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REGENERATIVE PAIN MEDICINE/INTERVENTIONAL PAIN MEDICINE (E CORNETT BRADLEY, SECTION EDITOR)

Platelet-Rich Plasma Injections: Pharmacological and Clinical Considerations in Pain Management

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Abstract

Purpose of Review Regenerative medicine through interventional pain procedures is evolving with data demonstrating efficacy for a number of pain states in recent years. Platelet-rich plasma (PRP), defined as a sample of plasma with a platelet concentration 3 to 5 times greater than the physiologic platelet concentration found in healthy whole blood, releases bioactive proteins which can restore anatomical function in degenerative states. PRP is dense in growth factors, such as platelet-derived growth factor, transforming growth factor-beta1, basic fibroblastic growth factor, vascular endothelial growth factor, and epidermal growth factors.

Recent Findings To date, well-designed case–control or cohort studies for the use of PRP have demonstrated efficacy in lumbar facet joint, lumbar epidural, and sacroiliac joint injections. At present, there is only level IV evidence indicating the need for larger and more carefully controlled prospective studies. PRP is utilized autogenously in order to facilitate healing and injection and has been studied in the long-term management of discogenic low back pain. In this regard, numerous studies have evaluated PRP to steroid injections in chronic pain states with favorable results.

Summary PRP represents an opportunity for a new strategy in the therapeutic treatment of degenerative states of spines, joints, and other locations throughout the body with evolving data demonstrating both safety and long-term efficacy.

Keywords Platelet-rich plasma · Chronic pain · Lumbar facet joint · Lumbar epidural · Sacroiliac joint injections

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Introduction

Americans spend millions of dollars every year to alleviate acute and chronic pain. However, few can find lasting relief. Therefore, it is not surprising that many providers and patients are hopeful for emerging treatment modalities. One of these therapeutic options gaining traction in pain management is platelet-rich plasma (PRP). The use of PRP as a therapeutic agent was first described in the 1950s in dermatology and oromaxillofacial surgery [1]. Since then, PRP has been used in medical fields ranging from otolaryngology, orthopedics, sports medicine, neurosurgery, ophthalmology, urology, cosmetic dermatology, and cardiothoracic surgery [2•].

PRP typically contains ~ 3–5 times as many platelets as that found in healthy whole blood [3, 4]. Preparing PRP is relatively straightforward—a patient's blood is obtained via venipuncture and then centrifuged to divide its components. Generally, an anticoagulant factor is used before centrifugation, which separates red blood cells (RBCs) from platelet-poor plasma (PPP) and the "buffy coat," containing the concentrated platelets and leukocytes. The platelets

are isolated using various methods and can then be directly injected into the patient or be "activated" via the addition of a combination of calcium chloride and/or thrombin, which then causes platelet degranulation and release of growth factors [4]. Patient-specific factors such as current medications and past medical history can influence the efficacy of PRP [5]. Additionally, its composition and commercial preparation methods can also affect outcomes [5]. This creates challenges in interpreting the available literature.

Given that there is no established protocol for obtaining PRP, various preparations currently exist. Formulations differ depending on the amount of whole blood obtained, the ratio of platelet capture efficiency, isolation method (one- or two-step centrifugation), the speed of centrifugation, and the type of collection tube system and operation. PRP preparations are typically further categorized into leukocyte-rich PRP (LR-PRP) preparations and leukocyte-poor PRP (LP-PRP) preparations, defined by their neutrophil concentration compared to baseline [4]. There is ongoing speculation regarding the benefit of LR-PRP as compared to LP-PRP. It is thought that LR-PRP produces pro-inflammatory effects necessary for tendon healing, but excessive inflammation can lead to more pain, scarring, and fibrosis [4].

There is significant basic science research describing how PRP could benefit pain management, wound healing, and connective tissue repair. In comparison, there is a sparsity of clinical trials. In addition, evidence of its efficacy has been highly heterogeneous depending on the specific indication. Additional high-quality clinical trials with longer follow-ups will be critical in shaping our perspective of this treatment option. This comprehensive review describes current knowledge of PRP and its use in various medical specialties, and summarizes the latest recommendations regarding its use.

PRP for Pain Management and Mechanism of Action

After PRP preparation, the final product is a substance dense in growth factors—specifically, platelet-derived growth factor (PDGF), transforming growth factor-beta1(TGF-β1), basic fibroblastic growth factor, vascular endothelial growth factor (VEGF), and epidermal growth factors [4]. The two most significant of these are PDGF and TGF-β1, as they play vital roles in stimulating fibroblast proliferation and wound healing [6]. Alpha granules within platelets release both pro- and anti-inflammatory mediators that locally reduce pain and inflammation. These factors also alter the wound environment by promoting tissue healing and regeneration via the complex effects of regulation of stem cell migration, proliferation, differentiation, and a combination of anabolic and catabolic processes [4]. This saturated content of growth factors can then be injected directly into the desired location and augment the natural healing process.

PRP works by delivering a supraphysiologic amount of growth factors and cytokines contained within the alpha granules of platelets. PRP is a promising treatment modality with a higher safety profile than any current alternatives in musculoskeletal medicine. However, given the lack of current data, it is impossible to provide recommendations for several conditions for which PRP is currently being used. Based on current data, LR-PRP injection is a beneficial treatment for lateral epicondylitis, but there is not sufficient evidence for its routine use in patellar tendinopathy [7•]. LP-PRP has been proven beneficial for knee osteoarthritis [7•]. The usage of PRP for rotator cuff tendinopathy, osteoarthritis of the hip, high ankle sprains, anterior cruciate ligament (ACL) reconstruction, Achilles tendinopathy, acute fractures, and rotator cuff repair is not currently recommended given available data [7•].

Studies regarding the use of PRP in chronic pain range from total pain alleviation to no reported clinical benefit. This discrepancy is the result of no uniform protocol method of PRP preparation. Some studies have shown that this variability is dictated by several factors, including patient health, methods used to prepare PRP, and methods of PRP application [5]. Maximizing chronic pain relief in a reproducible fashion has become the goal of studies in various fields of medicine. New and larger studies involving comparable protocols and minimal other variables are needed to assess the true potential of PRP. Additional future high-quality, large clinical trials will be critical in shaping our perspective of PRP. The heterogeneity of PRP preparations, both presently and historically, has made interpreting the existing literature difficult and limits our ability to make definitive treatment recommendations.

PRP for Knee Pain

Osteoarthritis (OA) is the most common form of arthritis and, by itself, a highly prevalent disease with an expensive disease burden. Knee osteoarthritis (KOA) specifically being the most common subtype while also being the second most expensive [8–10]. The pathophysiology of KOA is relatively unknown. Still, inflammation being the most common culprit pointed to as either a causative agent or a response to OA leading to further damage. Treatment is also often difficult due to the physiology of the knee and specifically the knee cartilage due to its avascular and lack of regenerative capacity. Finally, there is currently no curative treatment available, with a knee arthroplasty being the closest treatment that comes with its issues [11]. The main one being continued pain even after the operation, which has been reported as high as 25% [12].

Treatment is often focused on slowing disease progression and treating symptoms using both pharmacological and non-pharmacological methods. Nonpharmacological approaches are usually patient education and managing risk factors with weight loss and exercise [13, 14]. Pharmacological treatments can be broken down into noninvasive and invasive approaches, with noninvasive categories being medications like topical anti-inflammatories and oral non-steroidal anti-inflammatory drugs (NSAIDs). Invasive pharmacological treatments have included intraarticular (IA) corticosteroids, hyaluronic acid (HA), and PRP injections [13, 15]. While IA corticosteroid and HA injections have been the standard, PRP injections have shown promise in recent studies [16–18].

In a single-arm prospective study by Taniguchi et al., 10 patients with early-phase KOA received three IA injections at 1-week intervals. Visual analog scale (VAS) pain scores were measured at baseline and then at 1-, 3-, and 6-month follow-up. During the study, all adverse effects were minor, including acute knee pain, stiffness, tingling, and walking pain, and all subsided within 48 h after injection. Eight out of ten patients had a decrease in VAS pain scores of greater than 50%, with benefits maintained during the 6-month follow-up. The authors concluded that IA-PRP was safe for use with the potential to reduce the pain that is maintained up to 6 months after injection in the majority of patients [16].

Yaradilmis et al. conducted a prospective randomized controlled trial comparing LR-PRP IA, LP-PRP IA, and HA-IA knee injections in 90 patients. Patients were split into three groups, with each group receiving their injection a set day per week in 1-week intervals for three total injections. They measured outcomes using the VAS pain scale and Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, with scores recorded at baseline and right after the last injection. They then recorded them over the next 2 months, 6 months, and 12 months postinjection. The group found that while all three injections were effective in reducing symptoms, LR-PRP injections were shown to have the greatest effect. However, they did find that these methods were less effective on patients over 70, those who were female, and those who were obese [17].

In another prospective randomized controlled trial, PRP injections were compared to a placebo group that received saline injections [18]. The purpose of this study, therefore, was to assess the effects of PRP therapy on pain, functioning, quality of life, and cartilage thickness in patients with KOA. Sixty patients were selected, and injections were done similarly to previous studies: three times a week with 1-week intervals between injections. Baseline VAS and WOMAC scores were recorded and similar between the groups at the beginning of the study, along with distal femur cartilage thickness, measured via ultrasound. When measured after 1- and 6 months following treatment, pain VAS scores were significantly lower in the PRP group compared to the control group, with only the pain subscore improving in the WOMAC assessment at 1 month. This improved all parameters of the WOMAC assessment at the 6-month follow-up for the PRP group. The cartilage thickness was unchanged in both the control and PRP group at the end of the study [18].

PRP has also been investigated in treatment for knee conditions outside of OA, one of the most common being meniscal tears, which occurs in 60 to 70 patients per 100,000 [19]. To analyze PRP effects on meniscal tears, we looked at Everhart et al. [20]. This was a retrospective cohort study of 550 patients who underwent isolated meniscal repairs with and without PRP injections post-op or meniscal repair with concomitant ACL repair that either did or did not receive PRP injections post-op. They looked at rates of meniscal repair failure up to 3 years after the operation, which was defined as subsequent meniscectomy, no evidence of healing on repeat arthroscopy, meniscal repair revision, or total knee arthroplasty. They found that in isolated meniscal repairs, PRP had a strong protective effect against meniscal failure at 3 years but showed no statistically significant benefit when a concomitant ACL repair was done during meniscal repair [18].

PRP for Back Pain

Back pain, specifically low back pain (LBP), is a highly common disease with a reported global prevalence of 7.3%. It can also be an incredibly debilitating disease limiting activities of daily living (ADLs) and is regarded as the fourth leading cause of disability worldwide, with an 18.6% increase from 2005 to 2015 [21, 22]. Epidemiological studies have shown the highest prevalence is in middle age, but a WHO collaborative cross-national survey showed that 37.0% of adolescents reported LBP monthly or more [23, 24]. This is especially troubling, considering twin studies have shown that persistent LBP in adolescents has a 3.5 times higher chance of continuing into adulthood [25]. Combine this with a globally aging population, and LBP appears to be an important condition that would benefit from an improved treatment regime moving forward.

A common etiology of LBP is intervertebral disc pathology, with lumbar disc disruption and degenerative disc disease being the two most common pathologies [26, 27]. To examine PRP injections in the context of degenerative disc disease, Jain et al. enrolled 20 patients in a prospective single-arm interventional study. Selected patients include those who had a 6-month or more history of LBP without response to conservative management and evidence of concordant pain with signs of degeneration on discography. Injections of LR-PRP were made into only the problematic discs identified on discography findings, with the tip of

the needle placed at the center of the disc. Pre-procedure numeric rating scale (NRS) pain scores and Oswestry disability index (ODI) scores were compared to the same metrics during follow-up at 3 and 6 months. A reduction in NRS and improvement in ODI scores were statistically significant at 3- and 6-month follow-ups, with over half of patients reporting greater than 50% improvement in both scores by 6-month follow-up. Four patients reported no pain relief at 6 months, and two initially having a decrease in pain and disability at 3 months, followed by an increase in scores at 6 months. However, the scores were still lower than the pre-procedure baseline scores [28].

When treating disc herniation with PRP injection, Xu et al. compared transforaminal injections of PRP to the standard treatment of steroids, specifically betamethasone being the control group in this study. This was a prospective, randomized-controlled study of 132 patients with 68 patients in the control group and 64 patients in the PRP group. Multiple outcome measures were taken, with VAS scores, pressure pain thresholds (PPTs), rate and latency of F-wave, and ODI scores being the primary ones. These were measured pre-injection, and then all but F-wave rate and latency were recorded at 1 week, 1 month, 3 months, 6 months, and 1 year post-operation; F-wave rate and latency were only obtained at 1 year post-procedure. It was found that while both treatment groups showed statistically significant improvements at the 1-year follow-up for all outcome measures, there were no statistically significant differences between the two groups. While this study did not show that PRP was superior to the traditional steroid treatment, PRP was not associated with side effects common with steroids, such as neurotoxicity, hypercortisolism, hyperglycemia, and neurological injury. Furthermore, the contraindications for steroid use that limits its use, such as diabetes, osteoporosis, pregnancy, and infection, are not contraindicated for PRP injections. Therefore, this study supports the idea that PRP injections may be a safer alternative to steroid injections for herniated discs without sacrificing efficacy [29].

PRP for Other Pain Conditions

Musculoskeletal Disorders

PRP has also been used in the treatment of soft tissue injuries, such as those of muscles, ligaments, and tendons. Muscle groups, such as hamstrings, quadriceps, gastrocnemius, and hip flexors, are especially prone to injury. A review by Setayesh et al. examined the efficacy of PRP in sports-related soft tissue injuries. In vitro studies supported the regenerative potential of PRP for acute soft tissue injuries. Using multiple clinical case series implementing PRP injections, they concluded that this could be an effective option for faster healing, less swelling, and decreased return to playtime in muscle strains [30].

In a systematic review and meta-analysis, Chen et al. explored the effectiveness of PRP in pain management for rotator cuff, tendinopathy, anterior cruciate ligament, patellar tendinopathy, hamstring tendinopathy, and lateral epicondylitis using the visual analog scale (VAS) [31]. After including 37 articles in review and 21 for quantitative analysis, it was found that compared to control (surgical repair without additional treatment), PRP may reduce pain associated with rotator cuff injuries and lateral epicondylitis [31].

Chronic Achilles Tendinopathy

Kearney et al. [32] conducted a participant-blinded, multicenter randomized control trial in which all patients received one single intra-tendinous injection (either PRP or sham). The primary outcome observed was the measurement of the Victorian Institute of Sport Assessment-Achilles (VISA-A) score, which was adjusted for age, sex, and baseline. After a 6-month follow-up, the VISA-A scores were 54.4 vs. 53.4, respectively. They concluded that a single injection of PRP could not be supported as an effective means of pain management for patients with chronic midportion Achilles tendinopathy [32].

Anterior Cruciate Ligament Injury

To explore the effectiveness of PRP in ACL tears, Zicaro et al. conducted a single institution study in which 40 patients were identified with partial ACL tears and treated nonsurgically [33]. Patients in the first cohort were treated with one intraarticular injection of PRP and a specific physical therapy protocol. The second cohort received only physical therapy. Outcomes observed were clinical physical exam findings, Tegner activity level, Lysholm, and International Knee Documentation Committee scores, MRI findings prior to treatment, and then at 6-months follow-up. No significant difference was observed between the two cohorts regarding failure rate (clinical instability at follow-up requiring ACL reconstruction), return to sport, subjective outcomes, or MRI findings. This prospective comparative study found that the addition of PRP with physical therapy did not enhance treatment with physical therapy alone [33]. Table 1 shows the clinical efficacy and safety of recent studies examining PRP.

Small Joint Osteoarthritis

Malahias et al. performed a blind, randomized, controlled trial using 33 patients with clinical and radiographic signs of OA in the first carpometacarpal joint [34]. After randomization, 16 patients were assigned to group A, where they received IA-PRP injections, and 17 were assigned to group

Table 1 Clinical efficacy and safety

Author (year)	Groups studied and intervention	Results and findings	Conclusions
Trull-Ahuir et al. [40]	A total of 50 patients with mild to extreme CTS confirmed by clinical and electromyography features aged 18–65 were randomized into receiving 3 mL of either PRP or PPP after CTS decompression	Pain, the severity of symptoms, and functional status improved after surgery for both groups; wound healing and amount of leave taken from work was normal and similar between groups; the PRP group showed quicker regain of hand grip strength compared to baseline than in PPP (18 ± 10.2 vs. 14.7 ± 6.9)	PRP injections after CTS decompression is safe and may even lead to quicker regain of preoperative hand strength, which may be beneficial, specifically for those patients whose work relies on their hand strength
Kearney et al. [32]	This participant-blinded, multicenter randomized control trial included 240 patients with chronic midportion Achilles tendinopathy from 24 locations. All patients received one single intratendinous (either PRP injection or sham injection)	The primary outcome observed was the measurement of the Victorian Institute of Sport Assessment-Achilles (VISA-A) score, which was adjusted for age, sex, and baseline. After 6 months of follow-up, the VISA-A scores for a single injection of PRP or the sham injection were 54.4 vs. 53.4, respectively	The use of a single injection of PRP could not be supported as an effective means of pain management for patients with chronic midportion Achilles tendinopathy
Zicaro et al. [33]	This was a single institution study in which 40 patients were identified with partial anterior cruciate ligament (ACL) tears and treated nonsurgically. Patients in cohort 1 were treated with one intraarticular injection of PRP and a specific physical therapy protocol. The second cohort received only physical therapy	Outcomes observed were clinical physical exam findings, Tegner activity level, and Lysholm and International Knee Documentation Committee scores. MRI findings prior to treatment and then at 6-mo follow-up. No significant difference was observed between the two cohorts in regards to failure rate (clinical instability at follow-up requiring ACL reconstruction), return to sport, subjective outcomes, or MRI findings	This prospective comparative study found that the addition of PRP with physical therapy did not enhance treatment with physical therapy alone

Table 2 Comparative studies

Author (year)	Groups studied and intervention	Results and findings	Conclusions
Peerbooms et al. [39]	Patients older than 18, with plantar fasciitis for more than 6 months that have not responded to nonoperative treatment Injections of 5–6 mL of triamcinolone acetonide 40 mg/mL vs. Injections of 5–6 mL of concentrated platelets and 8.4% $NaHCO_3$ with a 1:0.05 mL ratio	FFI pain scores: mean difference of 14.4 with 95% CI 3.2–25.6 improvement between control and PRP group FFI disability scores: mean difference of 12.0 with 95% CI 2.3–21.6 improvement in PRP group vs. control # of patients with ≥ 25% improvement in FFI pain scores: 84.4% in the PRP group vs. 55.6% in the control	Injections of autologous PRP may give similar pain relief over a longer time period with less side effects than corticosteroid injections for treating treatment-resistant plantar fasciitis
Chandra et al. [37]	A total of 44 patients age ranging from 15 to 54 years old, with the average age being 30.5 years who have TMJ pain not responding to conservative management The control group received arthrocentesis of TMJ with 50–60 mL of ringer lactate The test group received 0.6 mL of PRP injected into the TMJ	VAS: significant improvements in both groups, PRP showed more improvement (1.00 vs. 3.17 $p < 0.05$) MIO: significant improvements in both groups. PRP showed more improvement (39.86 mm vs. 37.59 mm $p < 0.05$) TMJ clicking: significant improvements in both groups, PRP showed more improvement (6/22 vs. 16/22 $p < 0.05$)	IA-PRP injection appears to be more effective in reducing pain, reducing jaw clicking, and restoring jaw function than arthrocentesis while being simpler to perform technically
Xu et al. [29]	This randomized controlled trial administered ultrasound-guided transforaminal injections of PRP or steroids to a total of 124 patients who suffered from radicular pain due to lumbar disk herniation. Patients were aged 20–60 with the presence of low back pain with unilateral lower limb radicular pain for at least 3 months resulting from either L4/L5 or L5/S1 herniation	Patients were assessed with the following scales: visual analog scale (VAS), pressure pain thresholds (PPTs), Oswestry disability index (ODI), and the physical function (PF) and the bodily pain (BP) sections of the short form health survey (SF-36) at 1 week, 1 month, 3 months, 6 months, and 12 months following the operation. Both treatment groups showed improvement using the described SF-36 sections, and there was no statistically significant difference in the sections of the SF-36 at 1-year follow-up	The two treatment interventions were not found to be significantly different. This RCT concluded that transforaminal injections of PRP may be a safer alternative to steroid injection in the management of radicular pain secondary to lumbar disk herniation
Malahias et al. [34]	A total of 32 patients with clinical and radiographic evidence of OA of the first CMCJ, were randomized into receiving either IA-PRP injections or IA-steroid and lidocaine injections	VAS: no difference between groups at baseline, both showed significant improvement at 3 months, only the PRP group maintaining that improvement at 12 months Q-DASH: no difference between groups at baseline and at 3 months with both showing improvement at 3-month follow-up, but at 12 months the PRP group had significantly reduced scores while the control group lost the function improvements Patient satisfaction: at 3 months more patients were satisfied by steroid injection than PRP (56% vs. 44%), but at 12 months significantly more were satisfied by the PRP injections than the steroid (69% vs. 12.5%)	While steroid + lidocaine injections provide similar, or slightly better, short-term pain relief and a return to functionality when compared to PRP injections. PRP injections appear to confer a longer period of pain relief and more satisfying results posttreatment

B, where they received IA methylprednisolone and lidocaine injections into the affected joint under ultrasound guidance. Their outcome measures were VAS pain score, truncated disabilities of the arm, shoulder, and hand questionnaire (Q-DASH) score, and the patient's subjective satisfaction with the treatment at baseline and at 3 and 12 month follow-up [34]. At 12 months, the patients who had a VAS score of less than 20 out of 100, which is considered mild pain, 62.5% were from the PRP group compared to only 12.5% in the steroid plus lidocaine group. The PRP group also showed improved function at the 12-month follow-up, as measured by the improvement in Q-DASH scores. Lastly, even the patient's subjective sense of how they felt the treatment improved their lives was higher with the PRP group, with almost 70% saying they were satisfied, much higher than the 12.5% in the control group at the 12-month follow-up [34].

Temporomandibular Disorder (TMD)

Temporomandibular disorder (TMD) is a musculoskeletal disorder caused by a massive insult like a hard strike to the jaw or many small insults like eating, yawning, teeth clenching, or anything that would require repetitive opening and close against resistance [35]. TMD is a highly prevalent disease, with as much as 33% of the population experiencing symptoms in their life and 4–7% having symptoms serious enough to seek treatment. The standard of treatment for TMD has been encouraging the patient to avoid hard or chewy foods and stress management/awareness techniques to prevent jaw clenching [36]. Invasive treatment with arthrocentesis of the temporomandibular joint (TMJ) has shown some benefit, but it has been suggested as an alternative treatment given PRP's proposed mechanism of action.

In a controlled clinical trial by Chandra et al., 52 patients with conservative treatment failure were randomized into receiving IA injection of PRP into the TMJ or arthrocentesis of the TMJ [37]. In both groups, all three outcome measures were improved at the 6-month follow-up compared to baseline. When comparing differences between groups, PRP had a clear, statistically significant improvement when compared to arthrocentesis. They concluded that IA-PRP injection was technically more simple and effective, provided better pain relief, and returned more jaw function than the standard treatment for refractory TMD [37].

Plantar Fasciitis

In plantar fasciitis that is resistant to conservative, noninvasive treatment, corticosteroid injections are the next line of therapy, then followed by surgery [38]. Steroid injections have short-term benefits but do not provide long-term pain relief and are known to have long-term side effects [39]. PRP injections have been suggested as a possible alternative to steroid injections as a more long-term therapy with fewer potential side effects. In a double-blind, randomized controlled trial by Peerbooms et al., they compared the standard steroid injection to an LR-PRP injection [39]. Once they adjusted for differing baseline FFI scores, the PRP group showed a significantly lower pain score than the control. The PRP group also showed improved FFI Disability scores when adjusting for baseline differences between the two groups. Finally, 84.4% of patients in the PRP group showed at least 25% improvement in FFI scores compared to only 55.6% of patients in the control group.

Carpal Tunnel Syndrome

While PRP injections are typically used as an alternative conservative treatment to standard treatment in carpal tunnel syndrome, it has shown promise as an adjuvant to more invasive procedures. In a prospective, randomized, controlled, triple-blinded clinical trial, 50 patients diagnosed with mild to extreme carpal tunnel syndrome were enrolled in a trial with 25 receiving PRP injections and 25 receiving PPP injections at the end of open carpal tunnel release surgery [40]. While outcomes improved for both groups, it was found that the PRP group regained their pre-surgery handgrip strength earlier than the PPP group [40]. This study concluded that PRP injections only significantly improved the speed with which patients regained their handgrip strength.

Conclusion

Given the lack of strong evidence regarding the use of PRP in a range of conditions currently, it is difficult to routinely recommend its use for the variety of the conditions for which it is currently being used to treat. Clinical trials with an emphasis on uniform PRP preparation and prolonged follow-up are required to validate its recommendation. By identifying different PRP formulations, including pinpointing the specific indications for leukocyte-rich and leukocyte-poor plasma that are effective in different diseases or different populations, the use of PRP as therapy will become more efficacious.

Our review of current clinical trials indicates that PRP injections are a promising treatment modality in knee and back pain, musculoskeletal pain and soft tissue trauma, small joint osteoarthritis, temporomandibular joint syndrome, plantar fasciitis, and carpal tunnel syndrome. However, recent clinical trials did not support the use of PRP for chronic midportion Achilles tendinopathy, ACL injury, and transforaminal injections of PRP for the management of radicular pain secondary to lumbar disc herniation.

A common theme seen in many of these studies was the safety of PRP (Table 2). Since the patient's own plasma was being used, negative reactions from the treatment were low

besides the typical reactions seen during injections. Many studies reported only minor site reactions that resolved within 48 h. Compared to various side effects seen with steroid injections, which were commonly used as controls, the threshold for using PRP as a treatment in other conditions should be low. Also, PRP injections may be useful for patient populations that cannot take steroids, such as diabetic patients. However, the technology and expertise needed to create consistent and safe PRP may not be accessible to all patients, which may be a barrier to its widespread adoption.

Compliance with Ethical Standards

Ethics Approval and Consent to Participate This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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

1. Hsu WK, Mishra A, Rodeo SR, Fu F, Terry MA, Randelli P, et al. Platelet-rich plasma in orthopaedic applications: evidence-based recommendations for treatment. J Am Acad Orthop Surg. 2013;21(12):739–48.
2. • Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-rich plasma: new performance understandings and therapeutic considerations in 2020. Int J Mol Sci. 2020;21(20):7794. **The article discusses the preparation and composition of PRP along with other pertinent points including drug interactions and rehabilitation protocols.**
3. Marx RE. Platelet-Rich Plasma (PRP): What is PRP and what is not PRP? Implant Dent. 2001;10(4):225–8.
4. Knezevic NN, Candido KD, Desai R, Kaye AD. Is platelet-rich plasma a future therapy in pain management? Med Clin North Am. 2016;100(1):199–217.
5. Kuffler D. Variables affecting the potential efficacy of PRP in providing chronic pain relief. J Pain Res. 2018;12:109–16.
6. Cole BJ, Seroyer ST, Filardo G, Bajaj S, Fortier LA. Platelet-rich plasma: where are we now and where are we going? Sports Health Multidiscip Approach. 2010;2(3):203–10.
7. • Le ADK, Enweze L, DeBaun MR, Dragoo JL. Current clinical recommendations for use of platelet-rich plasma. Curr Rev Musculoskelet Med. 2018;11(4):624–34. **This review succinctly summarizes the level of evidence supporting PRP for different musculoskeletal indications.**
8. Cisternas MG, Murphy L, Sacks JJ, Solomon DH, Pasta DJ, Helmick CG. Alternative methods for defining osteoarthritis and the impact on estimating prevalence in a US population-based survey: OA prevalence in a population-based survey. Arthritis Care Res. 2016;68(5):574–80.
9. Sibille KT, Chen H, Bartley EJ, Riley J, Glover TL, King CD, et al. Accelerated aging in adults with knee osteoarthritis pain: consideration for frequency, intensity, time, and total pain sites. Pain Rep. 2017;2(3):e591.
10. Torio CM, Moore BJ. National inpatient hospital costs: the most expensive conditions by payer, 2013: statistical brief #204. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006 [cited 2021 Aug 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK368492/.
11. Walker LC, Clement ND, Deehan DJ. Predicting the outcome of total knee arthroplasty using the WOMAC score: a review of the literature. J Knee Surg. 2019;32(08):736–41.
12. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012;2(1):e000435.
13. Cook CS, Smith PA. Clinical update: why PRP should be your first choice for injection therapy in treating osteoarthritis of the knee. Curr Rev Musculoskelet Med. 2018;11(4):583–92.
14. Martel-Pelletier J, Boileau C, Pelletier J-P, Roughley PJ. Cartilage in normal and osteoarthritis conditions. Best Pract Res Clin Rheumatol. 2008;22(2):351–84.
15. Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World J Orthop. 2014;5(3):351–61.
16. Taniguchi Y, Yoshioka T, Kanamori A, Aoto K, Sugaya H, Yamazaki M. Intra-articular platelet-rich plasma (PRP) injections for treating knee pain associated with osteoarthritis of the knee in the Japanese population : a phase I and IIa clinical trial [Internet]. Nagoya University Graduate School of Medicine, School of Medicine; 2018 [cited 2021 Aug 1]. Available from: https://doi.org/10.18999/nagjms.80.1.39.
17. Yaradilmis YU, Demirkale I, Tagral AS, Okkaoglu MC, Ates A, Altay M. Comparison of two platelet rich plasma formulations with viscosupplementation in treatment of moderate grade gonarthrosis: a prospective randomized controlled study. J Orthop. 2020;20:240–6.
18. Elik H, Doğu B, Yılmaz F, Begoğlu FA, Kuran B. The efficiency of platelet-rich plasma treatment in patients with knee osteoarthritis. J Back Musculoskelet Rehabil. 2020;33(1):127–38.
19. Greis PE, Bardana DD, Holmstrom MC, Burks RT. Meniscal injury: I. Basic science and evaluation. J Am Acad Orthop Surg. 2002;10(3):168–76.
20. Everhart JS, Cavendish PA, Eikenberry A, Magnussen RA, Kaeding CC, Flanigan DC. Platelet-rich plasma reduces failure risk for isolated meniscal repairs but provides no benefit for meniscal repairs with anterior cruciate ligament reconstruction. Am J Sports Med. 2019;47(8):1789–96. https://doi.org/10.1177/0363546519852616.
21. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, et al. A systematic review of the global prevalence of low back pain. Arthritis Rheum. 2012;64(6):2028–37.
22. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Lond Engl. 2016;388(10053):1603–58.
23. Kaye AD, Manchikanti L, Abdi S, Atluri S, Bakshi S, Benyamin R, et al. Efficacy of epidural injections in managing chronic spinal pain: a best evidence synthesis. Pain Physician. 2015;18(6):E939-1004.

24. Swain MS, Henschke N, Kamper SJ, Gobina I, Ottová-Jordan V, Maher CG. An international survey of pain in adolescents. BMC Public Health. 2014;14(1):447.
25. Hestbaek L, Leboeuf-Yde C, Kyvik KO. Is comorbidity in adolescence a predictor for adult low back pain? A prospective study of a young population. BMC Musculoskelet Disord. 2006;7(1):29.
26. DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? Pain Med. 2011;12(2):224–33.
27. Levi D, Carnahan D, Horn S, Levin J. Is a history of severe episodic low back pain an indicator of a discogenic etiology? Pain Med. 2018;19(7):1334–9.
28. Jain D, Goyal T, Verma N, Paswan AK, Dubey RK. Intradiscal platelet-rich plasma injection for discogenic low back pain and correlation with platelet concentration: a prospective clinical trial. Pain Med Malden Mass. 2020;21(11):2719–25.
29. Xu Z, Wu S, Li X, Liu C, Fan S, Ma C. Ultrasound-guided transforaminal injections of platelet-rich plasma compared with steroid in lumbar disc herniation: a prospective, randomized, controlled study. Wang XQ, ed. Neural Plast. 2021;27(2021):1–11. https://doi.org/10.1155/2021/5558138.
30. Setayesh K, Villarreal A, Gottschalk A, Tokish JM, Choate WS. Treatment of muscle injuries with platelet-rich plasma: a review of the literature. Curr Rev Musculoskelet Med. 2018;11(4):635–42.
31. Chen X, Jones IA, Park C, Vangsness CT. The efficacy of platelet-rich plasma on tendon and ligament healing: a systematic review and meta-analysis with bias assessment. Am J Sports Med. 2018;46(8):2020–32.
32. Kearney RS, Ji C, Warwick J, Parsons N, Brown J, Harrison P, et al. Effect of platelet-rich plasma injection vs. sham injection on tendon dysfunction in patients with chronic midportion achilles tendinopathy: a randomized clinical trial. JAMA. 2021;326(2):137.
33. Zicaro JP, Garcia-Mansilla I, Zuain A, Yacuzzi C, Costa-Paz M. Has platelet-rich plasma any role in partial tears of the anterior cruciate ligament? Prospective comparative study. World J Orthop. 2021;12(6):423–32.
34. Malahias M-A, Roumeliotis L, Nikolaou VS, Chronopoulos E, Sourlas I, Babis GC. Platelet-rich plasma versus corticosteroid intra-articular injections for the treatment of trapeziometacarpal arthritis: a prospective randomized controlled clinical trial. Cartilage. 2021;12(1):51–61.
35. Fricton J. Myogenous temporomandibular disorders: diagnostic and management considerations. Dent Clin North Am. 2007;51(1):61–83.
36. Wright EF, North SL. Management and treatment of temporomandibular disorders: a clinical perspective. J Man Manip Ther. 2009;17(4):247–54.
37. Chandra L, Goyal M, Srivastava D. Minimally invasive intraarticular platelet rich plasma injection for refractory temporomandibular joint dysfunction syndrome in comparison to arthrocentesis. J Fam Med Prim Care. 2021;10(1):254–8.
38. Buchbinder R. Plantar fasciitis. N Engl J Med. 2004;350(21):2159–66.
39. Peerbooms JC, Lodder P, den Oudsten BL, Doorgeest K, Schuller HM, Gosens T. Positive effect of platelet-rich plasma on pain in plantar fasciitis: a double-blind multicenter randomized controlled trial. Am J Sports Med. 2019;47(13):3238–46.
40. Trull-Ahuir C, Sala D, Chismol-Abad J, Vila-Caballer M, Lisón JF. Efficacy of platelet-rich plasma as an adjuvant to surgical carpal ligament release: a prospective, randomized controlled clinical trial. Sci Rep. 2020;10(1):2085.