.3</td>
<td>HA: WOMAC</td>
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<td></td>
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<td>(P &lt; .001) between</td>
<td>(P &lt; .001) between</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>groups</td>
<td>groups</td>
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<tr>
<td>Filardo et al.28</td>
<td>PRP: IKDC score</td>
<td>50.2 ± 15.7</td>
<td>PRP: IKDC score</td>
<td>62.8 ± 17.6</td>
<td>PRP: IKDC score</td>
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<tr>
<td></td>
<td>Tegner score</td>
<td>2.9 ± 1.4</td>
<td>HA: IKDC score</td>
<td>61.4 ± 16.2</td>
<td>HA: IKDC score</td>
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<tr>
<td></td>
<td>HA: IKDC score</td>
<td>47.4 ± 15.7</td>
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<td>64.3 ± 16.4</td>
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<td></td>
<td>Tegner score</td>
<td>2.6 ± 1.2</td>
<td></td>
<td>61.0 ± 18.2</td>
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<tr>
<td>Patel et al.29</td>
<td>PRP1: WOMAC</td>
<td>49.86 ± 17.83</td>
<td>PRP1: WOMAC 25.36</td>
<td>53.20 ± 16.18</td>
<td>PRP1: WOMAC 27.18</td>
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<tr>
<td></td>
<td>VAS 4.56 ± 0.61</td>
<td></td>
<td>PRP2: WOMAC 24.96</td>
<td>53.20 ± 16.18</td>
<td>PRP2: WOMAC 30.48</td>
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<td></td>
<td>PRP2: WOMAC</td>
<td>53.20 ± 16.18</td>
<td>PRP2: WOMAC 25.70</td>
<td>53.20 ± 16.18</td>
<td>PRP2: WOMAC 30.48</td>
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<tr>
<td></td>
<td>VAS 4.56 ± 0.56</td>
<td></td>
<td>Saline: WOMAC 46.78</td>
<td>53.20 ± 16.18</td>
<td>Saline: WOMAC 53.09</td>
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<tr>
<td></td>
<td>Saline: WOMAC</td>
<td>45.54 ± 17.29</td>
<td></td>
<td>53.20 ± 16.18</td>
<td>VAS 4.61 ± 0.745</td>
</tr>
<tr>
<td></td>
<td>VAS 4.57 ± 0.62</td>
<td></td>
<td></td>
<td></td>
<td>WOMAC: percentage benefit from baseline at each follow up was greater in PRP1 and PRP2 than Saline (P &lt; .001) with no difference between PRP1 and PRP2.</td>
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<td>VAS pain reduction benefit for the PRP1 and PRP 2 groups (P = .001) with no significant benefit between the groups (P = .410). No VAS pain reduction benefit for saline group (P = .598)</td>
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<tr>
<td>Sanchez et al.30</td>
<td>PRGF: WOMAC</td>
<td>121.8 ± 44.4</td>
<td>DNR</td>
<td>DNR</td>
<td>PRGF: WOMAC 74.0 ± 42.7</td>
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<td></td>
<td>Lequesne 9.5 ± 3.0</td>
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<td>38.2% of patients had 50% decrease in WOMAC pain score 57.3% of patients had 20% decrease in WOMAC pain score Lequesne 5.2 ± 3.4</td>
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<tr>
<td></td>
<td>HA: WOMAC</td>
<td>115.6 ± 45.1</td>
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<tr>
<td></td>
<td>Lequesne 9.1 ± 3.2</td>
<td></td>
<td></td>
<td></td>
<td>HA: WOMAC 78.3 ± 48.1</td>
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<td>24.1% of patients had 50% decrease in WOMAC pain</td>
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Table 3. Continued

<table>
<thead>
<tr>
<th>Articles</th>
<th>Pretreatment</th>
<th>Early (4-6 Weeks)</th>
<th>Mid (6-12 Weeks)</th>
<th>Late (12-26 Weeks)</th>
<th>Extended (26-52 Weeks)</th>
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<tr>
<td>Vaquerizo et al. 31</td>
<td>PRGF: WOMAC</td>
<td>45.9 ± 12.7</td>
<td>DNC</td>
<td>DNC</td>
<td>DNC</td>
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<tr>
<td></td>
<td>Lequesne</td>
<td>12.8 ± 3.8</td>
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<tr>
<td></td>
<td>HA: WOMAC</td>
<td>50.8 ± 18.4</td>
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<tr>
<td></td>
<td>Lequesne</td>
<td>13.1 ± 38</td>
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<tr>
<td>Raeissadat et al. 32</td>
<td>PRP: WOMAC</td>
<td>39.5 ± 17.06</td>
<td>DNC</td>
<td>DNC</td>
<td>DNC</td>
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<tr>
<td></td>
<td>SF-36 (PCS)</td>
<td>178.14 ± 81.0</td>
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<td></td>
<td>SF-36 (MCS)</td>
<td>229.22 ± 95.62</td>
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<tr>
<td></td>
<td>HA: WOMAC</td>
<td>28.69 ± 16.69</td>
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<td></td>
<td>SF-36 (PCS)</td>
<td>180.4 ± 68.52</td>
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<td></td>
<td>SF-36 (MCS)</td>
<td>226.43 ± 97.39</td>
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</table>

score. 52.9% of patients had 20% decrease in WOMAC pain score. Lequesne 5.4 ± 3.3
Differences between PRGF and HA for 50% decrease in WOMAC pain score
\( P = .044 \), for 20% decrease \( P = .555 \), for total WOMAC score \( P = .561 \), and for Lequesne score \( P = .714 \)

For patients with 30% decrease in:
WOMAC summed score: rate of response of PRGF was 66, 43, and 23 percentage points higher than that of HA for pain, physical function and stiffness, respectively \( P < .001 \), \( P < .001 \), \( P = .02 \), respectively.
Lequesne score: PRGF group is 56 percentage points higher than HA group \( P < .001 \)
For patients with 50% decrease in:
WOMAC summed score: rate of response of PRGF was 43, 29, and 19 percentage points higher than that of HA for pain, physical function and stiffness, respectively \( P < .001 \), \( P = .001 \), \( P = .035 \), respectively.
Lequesne score: PRGF group is 25 percentage points higher than HA group \( P = .002 \)

For patients with 30% decrease in:
WOMAC summed score: rate of response of PRGF was 46, 37, and 40 percentage points higher than that of HA for pain, physical function and stiffness, respectively \( P < .001 \), \( P < .001 \), \( P < .001 \), respectively.
Lequesne score: PRGF group 46 percentage points higher than HA group \( P < .001 \)
For patients with 50% decrease in:
WOMAC summed score: rate of response of PRGF was 29, 31, and 28 percentage points higher than that of HA for pain, physical function and stiffness, respectively \( P < .001 \), \( P < .001 \), \( P = .001 \), respectively.
Lequesne score: 19 and 2 percentage points in the PRGF and HA groups, respectively
symptomatic knee OA. PRP was also shown to be significantly better than HA or placebo for the treatment of symptomatic knee OA. Treating OA nonoperatively has been ongoing for several decades. Multiple studies have reported the use of HA, PRP, and corticosteroids, among other agents, in the nonoperative treatment of OA. While there are a good amount of studies documenting the use of HA in the treatment of knee OA, there are limited studies documenting the use of PRP for the same purpose. More importantly, there are very limited studies comparing the use of PRP with that of HA or PRP with placebo in the treatment of knee OA.27-32 This study’s aim was to determine whether PRP injection is able to significantly improve validated patient-reported outcomes in patients with OA of the knee, determine whether there is a significant difference in outcomes between PRP and viscosupplementation or PRP and placebo injections, and evaluate the similarities and differences between the variety of PRP formulations used in the analyzed studies. The hypotheses that (1) PRP injections will significantly improve validated patient-reported outcomes in patients with OA of the knee and (2) that there will be significant differences in outcomes between PRP and viscosupplementation or PRP and placebo were confirmed; the third hypothesis that different preparations of PRP will yield significantly different results was inconclusive. Clinicians should use PRP in patients with symptomatic knee OA with Ahlback grades I to III or Kellgren-Lawrence grades I to III. PRP injections can be administered in 2 to 4 sessions, 2 to 4 weeks apart. This recommendation is based on ranges used in the studies included in this review.

Multiple studies have shown improved patient outcomes with the use of PRP for the treatment of knee OA. Gobbi et al. tried to determine the effectiveness of intra-articular PRP injections in active patients with knee OA and to evaluate clinical outcomes in patients with and without previous surgical treatment for cartilage lesions.33 The PRP treatment showed positive effects in patients with knee OA. Operated and non-operated patients showed significant improvement by means of pain reduction and improved symptoms and quality of life.

Autologous PRP injections have shown more and longer efficacy than HA injections in reducing pain and function and recovering articular function.15 Three homogenous groups of patients were treated with 3 injections of PRP, low molecular weight HA, and high molecular weight HA. The results showed better performance for PRP group at 6 months of follow-up. This study also showed that younger and more active patients achieved better results with a low degree of cartilage degeneration.

There are many PRP systems, some of which have higher concentrations of WBCs, with others having
higher concentrations of growth factors but not the additional concentration of WBCs. Since neutrophils are the most abundant type of WBCs, excessive neutrophil infiltration has been associated with chronic inflammation and delayed wound healing. Through phagocytosis, macrophages are known to clear up the particulate debris that accumulates after neutrophil activation and release of proteolytic enzymes.34 Several studies have investigated the effects of leukocyte-poor versus leukocyte-rich PRP in tissue healing. PRP rich in leukocytes have been shown to cause a significantly greater acute inflammatory response and increased synoviocyte cell death.35,36 Despite having similar safety profiles, leukocyte-rich PRP and leukocyte-poor PRP were shown to both induce more transient reactions than does HA.37 Of the studies included in this review, the Filardo et al. study used leukocyte-rich PRP, which showed improved outcomes in the parameters measured but no significant differences when compared to HA. All other studies included in this review used leukocyte-poor PRP and all showed improved outcomes in the parameters measured as well as significant differences when compared to HA or placebo. Given data from the MCMS, future studies can improve on looking at longer-term follow-ups of at least 2 years, including postinjection rehabilitation protocols, and providing adequate and consistent description of injection techniques used.

### Table 4. Platelet-Rich Plasma (PRP) Preparation and Characteristics and Use of Ultrasound Guidance for Verification of Injection in Knee Joint

<table>
<thead>
<tr>
<th>Article</th>
<th>PRP Spinning Approach</th>
<th>Duration of Spin (Minutes)</th>
<th>Company</th>
<th>PRP Activator</th>
<th>PRP Volume Injected (mL)/No. of Injections</th>
<th>Platelet Concentration</th>
<th>White Blood Cell Count</th>
<th>PAW Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerza et al.27</td>
<td>Single</td>
<td>NR</td>
<td>BioCore, Arthrex Inc, Karlsfeld, Germany</td>
<td>None</td>
<td>5,5/4</td>
<td>&gt;5× baseline</td>
<td>Low</td>
<td>PAW Classification</td>
</tr>
<tr>
<td>Filardo et al.28</td>
<td>Double</td>
<td>6 and 15 b</td>
<td>NR</td>
<td>CaCl2</td>
<td>8/3</td>
<td>5× baseline</td>
<td>1.2× baseline</td>
<td>P4-A</td>
</tr>
<tr>
<td>Patel et al.30</td>
<td>Single</td>
<td>15</td>
<td>Arthrex, Inc, Karlsfeld, Germany</td>
<td>CaCl2</td>
<td>8/1 and 2 b</td>
<td>5× baseline</td>
<td>0</td>
<td>P2-B/P3-B</td>
</tr>
<tr>
<td>Sanchez et al.30</td>
<td>Single</td>
<td>8</td>
<td>BTL Biotechnology Institute, Vitoria, Spain</td>
<td>CaCl2</td>
<td>8/3</td>
<td>&lt;5× baseline</td>
<td>Low</td>
<td>P2-B/P3-B</td>
</tr>
<tr>
<td>Vaquerizo et al.33</td>
<td>Single</td>
<td>8</td>
<td>NHL, Biotechnology Institute, Vitoria, Spain</td>
<td>CaCl2</td>
<td>8/3</td>
<td>&lt;5× baseline</td>
<td>Low</td>
<td>P2-B/P3-B</td>
</tr>
<tr>
<td>Racisadat et al.32</td>
<td>Double</td>
<td>15 and 7 c</td>
<td>Arya Mabna Tashkis Corp.</td>
<td>None</td>
<td>4-6/2</td>
<td>5.2× and 4.8× baseline</td>
<td>780 and 808 cells/μL</td>
<td>P4-B</td>
</tr>
</tbody>
</table>

**NOTE.** No ultrasound guidance was used in any study. NR, not recorded; PAW classification, classification system for PRP that looks at platelet concentration, activation method, and white blood cell count25; PGIMER, Department of transfusion Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

*Represents times for first and second centrifugation.

One group received one injection, and the other group received 2 injections.

Averages for first and second injections, respectively.
All but one study used WOMAC scores, with the outlier using IKDC scores together with KOOS and Tegner. WOMAC and IKDC both meet MCID and MDC criteria and have better test-retest reliability and internal consistency compared with KOOS and Tegner.24 Thus WOMAC and IKDC are the best outcome scores for knee OA studies. Future studies can improve with using both WOMAC and IKDC tools simultaneously.

There are several limitations of this review. The number of studies (n = 6) included in this review is small. Also, one of the 6 studies included compared PRP to placebo, while the others compared PRP to HA. Another possible limitation of this review is that other relevant studies on this topic could have been excluded, despite conducting a systematic search. Given that we found many duplicate studies among several databases, we do not feel that many studies, if any at all, were omitted.

Conclusions
In patients with symptomatic knee OA, PRP injection results in significant clinical improvements up to 12 months postinjection. Clinical outcomes and WOMAC scores are significantly better after leukocyte-poor PRP versus HA at 3 to 12 months postinjection. There is limited evidence for comparing leukocyte-rich versus leukocyte-poor PRP in this study.

References


