

# The Use of Platelet-Rich Plasma in Symptomatic Knee Osteoarthritis

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## Abstract

With average life expectancy and the rising prevalence of obesity, osteoarthritis (OA) is creating an increasingly large financial and physical burden on the U.S. population today. As the body ages and experiences trauma, articular cartilage surfaces in joints are gradually worn away, leading to OA. Traditionally, treatment options have included lifestyle modifications, pain management, and corticosteroid injections, with joint replacement reserved for those who have exhausted nonsurgical measures. More recently, hyaluronic acid, micronized dehydrated human amniotic/chorionic membrane tissue, and platelet-rich plasma (PRP) injections have started to gain traction. PRP has been shown to have both anti-inflammatory effects through growth factors such as transforming growth factor- $\beta$  and insulin-like growth factor 1, and stimulatory effects on mesenchymal stem cells and fibroblasts. Multiple studies have indicated that PRP is superior to hyaluronic acid and corticosteroids in terms of improving patient-reported pain and functionality scores. Unfortunately, there are many variations in PRP preparation, and lack of standardization in factors, such as speed and duration of centrifugation, leads to wide ranges of platelet and leukocyte concentrations. This review examines the current literature addressing the use of PRP in symptomatic knee OA and addresses suggestions for future studies in this area.

## Keywords

- ▶ knee
- ▶ articular cartilage
- ▶ articular cartilage restoration

Articular cartilage is vital in optimizing the efficiency of locomotion by minimizing friction and providing support for mechanical loading of any joint.<sup>1</sup> Trauma, aging, and metabolic changes are just a few factors that can accelerate the reduction and degeneration of the articular surfaces of joints in a process known as osteoarthritis (OA).<sup>2</sup> In the knee, these surfaces include the menisci, ligaments, periarticular muscle, and articular cartilage. With an increased emphasis on physical activity coupled with a longer life span of the general population, society has experienced a marked increase in the incidence of OA.<sup>3,4</sup> Between 1995 and 2008, the incidence of OA in the United States grew from 21 million to 27 million and is projected to increase to 67 million by 2030, making it a huge financial and physical burden on today's population.<sup>5</sup>

Due to its avascular and aneural nature, articular cartilage exhibits limited spontaneous healing and repair. Thus, intervention is often necessary for the resolution of symptoms.<sup>3</sup>

Standard of care has historically included either nonoperative management, including lifestyle modification, anti-inflammatory medications, physical therapy, and intra-articular injections, and surgical management, such as joint arthroscopy and, ultimately, joint arthroplasty.<sup>6,7</sup> Joint injection therapy is of particular interest as it is often the final nonsurgical intervention prior to performance of arthroscopic debridement or the even more costly and invasive total joint replacement or osteotomy, which is reserved for patients with extreme pain and limitation of daily activities.<sup>2,6,8</sup>

Current office-based options for intra-articular injections include corticosteroids, hyaluronic acid (HA) viscosupplementation, micronized dehydrated human amniotic/chorionic membrane tissue,<sup>9,10</sup> and platelet-rich plasma (PRP).<sup>8</sup> Short-term symptomatic relief has been seen in patients with knee OA using HA as well as corticosteroid injections, but improvement has not been shown to be sustained at 2-year follow-up.<sup>11</sup>

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Due to the lack of long-term benefit, patients often request multiple injections and require subsequent treatment options. The use of amniotic allograft tissue has not been studied clinically at follow-ups longer than 3 months, although it has shown pain reduction in patients with joint and tendon pathologies at that time point.<sup>10</sup> Given these limitations of these options, there is a desire for alternative injections such as PRP.

Clinical use of PRP injections has gained traction in plastic surgery,<sup>12</sup> maxillofacial surgery,<sup>13</sup> wound healing,<sup>14</sup> and dermatology.<sup>15</sup> In the practice of sports medicine, PRP injections have been used in the treatment of lateral epicondylitis, showing reduced rates of conversion to surgical treatment from medical management,<sup>16</sup> as well as marked improvement in visual analog scale (VAS) pain scale and tendon appearance on magnetic resonance imaging (MRI).<sup>17</sup> Furthermore, PRP has been shown to provide relief from pain and inflammation associated with OA, making it a therapeutic treatment in the management of OA.<sup>3,8</sup> PRP can be obtained from the patient on the same day as the injection is given and is processed through minimal steps, making it both cost-effective and convenient for treatment in patients with OA.<sup>18</sup>

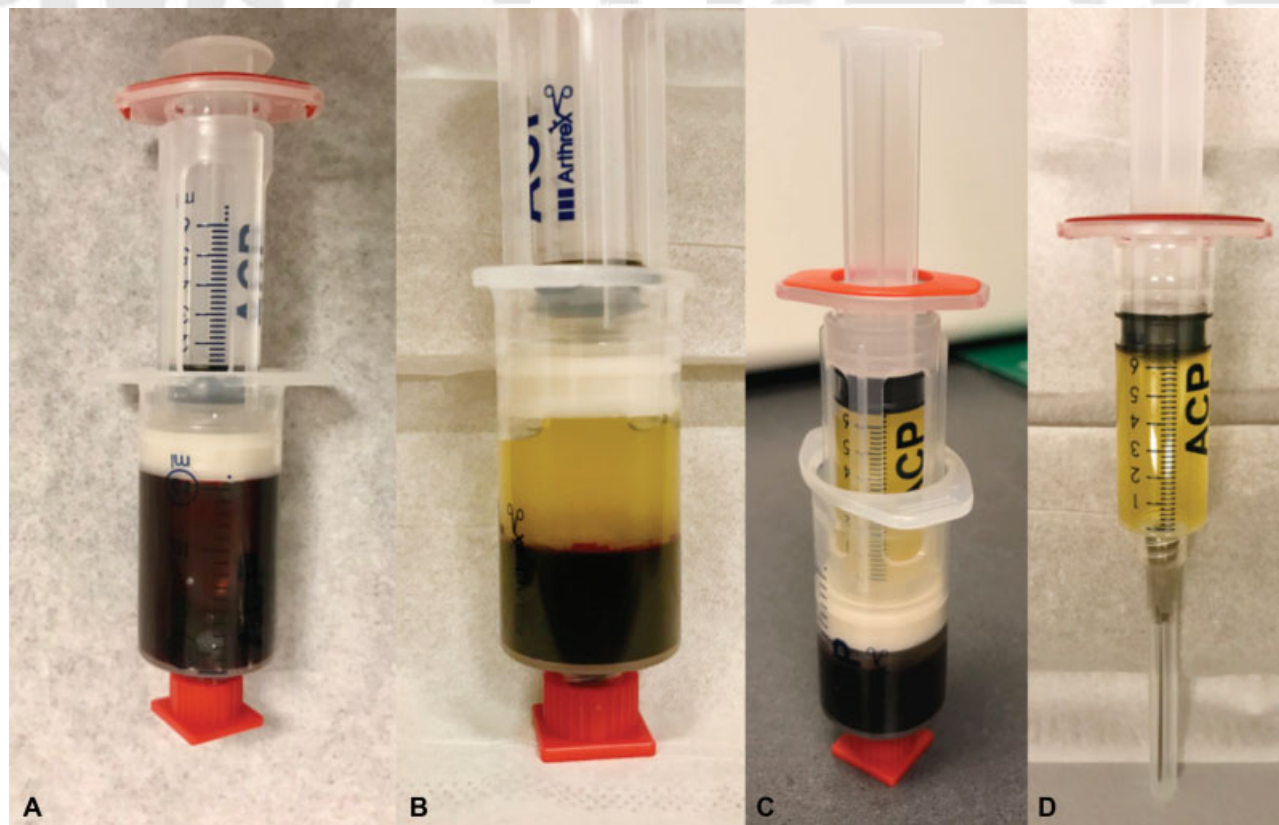
### What Is Platelet-Rich Plasma and How Does It Work

PRP is defined as plasma that contains a higher concentration of platelets than whole blood, which typically has 150,000 to 300,000 platelets per microliter.<sup>19,20</sup> Preparations of PRP

traditionally have a three- to fivefold higher platelet count compared with normal plasma, with some reaching as high as 9.3 times the concentration found in whole blood.<sup>21</sup>

To obtain PRP, venous blood is first drawn from the patient and centrifuged, creating a concentrated suspension. Due to the differing densities of components of whole blood, spinning down the specimen is able to separate the different components into different layers: platelet-poor plasma, buffy coat, and red blood cells (RBCs). Platelets, along with white blood cells (WBCs) and some proteins, are found in highest concentration in the buffy coat located between the RBCs and the platelet-poor plasma (→Fig. 1). DeLong et al classified PRP preparations into two separate forms: plasma-based and buffy coat based. Plasma-based preparations of PRP attempt to include only plasma and platelets while excluding WBCs. This slower and shorter centrifuge method typically yields products with two to three times the baseline levels of platelets with minimal WBC. In contrast, buffy coat based preparation uses both the platelet-poor plasma and the buffy coat layer. This preparation technique involves higher spin rates and longer centrifugation to produce three to eight times the baseline levels of platelet concentrations but also includes WBC/leukocytes as well as RBCs.<sup>22</sup> The different preparations results in different concentrations of platelets, WBCs, and RBCs, the importance of which is discussed in detail in the following.

Interestingly, Wu et al reported on their preparation of PRP using ultrasonic standing waves rather than centrifuge.



**Fig. 1** Stepwise platelet-rich plasma (PRP) preparation. (A) Venous blood. (B) Separation of red blood cells, platelets, and plasma after centrifuge. (C) Extraction of PRP from sample. (D) Isolated PRP.

Porcine blood was collected and mixed with an anticoagulant. Next, 10 mL of this mixture was placed in a hexagonal transducer, with degassed water used as the coupling medium to produce PRP. The resonant frequency of the transducer is approximately 4.5 MHz, and opposite surfaces of piezoelectric ceramics were used as reflectors to generate the ultrasonic standing waves. This enhanced the accumulation of RBCs and increased the sedimentation speed. PRP was also prepared through single centrifugation with a double syringe system, as discussed later. The authors report that while this method was able to separate whole blood into two layers, no buffy layer was found after sonification. However, the study noted greater RBC removal and greater platelet concentration in the ultrasound prepared group. Additionally, there was no significant difference in the platelet-derived growth factor (PDGF)-BB concentrations between the groups.<sup>23</sup>

PRP contains a high concentration of platelets, which contain more than 1,100 proteins such as growth factors.<sup>24</sup> Platelets play a large role in the initiation of healing as they

are responsible for forming the scaffolding for clot formation, which leads to chemotaxis of appropriate cytokines. Platelet  $\alpha$ -granules contain growth factors and anti-inflammatory cytokines such as insulin-like growth factor 1 (IGF-1), IGF-2, vascular endothelial growth factor (VEGF), transforming growth factor- $\beta$ (TGF- $\beta$ ), fibroblast growth factor (FGF), endothelial growth factor, and PDGF. These are released at the healing site<sup>25,26</sup> and have been shown to help stimulate the growth of autologous chondrocytes and mesenchymal stem cells, as well as components of the extracellular matrix such as proteoglycans and types I and II collagen.<sup>27-31</sup> In addition, PRP injections have been shown to increase the mitogenic effect of osteoblasts through the stimulation of TGF- $\beta$ .<sup>3,4,32,33</sup>

Following PRP injections,  $\beta$ -FGF, VEGF, PDGF-BB, and IGF-1 all increase at different points over the next 96 hours, suggesting that PRP activates biological pathways to release growth factors rather than simply delivering growth factors in the concentrate.<sup>34</sup> Similarly, human fibroblasts treated with leukocyte-poor PRP (LP-PRP) demonstrate a significant

**Table 1** Studies evaluating PRP use in symptomatic knee OA

Halpern et al <sup>4</sup>	Forough et al <sup>68</sup>	Cole et al <sup>8</sup>	Raeissadat et al <sup>65</sup>	Patel et al <sup>38</sup>	Rahimzadeh et al <sup>6</sup>
Clinical Journal of Sports Medicine, 2013	Journal of Sports Medicine and Physical Fitness, 2016	American Journal of Sports Medicine, 2017	Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders, 2015	American Journal of Sports Medicine, 2013	Clinical Interventions in Aging, 2018
Single 6-mL PRP injection from 20-mL venous blood prepared through the MTF Biologics Cascade system	20-mL venous blood drawn from the patient and added to 2-mL ACD-A. Blood was centrifuged for 6 min at 1,600 relative centrifuge force and then for 6 min at 2,000 relative centrifuge force to produce 5-mL PRP. Patients were given a single injection	10-mL venous blood drawn and spin via low-leukocyte ACP system (Arthrex Inc.) at 1,500 rpm for 5 min to yield 4-mL LP-PRP. Injections were given at weekly intervals for 3 wk for a total of three injections	35- to 40-mL venous blood drawn and added to 5 mL of ACD-A, which was centrifuged with the Rooyagen Kit for 15 min at 1,600 rpm and again for 7 min at 2,800 rpm, producing 4- to 6-mL LR-PRP. Patients were given a single injection	100-mL venous blood drawn and combined with citrate phosphate dextrose and adenine prior to being centrifuged to at 1,500 rpm for 15 min. A leukocyte filter was used and 8-mL LP-PRP was obtained. Patients were given either a single injection of PRP or two injections of PRP 3 wk apart	20-mL venous blood drawn and processed through the Standard Kit by centrifuge for 20 min at 3,200 rpm followed by 5 min at 1,500 rpm. This resulted in 7-mL PRP. Patients received two injections 1 mo apart or either PRP or prolotherapy (7-mL 25% dextrose)
Patients aged 30–70 y with K-L grade 0–II knee OA <ul style="list-style-type: none"> <li>• Significant reduction in VAS pain score and WOMAC pain score at 6 mo and at 1 y</li> <li>• Significant improvement in ADL score at 6 mo and at 1 y</li> <li>• 12/15 patients with patellofemoral OA demonstrated no significant worsening of OA on MRI at 1 y</li> <li>• No significant change in MRI appearance in 83.3% in lateral femoral and tibial compartment OA</li> </ul>	Patients aged 50–75 y with K-L grade II/III knee OA <ul style="list-style-type: none"> <li>• PRP patients showed significantly more improvement in VAS pain score, 20-m walk test, KOOS questionnaire and in all subcategories of KOOS questionnaire (pain relief, symptom relief, ADL, quality of life) except for sport</li> </ul>	Patients aged 18–80 y with K-L grade I–IV knee OA were injected with either LP-PRP or HA <ul style="list-style-type: none"> <li>• WOMAC pain score improved significantly in both groups</li> <li>• No significant difference between WOMAC score between groups</li> <li>• Significant difference in IKDC and VAS pain score seen at 24 and 52 wk, with PRP exhibiting more improvement</li> </ul>	Patients aged 40–70 y with K-L grade I–IV knee OA received a single injection of LR-PRP or HA <ul style="list-style-type: none"> <li>• WOMAC pain scores significantly improved in both groups at 1-y follow-up, with a significantly greater improvement in the PRP group</li> <li>• Other WOMAC subcategories such as stiffness and physical function only improved significantly in PRP group at 1 y</li> </ul>	Patients with Ahlback grade 1 or 2 with bilateral knee OA <ul style="list-style-type: none"> <li>• VAS pain score and WOMAC score significantly improved at 1, 2, and 6 mo</li> <li>• No significant difference was seen between a single injection or two injections</li> <li>• Adverse effects including syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia were seen more often in patients injected with higher platelet quantities</li> </ul>	Patients aged 40–70 y with K-L grade I/II knee OA <ul style="list-style-type: none"> <li>• Greater improvement seen with PRP than with PRL in terms of functional limitation, pain, and stiffness at 2 and 6 mo</li> <li>• A small and non-significant decrease in scores was seen between 2 and 6 mo, although scores at 6 mo were still significantly improved compared with baseline</li> </ul>

(Continued)

Kon et al <sup>37</sup>	Huang et al <sup>69</sup>	Lana et al <sup>66</sup>	Gobbi et al <sup>44</sup>	Filardo et al <sup>47</sup>	Smith <sup>64</sup>
Arthroscopy: Journal of Arthroscopic and Related Surgery, 2011	International Journal of Surgery, 2017	Journal of Stem Cells and Regenerative Medicine, 2016	Sports Health, 2012	Knee Surgery, Sports Traumatology, Arthroscopy, 2011	American Journal of Sports Medicine, 2016
150-mL venous blood drawn and centrifuged at 1,480 rpm for 6 min and again at 3,400 rpm for 15 min to produce 20-mL PRP divided into 5-mL injections. Patients received either three PRP injections, high molecular weight HA, or low molecular weight HA 14 d apart	10-mL venous blood collected and added to 5-mL ACD-A. The blood was centrifuged through the Regen Kit. Patients received either a single injection of PRP, two injections of PRP separated by 1 mo, or three injections of PRP separated by 1 mo	60-mL venous blood drawn and added to 8.6-mL ACD. The sample was centrifuged at 300G for 5 min followed by 700G for 17 min to produce 5-mL PRP. Three injections separated by 2-wk intervals of either 5-mL PRP, 2-mL HA, or both	8-mL venous blood drawn and centrifuged for 9 min at 3,500 rpm to produce 4-mL PRP. Patients were given two injections of PRP separated by 1 mo	Single spin: 36-mL venous blood drawn and centrifuged at 580 g for 8 min Double spin: 150-mL venous blood drawn and centrifuged at 1,800 rpm for 15 min followed by 3,500 rpm for 10 min to produce 20-mL PRP Three injections of 5-mL PRP after either single spin or double spin	15-mL venous blood was drawn into a double syringe system and centrifuged at 1,500 rpm for 5 min to produce 4- to 7.1-mL PRP. Patients received 3- to 8-mL injections of either PRP or saline at 1-wk intervals for 3 wk
<p>Patients with K-L grade 0–IV (grade 0 with focal cartilage lesion)</p> <ul style="list-style-type: none"> <li>Improvement in IKDC and VAS pain scores seen in all groups at 2 and 6 mo</li> <li>Similar improvement seen between PRP and low molecular weight HA at 2 mo, significantly more improvement seen in PRP group at 6 mo</li> <li>Further improvement seen in the PRP group from 2 to 6 mo, no improvement seen in the HA group during this time</li> <li>In the PRP group, patients with grade 0 cartilage degeneration had better results than those with grade I–II as well as grade III–IV PRP showed better results in patients under the age of 50</li> </ul>	<p>Patients with Ahlback stage I–III</p> <ul style="list-style-type: none"> <li>At 1 y, all groups showed significant improvement in pain scores and WOMAC scores</li> <li>No significant difference seen between one injection and two injection groups</li> <li>The three injection group had the greatest improvement in pain score, functionality score, and WOMAC score</li> </ul>	<p>Patients aged 40–70 y with K-L grade I–III knee OA</p> <ul style="list-style-type: none"> <li>Baseline significant difference in pain in the HA group compared with the PRP group or the combined group</li> <li>More significant improvement in VAS pain scores and WOMAC scores in PRP compared with HA up to 1 y</li> <li>Significant improvement in WOMAC score in HA + PRP compared with HA alone and PRP alone</li> </ul>	<p>Patients aged 30–60 y with K-L grade I–III knee OA</p> <ul style="list-style-type: none"> <li>All patients showed significant improvement in pain and functionality scores at 6 and 12 mo</li> <li>All patients returned to the previous level of sport</li> <li>Significant improvement also seen in patients with previous microfracture or cartilage shaving</li> </ul>	<p>Patients with K-L grade 0–IV knee OA</p> <ul style="list-style-type: none"> <li>Both groups showed a statistically significant improvement in IKDC scores and VAS pain scores at 2, 6, and 12 mo</li> <li>Better results were seen in younger patients with a lower degree of cartilage degeneration</li> <li>More swelling and pain were noted in patients after the double-spin injection</li> </ul>	<p>Patients aged 30–80 y with K-L grade II/III knee OA</p> <ul style="list-style-type: none"> <li>Overall WOMAC scores and all subcategories in the PRP group were significantly improved compared with baseline and placebo starting at 2 wk and continuing through 1 y, except stiffness at 2 mo where PRP was not significantly improved compared with saline</li> <li>WOMAC scores for the placebo group improved significantly at 2 mo but did not remain significant at any other time point</li> <li>One patient in the placebo group felt the pain was worsening</li> </ul>

Abbreviations: ACD-A, anticoagulant citrate dextrose solution A; ACP, autologous conditioned plasma; ADL, activity of daily living; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; K-L, Kellgren–Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; LP-PRP, leukocyte-poor platelet-rich plasma; LR-PRP, leukocyte-rich platelet-rich plasma; MRI, magnetic resonance imaging; OA, osteoarthritis; PRL, prolotherapy; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

increase in proliferation with cytokines peaking at various time points after injection.<sup>35</sup>

Lee et al studied PRP-containing hydrogels and reported a decrease in joint inflammation as well as an increase in the messenger RNA levels of cannabinoid receptors CB1 and CB2, which have analgesic effects in addition to anti-inflammatory effects, suggesting an additional possible mechanism for improved pain scores after PRP injections.<sup>36</sup>

PRP has been shown to simultaneously stimulate anabolic growth factors while reducing catabolic proinflammatory cytokine concentrations.<sup>8,37,38</sup> PRP uses this dual effect to stimulate fibroblasts, mesenchymal stem cells, and autologous chondrocytes while also decreasing inflammation

through the inhibition of interleukin (IL)-1 mediated nuclear factor (NF) light-chain-enhancer NF- $\kappa$ B activation.<sup>39,40</sup>

## Different Preparations

With more than a dozen commercially available PRP preparation systems to choose from, properties of the final product can vary greatly.<sup>34,41</sup> An understanding of the many variables that impact PRP treatment is critical when implementing its use in clinical practice. Interestingly, Magalon et al studied multiple PRP preparations from a single donor and found significant variations when comparing the different systems. They concluded that these different

variations could account for the discrepancies noted regarding PRP use in the literature.<sup>42</sup>

Fitzpatrick et al evaluated the concentrations of platelets, leukocytes, and RBCs in four different commercially available PRP preparation kits including GPS III (Biomet Biologics), Smart-Prep2 (Harvest Terumo), Magellan (Arteriocyte Medical Systems), and ACP (Arthrex Inc.). The study found that in terms of platelets, ACP (autologous conditioned plasma) produced a product with 1 to 1.7 times the whole blood baseline level of platelets, and Magellan, GPS, and SmartPrep produced products with three to six times the baseline platelet concentrations. For RBCs, ACP reduced the count to almost 0, whereas GPS, Magellan, and SmartPrep reduced the count by three to six times the baseline whole blood levels. When considering WBC concentration, ACP reduced the concentration by 5 to 22 times, nearly eliminating WBCs from the final product. The other preparation kits produced leukocyte-rich (LR) preparations and products with three to five times the baseline levels.<sup>43</sup>

One important consideration is the platelet concentration. While clinical improvements in the knee have been seen in platelet concentrations that are two to three times the mean,<sup>28–30,44</sup> *in vitro* studies correlate a higher platelet concentration with an increased amount of growth factors.<sup>8,45</sup> *In vivo* studies, however, have not been able to replicate this finding in terms of improved healing and patient outcomes.<sup>46</sup> Filardo et al found patients who received dual-spin PRP injections with theoretically higher platelet counts were more likely to experience pain and swelling compared with those who received single-spin PRP injections but did not find any significant clinical difference in terms of benefits between the two groups.<sup>47</sup> Additionally, some techniques have found the second-spin decreased platelet viability depending on the duration of spin and centrifuge speed.<sup>48</sup> Mazocca et al studied different platelet concentrations using single and double-spin techniques and found that they were unable to determine which platelet concentrations and PRP preparations would be optimal for each cell type, suggesting that future research needs to focus on determining optimal PRP preparation for each specific disease.<sup>46</sup> Other variables associated with platelets in PRP include the quantity of granule secretion observed with each patient and the possibility of premature activation caused by smaller bore needles.<sup>49</sup>

Another controversial difference in preparations of PRP is leukocyte concentration.<sup>50</sup> PRP is considered either LR or LP. LR-PRP has greater than 100% leukocyte concentration compared with whole blood, whereas LP-PRP has less than 100% leukocyte concentration compared with whole blood.<sup>51,52</sup> Whether PRP is LR or LP depends on how the sample is prepared. As mentioned previously, plasma-based preparations result in LP-PRP as they exclude WBCs. In contrast, buffy coat based preparations result in LR-PRP. *In vitro*, it has been shown that there is not a significant difference between the effect of LR-PRP and LP-PRP on wound healing, suggesting that the major benefits of PRP stem from growth factors rather than leukocytes.<sup>53</sup>

Raeissadat et al studied LR-PRP injections in patients with knee OA and found significant improvement in pain, stiffness, functional capacity, and quality of life 6 months post-

injection.<sup>54</sup> However, when comparing LR-PRP and LP-RPR, Braun et al reported that LR-PRP led to significantly increased cell death and expression of multiple proinflammatory markers such as IL-1 $\beta$ , IL-6, interferon gamma, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>52</sup> Furthermore, studies have shown increased concentration of leukocytes increases the expression of catabolic cytokines and inflammatory markers, which create a nonideal environment for the repair of injured tissue and can be detrimental to clinical outcomes.<sup>45,55</sup> Specifically, Roman-Blas et al found a positive correlation between leukocytes and matrix metalloproteinase-9, as well as between leukocytes and IL-1 $\beta$ , both of which degrade collagen and the extracellular matrix, ultimately leading to poor articular cartilage healing.<sup>56</sup> Moreover, a meta-analysis by Riboh et al found that LP-PRP resulted in improved outcomes compared with HA and placebo, whereas LR-PRP did not prove to have the same effect.<sup>51</sup> These studies demonstrate that the best evidence for the use of PRP in the treatment of symptomatic knee OA is with the use of LP-PRP rather than LR-PRP.

Also controversial regarding LP/LR-PRP is the difference between acute reactions at the time of injection. Animal and prospective studies have shown that patients receiving LR-PRP are more likely to experience painful reactions,<sup>47</sup> while Riboh et al have shown no differences in acute reactions, such as localized swelling, when comparing the two preparations.<sup>51</sup>

Besides using autologous PRP, there is also the option to use allogeneic PRP.<sup>57,58</sup> Bottegoni et al studied 60 patients with knee OA who were not candidates for autologous PRP due to hematological disorders. These patients received a series of three allogeneic PRP injections spaced 2 weeks apart. This study demonstrated a statistically significant improvement in the International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS), and VAS scores at 2 and 6 months compared with baseline, although there was also a statistically significant worsening in these scores from 2 to 6 months. However, 90% of patients were satisfied at their 6-month evaluation as these scores remained improved from baseline. This study suggests that allogeneic PRP is a safe and efficacious treatment for knee OA, especially in patients under the age of 80 with less advanced arthritis.<sup>59</sup>

Considering the transport involved in allogeneic PRP and the discomfort of a blood draw involved with autologous PRP, it is important to consider the possibility of PRP storage. It has been reported by Wilson et al that prior to preparing PRP, whole blood can be stored for up to 4 hours at room temperature without a change in platelet, WBC, TGF- $\beta$ 1, or matrix metalloproteinase-9. Additionally, both LR-PRP and LP-PRP can be stored for up to 4 hours at room temperature prior to injection without a change in these same growth factors or catabolic cytokines.<sup>60</sup> Bausset et al analyzed PRP storage at room temperature for up to 24 hours and found that PRP stored for longer than 6 hours was associated with an altered response to PRP agonist and that PRP stored for 24 hours released significantly less VEGF compared with PRP stored for 6 hours or less, suggesting that 6 hours of storage at room temperature may be the maximum storage for PRP to maintain its efficacy.<sup>61</sup>

For longer term storage, Wen et al conducted an experiment in which LR-PRP was produced through dual-spin centrifuge and stored in a platelet incubator at 22°C for 7 days with agitation. Platelet and WBC concentrations were measured daily from the room temperature PRP, whereas growth factor release was measured daily after deep-freeze thawing to induce release. Wen et al found that platelet concentrations were 1.6 to 5.7 times the baseline of the donor whole blood, and the samples maintained this concentration for the full 7 days of storage on agitation. Levels of VEGF, hepatocyte growth factor, IGF-1, PDGF-AB, FGF, and endothelial growth factor were also all increased after PRP preparation and maintained or increased this level throughout storage. This study suggests that storage of PRP preparations on agitation may be possible for storage of PRP between injections.<sup>62</sup>

## Clinical Science

Interest in PRP and its clinical applications has been steadily increasing as more researchers are seeing consistent positive results in multiple fields. With such great success in the treatment of lateral epicondylitis,<sup>16,63</sup> the first goal of clinical research was to determine if PRP injections were superior to other current injection options in the management of OA (→ Table 1).

In a U.S. Food and Drug Administration (FDA) sanctioned, double-blind randomized controlled trial, Smith et al evaluated the use of ACP PRP in 30 patients with knee OA who failed at least 6 weeks of nonoperative management. These patients received weekly intra-articular injections of either ACP PRP or saline for 3 weeks and were evaluated for 1 year. This study revealed that patients who received ACP PRP had statistically significant improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score as compared with baseline as well as placebo group starting at 2 weeks and continuing through 12 months. These results demonstrate that ACP PRP is safe and efficacious for the treatment of knee OA.<sup>64</sup>

Raeissadat et al studied patients who received either two PRP intra-articular injections at 4-week intervals or three HA injections at 1-week intervals, the standard timeline for HA, using the WOMAC and Medical Outcome Study 36-item Short-Form Health Survey (SF-36) questionnaires to report patient outcomes. At 12-month follow-up, pain scores were improved in both groups, but PRP scores improved significantly more than HA scores. Other aspects of the WOMAC and SF-36 were improved only in the PRP group, suggesting PRP to be more effective than HA in improving patient quality of life in OA.<sup>65</sup>

Furthermore, Kon et al reported there was similar improvement between PRP injection and low molecular weight HA when compared at 2-month follow-up, but PRP injection results were improved compared with HA at 6-month follow-up, suggesting a longer term benefit of PRP as compared with HA in terms of reducing pain and symptoms as well as recovering articular function. When compared by age and degree of OA, the study reported that PRP and low molecular weight HA showed similar results in patients over the age of 50 and in those with

more advanced OA even at the further time points, suggesting that PRP provides better outcomes in younger patients with either cartilage lesions or early OA.<sup>37</sup>

Cole et al studied patients with symptomatic and unilateral knee OA in a double-blind randomized clinical trial comparing LP-PRP injections and HA injections under ultrasound guidance, and measured outcomes including WOMAC, IKDC, VAS, and Lysholm knee scores for 1 year. No difference was seen between the groups in regard to the WOMAC pain score, but there was a significant improvement in IKDC score and VAS score in LP-PRP compared with HA. They also found that patients with mild OA and lower body mass index had statistically significant improvement compared with other patients. Additionally, analysis of intra-articular biochemical markers approached statistical significance with a decrease in proinflammatory markers, IL-1 $\beta$  and TNF- $\alpha$ .<sup>8</sup>

In another randomized controlled trial, Lana et al reported that PRP alone showed improved outcomes compared with HA alone, and, interestingly, PRP combined with HA resulted in a further decrease in pain and functional limitations compared with either group alone.<sup>66</sup> Similarly, Russo et al showed that PRP/HA blended injections have higher proliferation rates of chondrocytes and concentrations of glycosaminoglycans when compared with HA individually.<sup>67</sup>

Studies have compared PRP to other injection options as well. Forogh et al completed a randomized controlled trial to study PRP injections in comparison to corticosteroid injections and reported that PRP provided superior pain and symptom relief for patients with OA as well as significantly improved their functionality and quality of life when compared with those patients who received corticosteroid injections.<sup>68</sup>

Rahimzadeh et al compared the effect of PRP to prolotherapy, an alternative medicine treatment in which joints are injected with hyperosmolar solution. This randomized, double-blind clinical trial showed that in patients with knee OA graded stage 1 or 2 on the Kellgren-Lawrence (K-L) scale, although both groups had improved WOMAC scores at 1 month, 2 months, and 6 months postinjection compared with baseline scores, PRP injections were more effective at improving WOMAC score.<sup>6</sup>

The current research supports the main advantage of using PRP, that is, its long-lasting and more efficacious function in restoring articular function as compared with HA injections, corticosteroid injections, and other alternatives such as prolotherapy. Furthermore, the studies previously mentioned support the combined application of PRP with HA as the optimal injection treatment for OA.

Once PRP's effectiveness in decreasing pain and increasing functional status in patients with OA has been established, the next step is to determine the appropriate uses, concentration, and injection schedule. There have also been different timelines for injection administration documented throughout studies. These studies have shown improvement in subjective outcomes such as quality of life and pain in patients receiving PRP regardless of injection schedule, but there has not been consistent timeline used across studies.<sup>54</sup>

Patel et al found that in terms of patient-reported outcomes, single injections of PRP were equivalent to two

injections of PRP through 6 months of follow-up.<sup>38</sup> A separate study by Huang et al evaluated PRP injections once monthly, twice monthly, or three times monthly and showed the positive effects of PRP began to slow at 12-month follow-up in those patients who received one or two monthly injections, whereas the effects were maintained in those patients receiving three injections monthly.<sup>69</sup> Most studies use multiple injections ranging from weekly to monthly, and it remains clear that the optimal preparation of PRP and injection schedule have yet to be determined.<sup>20</sup>

Of note, nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for pain control and management in OA. In terms of healing, previous studies have shown NSAIDs, celecoxib and indomethacin specifically, inhibit rotator cuff tendon-to-bone healing even if only used for 2 weeks.<sup>70</sup> It is possible that NSAIDs may have a similar effect on PRP-stimulated healing of articular surfaces. Meadows et al compared rats treated with PRP ± NSAIDs. There was no significant difference between rats treated with PRP + NSAIDs versus rats treated with just PRP when comparing biomechanical strength of the rotator cuff tendon,<sup>71</sup> suggesting that NSAID use does not affect PRP's effectiveness. However, it is the hope that with decreased pain scores reported by patients receiving PRP injections, further NSAID use would not be necessary.

## Limitations

The major limitation of PRP studies thus far is the lack of consistency among PRP processing techniques and concentrations. These results show why it is difficult to distinguish the ideal preparation and concentration in each type of injury and tissue. The variability in PRP concentrations, even when comparing single-donor preparations, suggests one possible reason for the variations in PRP literature.

Additionally, while PRP is becoming a greater research focus, there still exist few randomized controlled studies on the topic, especially with regard to long-term follow-up. Most studies do not extend past 6-month follow-up and those that do suggest a possible decline in pain relief around 6 to 12 months, although scores remain significantly improved from baseline. According to these studies, PRP's efficacy may begin to lessen around 6 months, but studies have not shown at what time point pain scores and functional outcomes return to preinjection baseline.

Multiple studies listed previously report that PRP exhibited the best outcomes in younger patients with less severe OA (grade I/II on K-L scale) or focal cartilage defects. While more research needs to be conducted on the effects of PRP on each K-L grade of OA, it appears that PRP is not as efficacious in reducing pain and improving functional outcomes in more advanced OA and cartilage degeneration.

Finally, due to the insurance companies considering PRP injections as experimental, they are often not covered by insurance policies and leave the patient to pay an out-of-pocket fee. According to Scientific American, this fee can range from US\$500 to US\$2,000 per injection, which makes cost a definite barrier for many patients with OA.<sup>72</sup>

## Regulation

One major limitation to the use of many biologics in orthopaedic treatments is the regulation and restriction of use by the FDA. In terms of PRP specifically, however, the FDA has not taken many regulatory steps. The FDA specifies that "the time and speed of the centrifugation shall have been shown to produce a product with at least 250,000 platelets per microliter" and that PRP should be stored with agitation at room temperature.<sup>73</sup> The machines used to process PRP are approved by the FDA under 501(K) or premarket notification, which allows the FDA to determine if the device is equivalent to a device already in use.<sup>74</sup>

With regard to the use of PRP in knee OA, the FDA has made few regulatory processes. This is likely because the preparation of PRP remains inconsistent, thus making it difficult to determine the ideal conditions of preparation of PRP for each disease treatment. As noted previously, Smith completed an FDA-sanctioned, double-blind, randomized controlled trial to assess the safety and efficacy of LP-PRP in patients with knee OA. In examining safety, the study found that one patient in the placebo group felt that the pain was worsening in the target leg, but no reactive effusions or episodes of acute pain were noted. In terms of efficacy, the study found a statistically significant improvement in post-operative patient-reported outcomes that were not present in the placebo group starting at 2 weeks and remaining throughout the 12-month follow-up period. Overall, the study confirmed that LP-PRP is a safe and efficacious treatment for knee OA.<sup>64</sup>

## Conclusion

There is clear evidence in the literature to support the use of LP-PRP in OA for improvement in patient-reported pain scores, joint stiffness, and physical functioning. Currently, PRP seems to be most beneficial for early/low K-L grade OA compared with more advanced OA. Better outcomes are seen with younger individuals with cartilage defects or earlier OA, and worse outcomes tend to be seen in patients over the age of 50 and those with further degenerated joints. Future studies to be conducted include standardization and optimization of PRP concentration for use in different grades of OA as well as in different joints throughout the body.

The current data support the use of LP-PRP in early OA to minimize symptoms and possibly prevent or slow progression to more advanced OA, although more research needs to be conducted into the long-term benefits of PRP injection in early OA. With more research into PRP, it is possible to decrease the financial expenditure associated with OA by diminishing the need for total joint replacements with early intervention through PRP injection.

### Conflict of Interest

Arthrex, Inc. manufactures one of the PRP centrifuges mentioned in the article. Brian Cole receives consulting fees, educational support and research support from Arthrex, Inc.

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