Current Reviews in Musculoskeletal Medicine (2018) 11:607–615
https://doi.org/10.1007/s12178-018-9521-0

PROTEIN-RICH PLASMA: FROM BENCH TO TREATMENT OF ARTHRITIS (S CHOATE AND J TOKISH, SECTION EDITORS)

Platelet-Rich Plasma and the Knee—Applications in Orthopedic Surgery

Alexander Wasserman[1] · Graeme Matthewson[1] · Peter MacDonald[1]

Published online: 13 September 2018
© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

Purpose of Review To consolidate and synthesize the most recent evidence on the effects of platelet-rich plasma (PRP) in the knee with respect to osteoarthritis, meniscal injuries, ACL reconstruction, total knee arthroplasty (TKA), and high tibial osteotomy.

Recent Findings PRP has been shown to be more beneficial in the context of knee osteoarthritis compared to both placebo and hyaluronic acid. Direct comparison with corticosteroid injections has been sparsely studied. It has also been shown to improve the clinical postoperative course in meniscal injuries and to a lesser extent TKA. Radiographic improvements without clinically significant benefits have been observed with ACL reconstructions treated with PRP.

Summary PRP injections may be more beneficial than other current non-surgical management options for specific knee pathologies. Further research should broaden the knowledge of PRP effects on the knee, and identify the type of PRP, growth factor distribution, and route of administration associated with the most benefit.

Keywords Platelet-rich plasma · Knee · Osteoarthritis · Meniscal tear · ACL reconstruction · Corticosteroid

Introduction

Platelet-rich plasma (PRP) was first introduced in regenerative medicine in the 1980s and 1990s, with the earliest documented uses for treatment of cardiac disease, dental damage, and maxillofacial surgery [1]. Since that time, it has also been used in a variety of conditions in musculoskeletal disease including knee pathology, which will be the focus of this review.

What Is PRP and How Is It Made?

PRP is an autologous blood product which contains a high concentration of platelets [2] and can be found in concentrations anywhere between two and eight times the normal concentration of peripheral blood. In order to produce PRP, there are three general methods employed [3, 4••]. The first method involves filtration and plasmapheresis of a collection of the patient's peripheral blood. Following this, the collection is then subject to centrifugation which separates it into distinct layers consisting of the plasma, platelets, and platelet-derived growth factors in one layer, separate from the erythrocytes and leukocytes. This results in a solution with very high concentration of platelets (a factor of 15 higher than physiologic levels) and platelet-derived growth factors, as well as very low levels of leukocytes [5]. Although effective, this method has proven quite costly, leading authors to look for alternative ways of isolating the concentrated platelet solution. The second method involves just a single centrifugation, which produces a platelet concentration that can be up to three times physiologic, with a relatively low level of leukocytes. In the third method, the collection is subject to double spin centrifugation, which can concentrate the platelet solution up to eight times that of normal; however, this comes with a higher concentration of leukocytes as well, which will be further discussed in the upcoming sections. The final product is a combination of a high concentration of platelets, which upon activation release a number of growth factors from their alpha granules. Although the total number of factors present is unknown, those that have been identified include platelet-derived growth factor (PDGF), transforming growth factor beta-1 (TGFβ-1), fibroblast growth factor (FGF), and hepatocyte growth factor (HGF) [2, 4••]. PDGF is a protein that simulates the proliferation and synthesis of new collagen formation. While TGFβ-1 counteracts the catabolic effects of

This article is part of the Topical Collection on *Protein-Rich Plasma: From Bench to Treatment of Arthritis*

✉ Peter MacDonald
PMACDONALD@panamclinic.com

[1] University of Manitoba, Winnipeg, Canada

interleukin-1 (IL-1) on tissues such as cartilage, by increasing chondrocyte synthesis as well as by increasing extracellular matrix production. FGF promotes tissue healing by activating anabolic pathways, while HGF increases tissue repair by promoting angiogenesis, as well as chemotaxis of mesenchymal stem cells, along with subchondral progenitor cells to promote chondral matrix formation and remodeling [3]. In combination, these factors have been found to decrease catabolism through an increase in anabolic activity, which promotes chondral remodeling in cartilaginous tissues. Chondral degeneration in the aging population has been shown to be related to the increases in metalloproteinases (MMPs), particularly MMP 13, as well as IL-1, which are well known promoters of chondral catabolism and cartilage degradation [3]. It has been proposed that PRP's anabolic and anti-catabolic properties are mediated through its ability to increase synthesis of type II collagen and prostaglandin production as well as an increase in chondrocyte proliferation through the increased production of hyaluronan synthetase-2 (HAS-2). Production of HAS-2 by synoviocytes causes an increase in the production of hyaluronic acid, which has been shown to increase cartilage synthetic activity, as well as decrease the concentration of inflammatory mediators [6]. In the setting of tissue injury or stress, PRP has been shown to cause a decrease in the rise of inflammatory mediators such as IL-1 and MMP 13 through the stimulation of HA synthesis [7, 8].

PRP Types, Methods of Delivery, and Concentrations

PRP is introduced through several different mediums, mostly dependent on the concentration of leukocytes as well as fibrinogen content for the activation of fibrin postinjection. PRP can be given as an injection or in conjunction with a scaffold for direct application to the injured site, resulting in four common variations [2]. The first is pure PRP (P-PRP) or leukocyte-poor PRP (L-PRP) which contains a very low leukocyte content allowing it to be introduced as a liquid solution or as an activated gel complex. Administration is through injection into the damaged tissue or through direct application to a wound in gel form. However, this form is generally produced through plasmapheresis or centrifugation requiring substantial forces, making it impractical for clinical implementation [9]. The second is leukocyte-rich PRP (L-PRP) with a high concentration of platelets due to the double spin centrifugation technique employed. However, this results in a higher concentration of leukocytes as well. Similar to P-PRP, L-PRP can be introduced as a liquid solution for direct injection as an activated gel and is easier to produce as it does not require as high of centrifugation forces or plasmapheresis. The third formulation is pure platelet-rich fibrin (P-PRF) which contains inactivated platelets and fibrinogen, and is collected through a slow centrifugation process. The solution is then subject to a fast centrifugation cycle in which an activator such as calcium chloride is introduced, forming a platelet-rich, fibrin scaffold. This produces a stiff membrane with a high concentration of platelets and low leukocyte count, which is applied directly to the wound site and usually secured through suture fixation. The final common preparation is leukocyte and platelet-rich fibrin (L-PRF) which is very similar to L-PRP but with a comparatively higher concentration of leukocytes. The advantage of which is its low cost of production. Due to the fibrin content, the solution forms a membrane-like clot, which aids in tissue healing. Due to the low cost and ease of application, it is the main form used in countries such as Italy, France, and Israel. Currently, there is a debate in the literature as to the effects an increased leukocyte concentration has on soft tissues, with some studies indicating an increased pro-inflammatory effect, promoting soft tissue healing [3], while others have shown no difference in the amount of pro-inflammatory cytokines generated when compared with other injections such as hyaluronic acid [10]. However, when comparing P-PRP to L-PRP, Dragoo et al. [11] showed in a rabbit model that L-PRP caused a greater inflammatory reaction when injected into a healthy patellar tendon compared to P-PRP. This leads the authors to conclude that P-PRP had greater anti-inflammatory properties in a soft tissue injury model. The effects of varying concentrations of PRP have been studied in knee osteoarthritis (OA) as well as anterior cruciate (ACL) and medial collateral ligament (MCL) reconstructions; however, most, this data was derived from animal studies. Fleming et al. [12•] investigated three different concentrations: one, three, and five times physiologic, following ACL transection in a mini pig model. In this study, surprisingly, the only significant difference was found in linear graft stiffness in the physiologic concentration group, with no differences found in the other two groups. Overall, there was no difference between groups regarding failure loads, anterior-posterior (AP) knee laxity, graft histology, and macroscopic tissue integrity. Following this, Laprade et al. [13•] compared PRP concentrations in a rabbit model following MCL transection using concentrations of 0.6 M platelets/μl (two times baseline physiologic concentration), 1.2 M platelets/μl (four times baseline physiologic concentration), and saline injection. At 6 weeks' post procedure, no differences were found in vascularity, tissue maturity, or maximal load to failure between the groups with a slight but not significant decreased load to failure and stiffness found in the 1.2 M group compared with controls. In the context of OA of the knee, Dernek et al. [14•] investigated the effects of 1 M platelets/μl compared with 3 M platelets/μl given in two injections 1 month apart on Western Ontario and McMaster (WOMAC) knee scores at 1, 3, and 6 months to find no

differences in pain, stiffness, overall function, or overall WOMAC scores.

Clinical Effects

The clinical effects of PRP have been studied in many conditions and procedures affecting the knee including OA, total knee arthroplasty (TKA), meniscal repair, ACL reconstruction, and high tibial osteotomy (HTO). When reviewing these effects, it is important to consider that standardization of reporting in the literature with respect to elements such as PRP type, collection protocol used, concentration, and method of delivery has been inconsistent. This often makes it challenging to equitably compare different studies and protocols. Consistent with what Laprade has pointed out in the literature, a more standardized method of reporting of these variables of PRP would allow for more meaningful results, reproducibility, and accuracy [15].

OA

The mechanism of action of PRP in OA is well studied with in vitro studies showing that PRP significantly increases chondrogenic (SOX9 and aggrecan) as well as osteogenic (type I and type II collagen) markers in synovial tissue. Due to these properties, PRP has been shown to induce mesenchymal stem cells (MSCs) to preferentially differentiate into chondrocytes and osteocytes in vitro [6]. In a study investigating the anti-inflammatory effects of PRP in mild to moderate OA and suprapatellar bursitis [16••], monthly injections of PRP over 3 months showed significant reductions in synovial fluid volume, as well as pro-inflammatory markers including apolipoprotein A1 (apo-A1), haptoglobin, immunoglobulin kappa constant (IGKC), MMPs (especially MMP-13), and transferrin. In addition, PRP has been shown to significantly increase inhibition of chondrocyte hypertophy, a known step in the pathophysiologic degeneration of cartilage in OA, as well as contributing to a twofold increase in matrillin proteins, which aids in the maintenance of the cartilaginous architecture [8]. As part of its anti-inflammatory effects, PRP-rich environments have been shown to reduce IL-1β expression in chondrocytes, a known inhibitor of type II collagen and aggrecan gene expression, as well as an inducer of MMP and nuclear factor kappa-light chain enhancer of activated B cells (NF-κB), a major contributor in the pathogenesis of OA [17, 18]. With respect to the effects of leukocyte concentrations in OA, an increased leukocyte concentration increases the pro-inflammatory markers IL-1β and MMP 13 as compared to leukocyte-poor concentrations. However, this came with a fivefold increase in the anti-inflammatory proteins IL-4 and IL-10 [19], so it is not clear whether the pro-inflammatory effect had a strong influence on the overall degenerative process.

Clinical Outcomes in OA

The treatment of knee OA with PRP has been well investigated in the clinical settings with positive effects. In one study [4], P-PRP was injected intra-articularly three times in 2-week intervals in 808 patients with 3 or more months of symptomatic knee OA. At 6 months, subjects reported significantly improved scores in the 36-item short-form health survey (SF-36), visual analog pain scale (VAS), and WOMAC as well as the Lequesne Algofunctional Index, an index analyzing the severity of knee OA symptoms. This index focuses on pain/discomfort, maximal distance walked, and performance in activities of daily living. However, these results were only temporary, with a decrease in all outcome scores at 12 and 24 months' postinjection, although improved from baseline. In this study, no effect of differing PRP concentrations was reported, confirming previous findings [14•]. These results suggest that the effects of PRP may be temporary and lie in the reduction of synovial membrane hyperplasia, due to decreased TGFβ levels, which have been shown at higher concentrations to increase synovial hyperplasia and osteophyte formation [20], as well as in reducing inflammatory cytokine production, rather than through a chondroprotective or regenerative effect [21]. The beneficial effects of PRP in OA appear to be influenced by patient factors and frequency of injections, with better outcomes seen in patients who are of younger age, male gender, having milder cartilage degeneration, lower BMI [4, 21, 22], as well as increased frequency of injection [23]. Patel et al. conducted a double-blind, randomized control trial comparing PRP to saline injections. It was found that regimens including either one or two injections of PRP resulted in improved WOMAC scores (specifically pain, stiffness, physical function, and total scores) as early as 2 weeks, and up to 6 months postinjection as compared to saline [24]. Further, in a well-designed, randomized controlled FDA-regulated feasibility trial, Smith [25] showed that three PRP injections administered weekly resulted in WOMAC scores that were significantly decreased in patients with knee OA as soon as 1 week after therapy, compared to placebo. These effects persisted for the duration of the study, with the overall WOMAC scores improving by 78% in the PRP group compared to just 7% for the placebo group, after 12 months of follow-up.

Comparison to Other Treatments in OA

Hyaluronic Acid Other treatments used in the management of OA include corticosteroid (CS) and hyaluronic acid (HA) intra-articular injections. In a study by Kon et al. [26], they compared clinical outcomes in the form of IKDC and VAS

scores in patients treated with a single dose of PRP, low molecular weight (LMW) HA, or high molecular weight (HMW) HA. While there were similar outcomes at 2 months in all groups, PRP showed sustained improvements at 6 months, while significant deteriorations in outcomes were observed in both HA groups. In a study by Sanchez et al. [27], they further found that PRP showed a trend toward superior outcomes over HMW HA, with significant WOMAC pain subscore improvements (defined as at least a 50% improvement) in 40% of PRP subjects compared with 24% in the HMW HA group. Furthermore, it has been shown that compared with a standard single dose Durolane™ injection, three weekly PRP injections showed an improvement in pain, function, and stiffness subscores of the WOMAC index [28]. This was confirmed in a systematic review of recent meta-analyses, showing that PRP injections were consistently associated with better VAS and IKDC scores compared to HA at 6 months, with differences maintained for up to 12 months [29•]. Consistent with previous studies [4••, 21, 22, 26], the effectiveness of PRP was maximized in younger individuals (< 50) and those with earlier stages of OA.

In the earlier stages of arthritis, a retrospective comparison study of PRP versus HA in stage I/II Kellgren-Lawrence scale gonarthrosis showed significant improvements in VAS and KSS scores in both the PRP and HA groups at 2 months and 6 months postinjection. However, the PRP group showed a greater improvement at each time point, as well as overall [30]. Therefore, PRP is felt to be more effective treatment option for patients in the early stages of OA. In fact, the current clinical practice guidelines set forth by the American Academy of Orthopedic Surgery (AAOS) recommend against the use of HA in symptomatic knee OA, with a designation of "strong" in the strength of recommendation [31].

CS CS injections have been extensively studied in knee OA, and have been used in practice for more than 50 years. CS injections are also recommended by the most recent American College of Rheumatology (ACR) [32] guidelines (updated in 2012) for symptomatic management of knee OA. To understand the comparative effects of PRP versus CS in the context of knee OA, Forogh et al. conducted a randomized controlled trial of one-time injections of PRP and CS in patients with moderate knee OA (K-L grade II/III). It was found that pain intensity (via VAS scores), 20-m walking (20 MW) test, and four of five KOOS outcome scores (with the exception of the sport parameter) were significantly improved in the PRP group compared to the CS group at 2 and 6 months postintervention [33••]. In addition, a pilot study evaluating the utility of combining CS and PRP showed a synergistic effect, with significantly lower WOMAC (at 1 and 3 months) and VAS (at 1, 3, and 6 months) scores in the combined group compared to PRP or CS alone. However, the benefits were no longer apparent at 12 months postinjection [34]. Based on these results, PRP may be a more effective treatment option for patients with moderate knee OA than CS with respect to pain relief and quality of life, and while more research is needed, the two interventions may have a synergistic effect at pain and disability reduction.

In more advanced OA (K-L grade III/IV), one study showed that a single injection of L-PRP and CS was similar in their effect. Both groups (PRP and CS) had their VAS scores significantly improve at 1, 3, and 6 months; however, there were no differences between groups. Secondary outcome measures including SF-36 (short-form 36) and Knee injury and Osteoarthritis Outcome Score (KOOS) were also not significantly different between groups [35].

HTO

HTO is a common procedure performed to treat medial compartment OA and varus malalignment [36]. The use of PRP in HTO is quite limited with only two studies to date evaluating its effects. In a canine model, PRP was compared with saline injections following an HTO for ACL rupture [37]. In this study, they reported no differences in ultrasonographic or MRI healing at 28, 49, and 70 days following the procedure. Furthermore, PRP was not found to attenuate osseous union in these subjects either. In fact, in a study by Giuseffie et al., they found an increased risk of non-union in patients whose HTO was performed with PRP mixed into the allograft bone as compared to those with allograft alone [38].

TKA

PRP injections intraoperatively or immediately post-TKA has been studied with respect to various clinical outcomes. In regard to pain scores, PRP has been shown to have a positive effect in the early postoperative period term from 0 to 2 months following surgery in some studies [39••, 40], but not others [41]. Although statistically significant, the studies showing improvements in pain subscores at 2–6 months postoperatively may not reach clinical significance [39••, 40]. A prospective randomized controlled clinical trial by Guerreiro et al. [40] using double-centrifuged L-PRP with platelet concentrations between 2 and 4 times that of physiologic showed that there was improvement in the verbal pain score in the PRP group compared to control from 24 h to 2 months postop. In contrast, a randomized controlled trial by Morishita et al. [41] in which 20 patients were each allocated to the PRP and control groups, it was found that intraoperative PRP gel applications did not significantly improve overall quality of life in the short term (0–28 days) as measured by the KSS and KOOS knee scores. Further, no significant differences in swelling, muscle power recovery, pain, bleeding, and range of motion were found between the two groups.

In a systematic review [39••] of 17 studies and 2328 patients, statistically significant differences in pain were found after PRP therapy following TKA in five of the studies (although with significant heterogeneity amongst the data). There was also an improvement in knee function in patients with OA after PRP injections. However, no improvements were found in post-TKA knee function and quality of life, as well as secondary outcomes such as wound scores and length of stay.

In addition, postoperative complications including blood loss, decrease in hemoglobin, and length of stay were also measured in a meta-analysis of six studies [42]. It was shown that intraoperative PRP may be effective at reducing blood loss and hemoglobin reduction associated with TKA (albeit with a significant amount of data heterogeneity), without a corresponding increase in postoperative complications. However, this difference has not been substantiated in other studies [40]. Interestingly, milder OA, which was also found to have the best response to PRP, was shown to be a positive predictive factor for PRP effectiveness following arthroplasty as well [39••]. It appears that any positive effect from PRP following TKA is likely limited to improvements in pain scores in the early postoperative period and may not reflect overall improved function.

Meniscus Repair

With respect to the healing effects to meniscal tissue, it has been proposed that PRP works through two main mechanisms. The first is its anti-inflammatory property which impacts the healing response of the injured meniscus, the integrity of the unaffected meniscus, and the response to injury by the articular cartilage. The second proposed mechanism is direct stimulation of synoviocytes, facilitating primary repair of meniscal tissue [43].

After intra-articular injury, it has been shown that synovial fluid levels of inflammatory cytokines are significantly elevated [44, 45]. Exposure of the meniscus to these factors (particularly IL-1β and TNF-α) has been shown to decrease extracellular matrix production [46], and impair meniscal healing. Therefore, inhibition of these inflammatory pathways is a potential mechanism through which PRP can aid in meniscal healing and repair.

Pujol et al. evaluated injected PRP's effect on open meniscal surgery in grade II and III horizontal cleavage tears extending into the avascular zone in young patients. It was found that at 2–3-year follow-up, the mean KOOS score was significantly improved in the pain and sports categories in the PRP group. In addition, MRI evaluation at 1 year showed complete resolution of meniscal hyperintensity in 75% of the patients in the PRP group, compared with 40% in the control group [47]. In the context of meniscal repair, PRP has also been utilized through intraoperative fixation of a platelet-rich fibrin matrix directly into the site of damage. In this study, there were no differences observed in postoperative range of motion, return to work, baseline level of activity/sport participation, or in the International Knee Documentation Committee (IKDC) scores between patients who had the fibrin matrix sutured into the meniscal defects, and controls. However, this study had several limitations, including small sample sizes of 15 and 20 in the PRP and control groups, a failure to differentiate meniscal tear type, and significant heterogeneity in the baseline characteristics between groups (including age and BMI) [48]. Following this, Kiminski et al. [49•] performed a prospective, double-blind randomized controlled trial in which they supplemented arthroscopically repaired vertical red-white zone meniscal tears with either L-PRP or saline injections. After 18 weeks, it was found that healing rates, as assessed with MRI and/or second-look arthroscopy, were significantly improved in the L-PRP group (85%) compared to the saline group (47%) with an odds ratio of 6.375. At 42 months, there were significantly higher KOOS, IKDC, and WOMAC scores in the L-PRP group as well [49•]. Therefore, the literature suggests that PRP facilitates earlier clinical and radiographic healing of meniscal tears extending into avascular zones, as well as long-term improvements in knee function and activity scores.

ACL Reconstruction

Anterior cruciate ligament (ACL) reconstruction is another procedure that has been evaluated with respect to PRP's role in the healing process. Typically, postoperative ligamentous healing occurs in three phases: inflammatory, proliferative, and remodeling/maturation phases. PRP is theorized to play the greatest role in the inflammatory phase, as it has been shown to increase the release of growth factors intra-articularly [3, 50]. In this section of the review, we will outline the literature assessing functional outcomes in animal models, followed by clinical outcomes in humans.

Animal models have been well studied in the context of PRP's effect on ACL repair. In a canine model, multiple injections of P-PRP without scaffolding were performed following ACL graft reconstruction. This resulted in significantly reduced pain and improved functional limb use/range of motion (ROM), as well as a tendency to promote graft healing, based on radiographic, arthroscopic, and histological assessment. Decreases in pain and improvements in ROM were noted at 1 week after injection, and persisted for 6 months. After this period, there were no significant differences noted in lameness, kinetics, and function [51]. Further, a porcine model was used to show encouraging results of ACL grafts treated with PRP in conjunction with a collagen-platelet composite scaffold with surgically created ACL tears [52]. However, a single PRP injection administered intraoperatively into in vivo

white rabbit models after an MCL injury did not show improvements in ligament maturity subscores, maximal loads, and vascularity subscores 6 weeks post-surgery when measured by histological analysis and biomechanical endpoint characterization [13•].

Clinical studies utilizing human subjects have also been well investigated with respect to the effect of PRP on ACL reconstructions and have shown conflicting results. PRP administered via a collagen scaffold was shown to be beneficial with regard to linear stiffness, maximal load, and yield following ACL repair in some studies [53] but not in others [54]. In a meta-analysis of eight studies, it was shown that PRP improved ACL graft maturation by an average of 20–30% compared to control [55]. With respect to graft maturation, it was found that patients treated with PRP rich in growth factors (PRGF) exhibited increased tension, width, synovial coverage, and a higher ligament maturity index on histology as compared to controls on second-look arthroscopy at 6–24 months after ACL reconstruction [56]. However, in a radiographic study, there was only a trend toward increased ligamentization and integration on follow-up MRI, with no difference in radiographic graft stability between PRP and control groups [57]. With respect to signal intensity on MRI, Orrego et al. showed that at 6-months post-surgery, MRI signal intensity of the reconstructed ACL returned to baseline in 100% of patients treated with PRP, compared to 78% in the control group [58]. This was supported by a study by Radice et al., in which they showed that time to a normal MRI following ACL reconstruction was also shown to improve from 369 to 177 days following PRP administration [59]. However, no differences in clinical outcomes have been found up to 2 years following surgery, nor were there any differences observed in tendon-bone healing [57, 58].

In bone-patellar tendon-bone (BPTB) ACL harvest procedures, PRP administration was shown to result in significant decreases in subjective pain scores, as well as healing of bone defects (> 70% filling) of the tibia and patella on follow-up MRI as compared with controls (85% and 60% respectively) [60].

In conclusion, radiographic and histologic differences in ACL reconstructions seem to be consistently observed between PRP-treated groups and control groups in both human and animal models. There is less certainty about PRP's effectiveness on the healing of extra-articular ligaments, however. In addition, while there may be some clinical benefits in animal models with respect to pain and range of motion up to 6 months after ACL reconstruction, there have been no human studies showing similar effects. Therefore, with the current knowledge in the area, the literature suggests that PRP treatment in ACL reconstruction is associated with significant radiographic and histologic improvements; however, this has not corresponded to significant clinical outcomes.

Conclusion

PRP comes in many different formulations and modes of delivery, without clear evidence of how different factors such as a leukocyte content and the process of preparation affect its efficacy. Part of the issue of determining this lies in the vague or poorly documented process of preparation, and inconsistency in delivery methods utilized in the majority of the literature. From the available literature, PRP's effects most plausibly come from its anti-inflammatory properties, as well as the growth factors and anabolic/anti-catabolic pathways stimulated with its use. PRP can be utilized as an injection, or as a matrix adhered to a scaffold which can be introduced directly to wounded tissues. PRP has shown efficacy in treating many knee conditions, but by far has been studied most extensively in the treatment of OA of the knee. When compared with hyaluronic acid and CS, PRP shows improved clinical effects as well as a longer duration of action, potentially delaying the need for total joint replacement. Much like hyaluronic acid injections, PRP seems to be more beneficial in a younger population, in the earlier stages of OA. Positive effects have also been shown in the case of meniscal tears, where PRP has been shown in the majority of studies to confer significant clinical benefit when used intraoperatively. Literature studying the effects of PRP following total joint arthroplasty is sparse and has shown conflicting results with some studies reporting a benefit while others do not. In regard to ACL reconstruction, PRP has been shown to assist in healing rates compared with placebo; however, most of this data is based on radiographic or second-look arthroscopy, without conferring a clinical benefit. Although still early in its use, PRP has shown some promising results following surgeries of the knee. At this stage, more studies need to be performed to elucidate the effects of the different PRP formulations and delivery methods, to produce a more standardized treatment algorithm for the physicians treating various pathologies of the knee. In addition, currently, the biggest barrier to the widespread utilization of PRP is the high cost of current formulations, producing modest improvements over current therapies. As production costs diminish, the use of PRP would be expected to become more widespread, allowing for more clinical studies to be performed to determine standardized protocols for therapeutic use.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. I-Kung Wu P, Diaz R, Borg-Stein J. Platelet-rich plasma. Phys Med Rehabil Clin N Am. 2016; https://doi.org/10.1016/j.pmr.2016.06.002.
2. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte-and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009; https://doi.org/10.1016/j.tibtech.2008.11.009.
3. Shahid M, Kundra R. Platelet-rich plasma (PRP) for knee disorders. EFORT Open Rev. 2017;2:28–34. https://doi.org/10.1302/2058-5241.2.160004.
4. •• Marmotti A, Rossi R, Castoldi F, Roveda E, Michielon G, Peretti GM. PRP and articular cartilage: a clinical update. Biomed Res Int. 2015;2015:542502. https://doi.org/10.1155/2015/542502. **This study shows the significant beneficial effects of PRP on knee OA with the use of a wide variety of functional outcomes, making it a convincing study in terms of the overall benefit of PRP in the first year after injection. It also importantly shows the relatively temporary nature of the effects, with significant diminishing benefits after 1 year. This temporary effect suggests that although in vitro studies show chondroproliferative effects of PRP, the micro-environment of an in vivo (i.e. human) model may only allow PRP to function as an anti-inflammatory agent (the reason for which is unclear) In addition, this study (along with others) reveals that PRP has the best effect on OA in patients that are younger and have milder disease. This is very important in future clinical considerations of who to treat.**
5. Zimmermann R, Reske S, Metzler P, Schlegel A, Ringwald J, Eckstein R. Preparation of highly concentrated and white cell-poor platelet-rich plasma by plateletpheresis. Vox Sang. 2008;95(1):20–5. https://doi.org/10.1111/j.1423-0410.2008.01062.x.
6. Mishra A, Tummala P, King A, et al. Buffered platelet-rich plasma enhances mesenchymal stem cell proliferation and chondrogenic differentiation https://www-ncbi-nlm-nih-gov.uml.idm.oclc.org/pmc/articles/PMC2819709/pdf/ten.tec.2008.0534.pdf. Accessed 3 Apr 2018.
7. Dhillon MS, Patel S, John R. PRP in OA knee – update, current confusions and future options. https://doi.org/10.1051/sicotj/2017004.
8. Xie X, Zhang C, Tuan RS. Biology of platelet-rich plasma and its clinical application in cartilage repair https://arthritis-research.biomedcentral.com/track/pdf/10.1186/ar4493. Accessed 3 Apr 2018.
9. Anitua E, Sachez M, Orive G, Andıá I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials. 2007;28:4551–60. https://doi.org/10.1016/j.biomaterials.2007.06.037.
10. Mariani E, Canella V, Cattini L, Kon E, Marcacci M, di Matteo B, et al. Leukocyte-rich platelet-rich plasma injections do not up-modulate intra- articular pro-inflammatory cytokines in the osteoarthritic knee. PLoS One. 2016;11(6):1–13. https://doi.org/10.1371/journal.pone.0156137.
11. Dragoo JL, Braun HJ, Durham JL, et al. Comparison of the acute inflammatory response of two commercial platelet-rich plasma systems in healthy rabbit tendons. Am J Sports Med. 2012;40(6):1274–81. https://doi.org/10.1177/0363546512442334.
12. • Fleming BC, Proffen BL, Vavken P, Shalvoy MR, Machan JT, Murray MM. Increased platelet concentration does not improve functional graft healing in bio-enhanced ACL reconstruction. Knee Surg Sports Traumatol Arthrosc. 2015; https://doi.org/10.1007/s00167-014-2932-6. **This study showed that changes in concentration of PRP does not significantly influence tendinous healing. This allows future applications of PRP in this context to use preparations that are more cost effective to produce.**
13. • LaPrade RF, Goodrich LR, Phillips J, et al. Use of platelet-rich plasma immediately after an injury did not improve ligament healing, and increasing platelet concentrations was detrimental in an in vivo animal model. Am J Sports Med. 2018; https://doi.org/10.1177/0363546517741135. **Same reason as (12).**
14. • Dernek B, Kesiktas FN, Duymus TM, et al. Effect of platelet concentration on clinical improvement in treatment of early stage-knee osteoarthritis with platelet-rich plasma concentrations. https://www.jstage.jst.go.jp/article/jpts/29/5/29_jpts-2017-001/_pdf/-char/en. Accessed March 18, 2018. **Same reason as (12, 13) but in the context of research pertaining to OA.**
15. Chahla J, Cinque ME, Piuzzi NS, Mannava S, Geeslin AG, Murray IR, et al. A call for standardization in platelet-rich plasma preparation protocols and composition reporting: a systematic review of the clinical orthopaedic literature. J Bone Joint Surg Am. 2017;99(20):1769–79. https://doi.org/10.2106/JBJS.16.01374.
16. •• CPC C, Cheng CH, Hsu CC, Lin HC, Tsai YR, Chen JL. The influence of platelet rich plasma on synovial fluid volumes, protein concentrations, and severity of pain in patients with knee osteoarthritis. Exp Gerontol. 2017;93:68–72. https://doi.org/10.1016/j.exger.2017.04.004. **Crucial study showing that the in vitro effect of PRP (including attenuation of pro-inflammatory cytokines, synovial fluid volume reductions) can actuallybe seen in a human in vivo model. This was expecially significant as these biochemical markers were correlated to significant benefits in clinical outcomes as outlined by the Lequesne Algofunctonal Index changes over time with subsequent PRP injections.**
17. van Buul GM, Koevoet WL, Kops N, et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. Am J Sports Med. 2011; https://doi.org/10.1177/0363546511419278.
18. Bendinelli P, Matteucci E, Dogliotti G, Corsi MM, Banfi G, Maroni P, et al. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of NF-κB inhibition via HGF. J Cell Physiol. 2010;225(3):757–66. https://doi.org/10.1002/jcp.22274.
19. Assirelli E, Filardo G, Mariani E, et al. Effect of two different preparations of platelet-rich plasma on synoviocytes. Knee Surg Sports Traumatol Arthrosc. 2015; https://doi.org/10.1007/s00167-014-3113-3.
20. Saito M, Takahashi KA, Arai Y, Inoue A, Sakao K, Tonomura H, et al. Intraarticular administration of platelet-rich plasma with biodegradable gelatin hydrogel microspheres prevents osteoarthritis progression in the rabbit knee. Clin Exp Rheumatol. 2009;27:201–7. https://pdfs.semanticscholar.org/3f9c/adb33f34242c1ea7dfeb3d95247a7c7b0593.pdf. Accessed 19 June 2018
21. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2011; https://doi.org/10.1007/s00167-010-1238-6.
22. Kon E, Buda R, Filardo G, et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc. 2010; https://doi.org/10.1007/s00167-009-0940-8.
23. Mangone G, Orioli A, Pinna A, Pasquetti P. Infiltrative treatment with Platelet Rich Plasma (PRP) in gonarthrosis. https://www-ncbi-

nlm-nih-gov.uml.idm.oclc.org/pmc/articles/PMC4064444/pdf/67-72.pdf. Accessed 23 Apr 2018.

24. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis a prospective, double-blind, randomized trial. Am J Sports Med. 2013; https://doi.org/10.1177/0363546512471299.
25. Smith PA. Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis. Am J Sports Med. 2015;44(4):884–91. https://doi.org/10.1177/0363546515624678.
26. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. YJARS. 2011;27:1490–501. https://doi.org/10.1016/j.arthro.2011.05.011.
27. Sánchez M, Fiz N, Azofra J, Usabiaga J, Aduriz Recalde E, Garcia Gutierrez A, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. YJARS. 2012;28:1070–8. https://doi.org/10.1016/j.arthro.2012.05.011.
28. Vaquerizo V, Plasencia MÁ, Arribas I, Seijas R, Padilla S, Orive G, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. Arthrosc J Arthrosc Relat Surg. 2013;29:1635–43. https://doi.org/10.1016/j.arthro.2013.07.264.
29.• Campbell KA, Saltzman BM, Mascarenhas R, et al. Does intra-articular platelet-rich plasma injection provide clinically superior outcomes compared with other therapies in the treatment of knee osteoarthritis? A systematic review of overlapping meta-analyses. Arthroscopy. 2015;31(11):2213–21. https://doi.org/10.1016/j.arthro.2015.03.041. **This comprehensive meta-analysis shows that the literature has consistently shown PRP to be superior to HA (with respect to both amount and duration of benefit) in the symptomatic treatment of knee OA.**
30. Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. Eur J Orthop Surg Traumatol. 2015;25:509–13. https://doi.org/10.1007/s00590-014-1517-x.
31. Treatment of osteoarthritis of the knee, 2nd edition summary of recommendations. www.aaos.org/guidelines. Accessed 8 Aug 2018.
32. Hochberg MC, Altman ROYD, April KT, et al. American College of Rheumatology 2012 Recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip and knee. Arthritis Care Res (Hoboken). 2012;64(4):465–74. https://doi.org/10.1002/acr.21596.
33.•• Forogh B, Mianehsaz E, Sajadi S. Effect of single injection of platelet-rich plasma in comparison with corticosteroid on knee osteoarthritis: a double-blind randomized clinical trial. J Sports Med Phys Fitness. 2015;56(7–8):901–8. **From what the authors could find, this is the only study that pits corticosteroid injections directly against PRP injections in a study of clinical outcomes of knee OA. This study shows that at 2 and 6 months, the PRP group had performed better than the CS group. More research is definitely needed to confirm these findings, however, as corticosteroids are one of the mainstays of symptomatic treatment of OA.**
34. Camurcu Y, Hakan S, Ucpunar H, Kockara N, Cobden A, Duman S. Single-dose intra-articular corticosteroid injection prior to platelet-rich plasma injection resulted in better clinical outcomes in patients with knee osteoarthritis: a pilot study. J Back Musculoskelet Rehabil 2018. https://outlook.office.com/owa/?realm=myumanitoba.ca. Accessed 8 July 2018.
35. Jubert NJ, Rodríguez L, Reverté-Vinaixa MM, Navarro A. Platelet-rich plasma injections for advanced knee osteoarthritis a prospective, randomized, double-blinded clinical trial. Orthop J Sports Med. 2017; https://doi.org/10.1177/2325967116689386.
36. Loia MC, Vanni S, Rosso F, Bonasia DE, Bruzzone M, Dettoni F, et al. High tibial osteotomy in varus knees: indications and limits. Joints. 2016;4(2):98–110.
37. Franklin SP, Burke EE, Holmes SP. The effect of platelet-rich plasma on osseous healing in dogs undergoing high tibial osteotomy. PLoS One. 2017; https://doi.org/10.1371/journal.pone.0177597.
38. Giuseffi SA, Replogle WH, Shelton WR. Opening-wedge high tibial osteotomy: review of 100 consecutive cases. Arthrosc J Arthrosc Relat Surg. 2015;31:2128–37. https://doi.org/10.1016/j.arthro.2015.04.097.
39.•• Muchedzi TA, Roberts SB. A systematic review of the effects of platelet rich plasma on outcomes for patients with knee osteoarthritis and following total knee arthroplasty. Surg. 2017; https://doi.org/10.1016/j.surge.2017.08.004. **This study pooled a large amount of data to see if the literature consistently shows any benefit of PRP in a post-TKA environment in terms of relevant clinical outcomes. While there may have been a slight reduction of pain (albeit only in 5/17 of the pooled studies), there were no significant improvements found in any other outcomes measures in more than 2300 patients across all studies. This suggests that PRP may not be an effective adjunct to knee arthroplasty, and should not be routinely used.**
40. Guerreiro JPF, Danieli MV, Queiroz AO, Deffune E, Ferreira RR. Platelet-rich plasma (PRP) applied during total knee arthroplasty. Rev Bras Ortop. 2015;50(2):186–94. https://doi.org/10.1016/j.rboe.2015.02.014.
41. Morishita M, Ishida K, Matsumoto T, Kuroda R, Kurosaka M, Tsumura N. Intraoperative platelet-rich plasma does not improve outcomes of total knee arthroplasty. J Arthroplast. 2014;29:2337–41. https://doi.org/10.1016/j.arth.2014.04.007.
42. Ma J, Sun J, Guo W, Li Z, Wang B, Wang W. The effect of platelet-rich plasma on reducing blood loss after total knee arthroplasty: a systematic review and meta-analysis. Medicine (Baltimore). 2017;96(26):e7262. https://doi.org/10.1097/MD.0000000000007262.
43. Hutchinson ID, Rodeo SA, Perrone GS, Murray MM. Can platelet-rich plasma enhance anterior cruciate ligament and meniscal repair? J Knee Surg. 2015;28:019–28. https://doi.org/10.1055/s-0034-1387166.
44. Irie K, Uchiyama E, Iwaso H. Intraarticular inflammatory cytokines in acute anterior cruciate ligament injured knee. Knee. 2003;10:93–6. https://ac-els-cdn-com.uml.idm.oclc.org/S0968016002000832/1-s2.0-S0968016002000832-main.pdf?_tid=129f3a04-9c20-4b3f-b6d1-879bd97fd9cd&acdnat=1527650671_6d044212d99f95334e10fb591053381e. Accessed 29 May 2018
45. Stone AV, Loeser RF, Vanderman KS, Long DL, Clark SC, Ferguson CM. Pro-inflammatory stimulation of meniscus cells increases production of matrix metalloproteinases and additional catabolic factors involved in osteoarthritis pathogenesis. Osteoarthr Cartil. 2014;22(2):264–74. https://doi.org/10.1016/j.joca.2013.11.002.
46. Fermor B, Jeffcoat D, Hennerbichler A, Pisetsky DS, Weinberg JB, Guilak F. The effects of cyclic mechanical strain and tumor necrosis factor alpha on the response of cells of the meniscus. Osteoarthritis Cartilage. https://doi.org/10.1016/j.joca.2004.08.007.
47. Pujol N, Salle De Chou E, Boisrenoult P, Beaufils P. Platelet-rich plasma for open meniscal repair in young patients: any benefit? Knee Surg Sports Traumatol Arthrosc. 2014; https://doi.org/10.1007/s00167-014-3417-3.
48. Griffin JW, Hadeed MM, Werner BC, Diduch DR, Carson EW, Miller MD. Platelet-rich plasma in meniscal repair: does

augmentation improve surgical outcomes? Clin Orthop Relat Res. 2015;473:1665–72. https://doi.org/10.1007/s11999-015-4170-8.

49.• Kaminski R, Kulinski K, Kozar Kaminska K, et al. A prospective, randomized, double-blind, parallel-group, placebo-controlled study evaluating meniscal healing, clinical outcomes, and safety in patients undergoing meniscal repair of unstable, complete vertical meniscal tears (bucket handle) augmented wit. Biomed Res Int. 2018; https://doi.org/10.1155/2018/9315815. **This well-designed study with long term followup showed quite convincing clinical (at 24 months) and radiographic (at 18 weeks) evidence that PRP injections into the avascular zone of meniscal repairs were beneficial as compared with saline. This supports the use of PRP injections in certain meniscal tears as outlined by this and other studies.**

50. Yang G, Rothrauff BB, Tuan RS. Tendon and ligament regeneration and repair: clinical relevance and developmental paradigm. Birth Defects Res C Embryo Today. 2013;99(3):203–22. https://doi.org/10.1002/bdrc.21041.

51. Cook JL, Smith PA, Bozynski CC, Kuroki K, Cook CR, Stoker AM, et al. Multiple injections of leukoreduced platelet rich plasma reduce pain and functional impairment in a canine model of ACL and meniscal deficiency. J Orthop Res. 2016;34(4):607–15. https://doi.org/10.1002/jor.23054.

52. Fleming BC, Spindler KP, Palmer M, Magarian E, Murray MM. Collagen-platelet composites improve the biomechanical properties of healing ACL grafts in a porcine model https://doi.org/10.1177/0363546509332257.

53. Steiner ME, Murray MM, Rodeo SA. Strategies to improve anterior cruciate ligament healing and graft placement. Am J Sports Med. 2008;36:176–89. https://doi.org/10.1177/0363546507311690.

54. Murray MM, Fleming BC. Use of a bioactive scaffold to stimulate anterior cruciate ligament healing also minimizes posttraumatic osteoarthritis after surgery. Am J Sports Med. 2013; https://doi.org/10.1177/0363546513483446.

55. Vavken P, Sadoghi P, Murray MM, Vavken P. The effect of platelet concentrates on graft maturation and graft- bone interface healing in ACL reconstruction in human patients: a systematic review of controlled trials. Arthroscopy. 2011;27(11):1573–83. https://doi.org/10.1016/j.arthro.2011.06.003.

56. Sánchez M, Anitua E, Azofra J, Prado R, Muruzabal F, Andia I. Ligamentization of tendon grafts treated with an endogenous preparation rich in growth factors: gross morphology and histology. YJARS. 26:470–80. https://doi.org/10.1016/j.arthro.2009.08.019.

57. Figueroa D, Melean P, Calvo R, et al. Magnetic resonance imaging evaluation of the integration and maturation of semitendinosus-gracilis graft in anterior cruciate ligament reconstruction using autologous platelet concentrate. Arthroscopy. 2010; https://doi.org/10.1016/j.arthro.2010.02.010.

58. Orrego M, Larrain C, Rosales J, et al. Effects of platelet concentrate and a bone plug on the healing of hamstring tendons in a bone tunnel. Arthroscopy. 2008; https://doi.org/10.1016/j.arthro.2008.07.016.

59. Radice F, Yánez R, Gutiérrez V, et al. Comparison of magnetic resonance imaging findings in anterior cruciate ligament grafts with and without autologous platelet-derived growth factors. Arthroscopy. 2010; https://doi.org/10.1016/j.arthro.2009.06.030.

60. Cervellin M, Girolamo L, Bait C, Denti M, Volpi P. Autologous platelet-rich plasma gel to reduce donor-site morbidity after patellar tendon graft harvesting for anterior cruciate ligament reconstruction: a randomized, controlled clinical study. Knee Surg Sports Traumatol Arthrosc. 2012;20:114–20. https://link-springer-com.uml.idm.oclc.org/content/pdf/10.1007%2Fs00167-011-1570-5.pdf. Accessed 30 Mar 2018.