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HOT TOPICS IN PAIN AND HEADACHE (N ROSEN, SECTION EDITOR)

Platelet-Rich Plasma for the Treatment of Low Back Pain: a Comprehensive Review

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Abstract

Purpose of Review Back pain is a growing problem worldwide, incurring enormous economic costs and disability. Current treatment modalities often provide adequate relief but fail to address underlying conditions. Regenerative cellular modalities aim to restore anatomical function in degenerative conditions which may cause low back pain. Platelet-rich plasma (PRP) consists of an increased concentration of autologous platelets suspended in a small amount of plasma. PRP can be administered via injection or topically and is prepared using various techniques.

Recent Findings While a unifying mechanism of action is not well understood, biochemical and cellular changes involved in inflammation and mechanical structure have been detected in both in vitro and in vivo studies. At a higher level, PRP injection research utilizing animal models and patient data have provided insights into pain relief, chondroprotection, and factors that impact the therapy's efficacy. Recently, a small number of studies have promoted PRP injection as a relatively safe means of treating patients with degenerative disc disease who have failed other means of managing their lower back pain. PRP injections for sacroiliac joint–related pain are not an accepted or common treatment modality; the evidence for their efficacy remains to be seen outside of small RCTs and case reports. A small number of prospective trials have suggested there may be some benefit to using PRP injection in the treatment of pain or functional decline caused by facet joint arthropathy.

Summary These commonly used modalities require further study to improve quality of evidence and to investigate the safety and efficacy of PRP injections for various common causes of chronic low back.

Keywords PRP · Back pain · Platelet-rich plasma · PRP injections · Chronic pain

Introduction

Back pain is a growing problem worldwide, incurring enormous economic costs and disability. The global prevalence of low back pain is 9.4%, and the prevalence within the USA is as high as 13.1% [1, 2]. Approximately, 59 million adults in the USA, roughly 28% of the population, have reported back pain in the last 3 months [3]. Certain populations are at

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increased risk of chronic low back pain, in particular those of low income and education level [1, 4, 5]. Other factors that have been linked to higher rates of chronic low back pain include older age, obesity, depression, tobacco use, and other medical comorbidities [1, 6, 7].

With a growing prevalence of low back pain, related costs have been found to be as high as $84 billion annually [8]. Expenditures associated with spinal surgery reached $34 billion in 2008, nearly an eightfold increase from the costs 10 years prior [9]. Back pain accounts for a loss of approximately 149 million workdays in the USA annually and costs employers up to $7.4 billion/year [10, 11]. Health services for chronic back pain have increased in recent years with more individuals seeking spinal injections, surgery, and opioid medication [12–14]. Chronic low back pain often limits involvement in physical activity and can cause disability and loss of productivity [15, 16]. Low back pain is ranked sixth in disability-adjusted life years (DALYs), with approximately 12.8% of adults in the USA with chronic low back pain collecting disability income [1, 8]. Thirty percent of the 21 million individuals who report work disability attribute the cause to back pain [16]. Individuals with back pain have mean lost productive times of 5.2 h per week [16, 17]. Patients with chronic pain often limit their social contacts and leisure activities; moreover, they have three to four times greater risk of developing depression than the average population [18, 19].

The etiology of low back pain is unidentifiable in nearly 85% of instances [20]. Known causes however include structural injury or malformations of ligaments, vertebral periosteum, facet joints, blood vessels, spinal nerve roots, and other structures [20]. Spinal stenosis is the narrowing of the central spinal canal or the lateral recesses and is a common cause of back pain [20]. Neuroforaminal stenosis is also possible and involves the narrowing of the opening in the spinal column through which the spinal nerves exit [21]. Symptoms can also stem from aberrant neurologic pain, which results in neuropathic low back pain [22]. Nociception involves relaying information regarding injury to your tissues to the brain, which is modulated by specialized receptors known as nociceptors. Nociceptors are activated when inflammatory mediators are released at the original injury site and allow for transmission of afferent signals to the spinal cord and initiation of neurogenic inflammation, which results in peripheral sensitization. Typically, nociception results in pain perception; however, in certain instances, they can occur independently such as in traumas [22]. Aberrant functioning of these processes can result in abnormal perception of pain.

An Overview of Degenerative Disc Disease

Lumbar disc degeneration is the most common cause of low back pain [23]. The number and activity of cells within the disc is dependent on a combination of genetics, nutrient transport, mechanical loading, and lifestyle [23–25]. Intervertebral discs are the largest avascular tissue in the body, and as such, nutrient supply to the disc is limited [26]. As patients age, there are fewer cells in the annulus and remaining cells lose their ability to proliferate, contributing to disc degeneration [27, 28]. Discs in the lumbar spine tend to have higher rates of degeneration, suggesting that mechanical load is also a factor [29]. The combination of genetics, nutrient transport, mechanical loading, and lifestyle alter aggrecan and collagen metabolism. As aggrecan is broken up and its molecular weight and number decreases, it causes the viscosity and hydrophilicity of the nucleus pulposus to decrease [30]. The change in hydrophilicity of the nucleus pulposus affects its hydrostatic pressure and thus its supply of nutrients via diffusion. The decrease in water content of the extracellular matrix reduces the intervertebral height thus reducing the resistance of the disc to axial load [30]. Decreased resistance to axial load allows for herniation of nuclear materials through the annulus fibrosis. Subsequent loss of disc height changes mechanics at the facet joint and results in the formation of osteophytes which lead to narrowing of neuroforaminal and spinal canals [31].

An Overview of Platelet-Rich Plasma

Platelet-rich plasma (PRP) consists of an increased concentration of autologous platelets suspended in a small amount of plasma [32]. Platelets are important for hemostasis and are a source of growth factors such as fibroblast growth factor (FGF), transforming growth factor beta-1 (TGF-β1), platelet-derived growth factor (PDGF), platelet-derived angiogenesis factor and several others [33]. Growth factors are important for wound healing and biological processes such as chemotaxis, neovascularization, synthesis of extracellular matrix, and scar formation [33]. PRP contains higher concentrations of growth factors and it is believed that it acts to initiate an inflammatory response. Thus, PRP is utilized to improve soft tissue healing, vascularization of grafts, and bone regeneration [34, 35].

Multiple studies report that the ideal platelet concentration for PRP to be therapeutic is four to six times greater than whole blood (200,000 mm^3) [35–37]. PRP can be given by injection or topically and can be prepared in several different techniques [38]. There are four primary types of PRP variations: pure PRP (P-PRP) or leukocyte-poor PRP, leukocyte-rich PRP, platelet-rich fibrin, and leukocyte- and platelet-rich fibrin (Table 1) [38].

The use of PRP was initially described for use in patients with thrombocytopenia [39]. It was later applied to bone in patients with mandibular continuity treated with autograft bone and PRP [40]. Patients who had received PRP had significant increases in bone formation and bone graft density. Since its original use, PRP as a treatment modality has been

Table 1 Recent advances in PRP

Author (year)	Subjects	Intervention	Outcomes measured	Results and conclusions
Tohidnezhad et al. (2017)	In vitro human inflammatory synoviocyte model	Autologous PRP injection	TNF-α and IL-1β cytokine expression and secretion	Autologous PRP reduces pro-inflammatory cytokine gene expression and secretion
Khalaf et al. (2015)	Porcine intervertebral discs denatured with trypsin	Denatured discs treated with PRP and control fluid	IVD stiffness, fluid outflow, disc bulging, and glycosaminoglycan content	PRP injections improved stiffness and fluid outflow in denatured intervertebral discs; increased glycosaminoglycan content
Yang et al. (2018)	OA rat model: in vitro chondrocytes and in vivo meniscal tears	Autologous PRP injection	Anabolic and catabolic gene expression, markers of autophagy, and in vivo cartilage degeneration	PRP injections increase anabolic gene expression, decrease catabolic gene expression, and ameliorated cartilage degeneration without impacting markers of autophagy
Khatab et al. (2018)	Rat model, induced OA with collagenase injections	Autologous PRP vs. saline injection in affected joint	Hind leg weight distribution (surrogate for pain), synovial inflammation, cartilage damage	Rats with PRP injection showed more equal wt. distribution; fewer anti-inflammatory cells in joints with saline injection
Andia & Maffulli (2018)	Patients with tendinopathy, OA, and other traumatic or degenerative disease	PRP injection(s)	Progression of disease, pain	Patients' microbiome, metabolic status, and inflammatory state impact PRP success

investigated in multiple fields including plastic surgery for use in facial rejuvenation, dermatology, cardiac surgery, gynecology, orthopedics, and urology [39, 41, 42].

PRP has gained popularity within the field of orthopedics as a conservative treatment option; however, studies investigating its efficacy have been mixed [39, 43–47]. Studies have investigated the use of PRP in ligament reconstruction, total knee arthroplasty, osteoarthritis, epicondylitis, rotator cuff repairs, hamstring injuries, meniscal repair, and high tibial osteotomy [48, 49]. A recent meta-analysis reviewed 36 studies comparing the use of PRP to local steroid injections, dry needling, autologous whole blood, and other conservative management therapies in a variety of orthopedic complaints [44]. They were unable to identify a clear benefit to PRP use when compared to controls. A separate meta-analysis specific to the use of PRP for osteoarthritis and after total knee arthroplasty (TKA) found no statistical clinical improvement but did report improved pain scores following TKA [50]. In contrast, a separate meta-analysis also investigated the use of PRP in total knee arthroplasties and concluded that there was improved ROM and pain intensity scores with PRP as compared to placebo [46]. This demonstrates the substantial variability of results with regard to the efficacy of PRP in musculoskeletal complaints and the need for additional investigation. Variability may be attributable to the fact that there is no standardization in the preparation techniques, delivery methods, and amount or frequency of use of PRP [49, 50].

The Basic Science of Platelet-Rich Plasma

As our understanding of the mechanism of action of PRP expands, so does the number of potential-use cases. Basic science research has revealed much about the numerous pathways modulated by PRP and its constituents. While a unifying mechanism of action is not well understood, biochemical and cellular changes involved in inflammation and mechanical structure have been detected in both in vitro and in vivo studies. At a higher level, PRP injection research utilizing animal models and patient data have provided insights into pain relief, chondroprotection, and factors that impact the therapy's efficacy.

Historically, treatments for intervertebral disc degeneration (IDD) have ameliorated pain without halting or reversing the underlying process. Wang et al. reviewed PRP and growth factor therapies for IDD and found multiple cellular-level benefits in intervertebral disc cells and tissues across 28 in vitro studies across several cellular and tissue models, including human. When activated, platelets release platelet-derived growth factor (PDGF), transforming growth factor beta 1 (TGF-β1), vascular endothelial growth factor (VEGF), epidermal growth factor, insulin-like growth factor, and other active substances; among these, PDGF and TGF-β are strongly associated with cellular remodeling and tissue repair. In the

complex homeostasis of intervertebral discs, these growth factors increased cell proliferation, matrix synthesis and repair, and nucleus pulposus survival [51].

Tohidnezhad et al. examined the impact of growth factors in a rheumatoid arthritis model and drew similar conclusions. The effect of platelet-released growth factors (PRGF) on inflammatory human synoviocytes was measured using ELISA and real-time PCR to determine the presence and expression of pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1 beta (IL-1β). The injection of PRGF concentrate derived from autologous, activated PRP significantly reduced levels of TNF-α and IL-1β gene expression and secretion in vitro [52]. While both Wang et al. and Tohidenezhad et al. found short-term benefits from PGRF injections, attributable primarily to cytokine and growth factor activities, the long-term benefits are largely unstudied and the mechanisms of action remain poorly understood. In addition, while growth factors appear to play a significant role in cellular repair and anti-inflammatory properties, autologous PRP therapy is often cheaper, has a prolonged half-life, and contains growth factors in biological ratios when compared to synthetic or derived growth factor therapies [51, 52].

Denatured intervertebral discs also stand to benefit from PRP therapy, according to Khalaf et al. in 2015. Their research on the mechanical properties of intervertebral discs showed that even after being denatured with trypsin, PRP injections can restore both disc stiffness and fluid flow capability. In addition, glycosaminoglycan content was significantly increased in PRP-treated discs compared to control discs, but did not return to levels prior to denaturation [53]. Based on this and aforementioned studies, PRP quiesces inflammation and disease processes while also restoring the structural integrity of the affected anatomy.

At a cellular level, autophagy is regulated by PRP separately from other protective effects. In a 2018 study by Yang et al., both leukocyte-rich PRP (L-PRP) and pure PRP (P-PRP) showed reductions in osteoarthritis (OA)-related and autophagy-related gene expression. Using an in vitro model of OA, PRP treatment upregulated anabolic and downregulated catabolic gene expression. In addition, in vivo studies in rat models of OA showed reduced cartilage degeneration without significant differences in markers of autophagy, as measured by light chain 3 expression. Since markers of autophagy were not significantly different in control versus PRP-treated groups in both in vitro and in vivo studies, PRP-induced chondroprotection is separate from mechanisms regulating autophagy [54].

PRP therapy may be effective in the treatment of osteoarthritis. When OA was induced in mice via collagenase injections, hind leg weight distribution improved significantly after the affected joint was injected with PRP therapy compared to saline injections. In addition, microscopic analysis of the synovial membrane lining the joint revealed significantly less inflammation at 21 days [55]. While this data does not reflect long-term outcomes from PRP injections, it reveals benefits in both pain and inflammation from repeated PRP injections in an OA model.

An extensive literature review by Yung et al. examined the value of localization, repeated application, and form of PRP injection. When given within a confined space (e.g., joint cavity and intervertebral disc) and given in a solid form (i.e., PRP after activation), outcomes and localization were more consistent and specific, respectively. Repeated application revealed better duration of action with regard to pain reduction, though must be weighed against the risk of infection and procedural discomfort [56].

PRP for Discogenic Pain

PRP injections are a promising means of regenerating or repairing disc tissue [57]. Recently, a small number of case studies, such as those presented by Lutz and colleagues [58, 59], have promoted PRP injection as a relatively safe means of treating patients with degenerative disc disease who have failed other means of managing lower back pain.

To explore the efficacy and safety of PRP injection as a treatment for discogenic low back pain, Levi et al. [60] performed a prospective trial on a cohort of 22 patients. The study population included adults (10 male, 12 female) ≥ 18 years old (median age = 47.5 years) with clinical or image-based features of discogenic back pain (median duration = 90 months) and visual analog score (VAS) [61] ≥ 40 mm. The Oswestry Disability Index (ODI) was also evaluated before administration of treatment [62]. Provocative discography, if performed previously, was used to determine the vertebral level of injection site; otherwise, imaging or clinical cues were used in place of discography. 1.5 mL PRP solution was administered to the target disc nucleus under fluoroscopy. A successful outcome was defined as ≥ 50% improvement in VAS and ≥ 30% improvement in ODI; these criteria were based on previously published standards of minimally important change in back pain after intervention [63, 64]. At 1 and 2 months post-injection, 22/22 patients were followed up; at 6 months, 19/22 continued to be followed up. 3/22 and 7/22 patients achieved successful outcomes at 1 and 2 months, respectively. At 6 months, 9/19 met the criteria for a successful outcome. No adverse effects of PRP injection therapy were reported to investigators during this study.

The prospective study conducted by Levi et al. provides limited evidence that PRP injection may be safe and useful in select patient populations. The small sample size, lack of control population, and lack of uniformly applied diagnostic parameters used in the trial substantially confound the data and conclusions that can be drawn therefrom. One interesting trend noted by the authors, however, was the delay in post-

injection score improvement for both pain and disability metrics from 1 to 6 months of follow-up among a subset of participants. This report may warrant a reevaluation or lengthening of post-PRP injection follow-up as well as further investigation of the underlying temporal properties of PRP-mediated disc regeneration.

In another prospective study of PRP injection as a treatment for LBP, Akeda et al. recruited 14 patients with chronic LBP, MRI evidence of degenerative lumbar discs, and positive provocative discography [65]. Before treatment, VAS and Roland-Morris Disability Questionnaire (RDQ) scores were measured as an indicator of baseline LBP. Radiographic and MR images of the lumbar spine were also stored for comparison to post-treatment images. Degenerative discs as confirmed by provocative discography and MRI were targeted. 2.0 mL of PRP was injected into disc nuclei under fluoroscopy. At 4 weeks, the sample population showed a significant decrease in mean LBP with 11/14 patients reporting greater than 50% improvement in RDQ. This reduction in sample LB was sustained through 1 year. Interestingly, no changes in sagittal MRI or radiograph characteristics were found in experimental vs. internal control vertebrae as quantified by disc height index or Pfirrmann disc degeneration grade [66, 67]. No safety concerns or adverse effects of PRP injection were reported during or after treatment.

Similarly, Akeda et al. performed a qualitative assessment of PRP injection efficacy for LBP pain management. They demonstrated sustained improvement in VAS and RDQ at 4 weeks of follow-up supporting the possible efficacy of PRP. Despite these results, limitations of these studies are a lack of a placebo-control and small sample size.

In a double-blind randomized controlled trial, Tuakli-Wosornu et al. recruited adults with a history of chronic LBP and annular tear confirmed by imaging [68]. Patients in the experimental group received PRP injection to degenerative discs while the control group received injected fluorescent dye. Functional Rating Index (FRI), Numeric Rating Scale (NRS), and the 36-Item Short Form Health Survey (SF-36) scores were gathered before treatment to establish baseline pain and function/disability [69–71]. At 8 weeks of follow-up, FRI and NRS best pain scores were significantly lower in the PRP versus the control group. Additionally, PRP-treated patients were significantly more satisfied with treatment than control participants as measured by the NASS Outcome Questionnaire [72]. A subset of treated patients demonstrated significantly improved pain and function scores relative to baseline but were not compared to the control population. No safety concerns arose during treatment or follow-up.

This randomized, controlled trial provides promising evidence from multiple, orthogonal metrics that PRP may be useful for the treatment of LBP and other consequences of degenerative vertebral discs. The authors address, in part, the confounding variables present in prospective studies by Levi et al. and Akeda et al. However, future trials could produce more robust data through larger sample sizes, longer follow-up periods, objective outcome metrics and investigation of the molecular mechanisms underlying disc regeneration. Findings of studies which assess the efficacy of PRP for the management of discogenic pain are summarized in Table 2.

PRP for Sacroiliac Joint Pain

Traditional interventions for sacroiliac joint (SIJ) pain serve both diagnostic and therapeutic roles. A 2015 systematic review by Simopoulos et al. graded the evidence for several diagnostic and therapeutic techniques and discovered mediocre evidence supporting some of the most commonly used interventions today [73]. On the other hand, PRP injections for SIJ pain appear promising in both the short term and long term, albeit most studies are of relatively small sample size [74, 75].

Diagnosing SIJ pain is challenging as there are a wide range of potential causes for persistent lower back pain. Common diagnostic studies include x-ray, MRI, and maneuvers such as sacral thrust, Patrick's test, and Gaenslen's test [74]. While these methods have diagnostic value, interventions that improve pain and mobility are also often used to diagnose pain secondary to SIJ dysfunction or instability. Simopoulos et al. examined the data from 11 studies to determine the reliability of the evidence for each intervention with regard to diagnostic success. The team graded evidence based on both qualitative and quantitative metrics, using USPSTF criteria. They focused on clinically significant outcomes that frequently required greater improvement in pain and mobility than the threshold used in many previous studies; for diagnostic studies, outcomes included 50% or greater, or 80% or greater, reduction in pain with the ability to perform previously painful movements [73]. The diagnostic data was very heterogenous, barring a true meta-analysis, but remained worthy of rating evidence using previously mentioned scoring systems. Evidence for controlled diagnostic blocks was considered to be level II when 70% or greater reduction in pain was used as the standard for diagnosis. Dual blocks had better evidence than single blocks, with level II to III evidence as compared to level III evidence. These diagnostic blocks also had low false-negative rates, as only 18% of patients with less-than-threshold relief on the first block were positive for the second block [73].

In the review of therapeutic interventions, the data was similarly too heterogenous for a formal meta-analysis; however, the evidence from six RCTs and eight observational studies was enough to grade the evidence for several commonly performed interventions. Intra-articular and periarticular injections only have level IV evidence. Cooled radiofrequency neurotomy fared better than conventional radiofrequency neurotomy, with level II to III evidence

Table 2 Preliminary trials assessing the safety and efficacy of PRP injection for treatment of discogenic low back pain

Authors (year)	Study type	Population	Intervention	Results	Conclusions
Levi et al. (2016)	Prospective trial	22 patients (10 male, 12 female) ≥ 18 years old (median age = 47.5 years) with clinical or image-based features of discogenic back pain (median duration = 90 months) and visual analog score ≥ 40 mm.	1.5 mL PRP injected at lumbar spine levels determined with prior discography, other imaging modality and/or clinical features. VAS and ODI measured at 1, 2 and 6 months of follow-up.	Successful outcome defined as ≥ 50% improvement in VAS and ≥ 30% improvement in ODI. 22/22 completed 2 months of follow-up, 19/22 completed 6 months of follow-up. 7/22 and 9/19 achieved a successful outcome at 2 and 6 months, respectively.	PRP injection may pose greatest benefit after 6 months. Results may be confounded by lack of uniform diagnostic criteria (provocation discography), control population and short follow-up period.
Akeda et al. (2017)	Prospective trial	14 patients (8 male, 6 female) ≥ 18y.o. (mean age = 33.8 years) with (i) > 3 months. Chronic LBP (ii) MR imaging evidence of degenerative lumbar discs with disc height > 50% and (iii) positive provocative discography. Patients with neurological symptoms were excluded.	2.0 mL PRP injected at symptomatic disc(s) confirmed by discography. LBP quantified via VAS and RDQ measured at 4, 8, 16, 24, 32, 40, and 48 weeks post-treatment. %△DHI in lumbar vertebrae evaluated by radiograph. Change in Pfirrmann disc degeneration grade evaluated by sagittal MRI.	14/14 followed up from 0 to 6 months. 10/14 followed up through 10 months and 9/14 completed follow-up through 1 year. 10/14 reported > 50% improvement in VAS score at 4 weeks and 11/14 reported > 50% improvement in RDQ. Significant reduction in mean VAS and RDQ was sustained through 1 year. No change in MR or radiograph metrics observed in experimental vs. control vertebrae.	PRP injection is a safe and potentially efficacious means of treating LBP. Randomized, placebo-controlled trials and mechanistic studies are needed to provide support for use of PRP for disc regeneration and pain management.
Tuakli-Wosornu et al. (2016)	Prospective, randomized, controlled trial	47 patients (16 male, 31 female) ≥ 18 years old (mean age = 42.3) with (i) LBP > 6months, (ii) disk height > 50% with protrusion < 5 mm and (iii) annular fissures confirmed via positive provocative discography; have failed conservative management.	Participants randomized into PRP treatment and control groups. FRI, NRS, SF-36 scores assessed at baseline. 1–2 mL PRP or contrast (control) injected. FRI, NRS, SF-36 and NASS scores compared post-treatment PRP and control groups. Follow-up surveys administered at 1, 4, and 8 weeks. At 6 months and 1 year post-treatment, PRP group pain and function scores compared against baseline.	PRP group FRI and NRS best pain scores significantly improved at 8 weeks compared to control group. PRP group significantly more satisfied than control with treatment (via NASS). At 1 year of follow-up, PRP group showed significant, sustained improvement in FRI, NRS worst pain and SF-36 metrics relative to baseline. No safety concerns raised during treatment or upon follow-up.	First randomized clinical trial to investigate the safety and efficacy of PRP as treatment for LBP. Introduced more uniform diagnostic standards and outcome metrics for future trials. Small sample size and 8-week control period limits data power. Clear trend in pain and function metrics not demonstrated.

PRP platelet-rich plasma, *VAS* visual analog scale, *ODI* Oswestry Disability Index, *LBP* low back pain, *RDQ* Roland-Morris disability questionnaire, *DHI* disc height index, *FRI* Functional Rating Index, *NRS* Numeric Rating Scale, *SF-36* 36-Item Short Form Health Survey, *NASS* North American Spine Society Outcome Questionnaire

compared to level III to IV evidence, respectively. In addition, many of these therapeutic studies did not examine outcomes in the past 3 months, and those that did often saw a significant reduction in the effectiveness of the intervention at 1 year [73].

In 2017, Singla et al. released the results of an RCT comparing steroid injections to PRP injections for SIJ pain with promising short-term results. Forty patients diagnosed with SIJ pathology on x-ray, MRI, or nuclear scan with three or more provocative tests were randomized into either steroid or PRP groups. The steroid group received an ultrasound-guided intra-articular injection of methylprednisolone while the PRP group received an ultrasound-guided injection of autologous, filtered (leukocyte-free) PRP. All patients were ASA grade I or II, between the age of 18 and 65, and none were lost to follow-up. Measured outcomes were pain via visual analog scores (VAS), modified Oswestry Disability Questionnaire (MODQ) scores, short-form health survey scores (SF-12), and immediate and short-term complications. Patients were evaluated at 2, 4, and 6 weeks and at 3 months using each of these metrics [74]. From pre-injection to 4 weeks post-injection, there was no significant difference in any metrics between the steroid and PRP groups, although both groups reported improvement in VAS, MODQ scores, and SF-12 scores. At 6 weeks and 3 months, the PRP group had significantly more improvement in VAS, MODQ, and both the physical and mental health component scores of the SF-12. The most notable difference was at 3 months, at which point 25% of patients in the steroid group reported being pain free as compared to 90% of patients in the PRP group. Notably, when examining complications, post-injection pain and stiffness was more common in the PRP group. These symptoms were brief, immediately following the injection, and all reported as being mild in nature [74].

This study was promising, but has its limitations, most notably a small sample. In addition, the exclusion criteria for this study included factors such as history of intervertebral disc disease, radicular pain, and excessive narcotic use [74]. A significant outcome of SIJ pain treatment would be a reduction in opioid usage, especially given the current epidemic in the USA. While these patients, and patients with additional potential sources of back pain such as IVD, may cloud the results of a study such as this one, these populations should be considered in the future to determine the potential impact on patients with established severe, refractory lower back pain and opioid dependence.

A case study of four female patients from 2017 showed very promising results for PRP injections in patients with chronic SIJ pain. These women were 45–67 years old, diagnosed with grades 2–3 SIJ instability, and had pain refractory to other therapies, including NSAIDs, tramadol, opioids, prolotherapy, and local injections. Each patient received two sessions of autologous PRP injections at Hackett's points A, B, and C under ultrasound guidance. Ko et al. used similar metrics to the RCT by Singla et al., including short-form McGill pain questionnaire (SFM), numerical rating scale (NRS), and Oswestry lower back pain and disability index. After obtaining baseline results and performing the intervention, patients were reassessed at 1 and 4 years after therapy. At 1 year, patients reported a 93%, 88%, and 75% improvement in SFM, NRS, and Oswestry index. Pain metrics remained significantly improved at 4 years, albeit less so than they were at 1 year, while disability improvement remained steady at years 1 and 4. In addition, all four patients returned to pre-injury levels of activity [75].

Still, PRP injections for SIJ pain are commonly utilized, as the evidence for their efficacy remains to be seen outside of small RCTs and case reports. More evidence is needed to better assess PRP injections, but given the underwhelming evidence for other diagnostic and therapeutic interventions, the introduction of novel therapies for lower back pain and SIJ pain should be welcomed. With time, additional data on PRP injections will become available, and the small studies that exist show promising short-term and long-term effectiveness in the improvement of both pain and mobility [74, 75].

PRP for Facet Arthropathy

The spinal facet joint contributes heavily to spinal mobility and carries a heavy mechanical burden. Facet Joint Syndrome (FJS) is a frequent cause of LBP and results from damage to the joint leading to osteoarthritis [76]. Patients with osteoarthritis of the facet joint typically present with morning stiffness, radiating lumbar pain, and pain with use of the joint and extension of the spine. The diagnosis is clinical and should exclude similar pathologies such as rheumatoid arthritis [77]. A small number of prospective trials have been published recently which suggest there may be some benefit to using PRP injection in the treatment of pain or functional decline caused by FJS.

Wu et al. assessed the efficacy of PRP injections in the treatment of back pain with clinical signs of FJS and imaging indicative of degenerative changes in facet joints [78]. PRP was administered by intra-articular injection into the facet joint under fluoroscopy. VAS showed a continued decrease at 3 months of follow-up. Mean RDQ and ODI were also significantly reduced in post-treatment patients at 3 months of follow-up compared to baseline. Beyond the 1-month follow-up period, McNabb status plateaued at "good" or "excellent" in 15/19 patients compared to 9/19 before treatment. No adverse effects of PRP injection were reported at any time during the study. The authors of this prospective trial suggest there may be a therapeutic benefit to PRP injection in the setting of FJS. Larger, controlled, randomized trials with more rigorous selection criteria will undoubtedly be necessary to validate the trends in pain/disability reduction supported by

Table 3 Preliminary trials assessing the safety and efficacy of PRP injection for treatment of facet joint arthropathy

Authors (year)	Study type	Population	Intervention	Results	Conclusions
Wu et al. (2016)	Prospective trial	19 patients (8 male, 11 female) ≥ 18 years old (mean age = 52.53) with back pain and (i) clinical signs of FJS or (ii) positive imaging. Did not include patients with neurological deficits or radiculopathy.	Intra-articular injection of 0.5 mL PRP into the facet joint. VAS (at rest, flexion), RDQ, ODI, and MacNab criteria surveyed before treatment, immediately following treatment and 1 week, 1 month, 2 months, and 3 months post-treatment.	Mean VAS (rest/flexion) decreased from baseline (7.05/8.42) to 3 months of follow-up (2.63/2.95). Mean RDQ was significantly ($p < 0.05$) reduced compared to baseline. ODI significantly was significantly (> 10%) reduced. McNabb status "good" or "excellent" in 15/19 patients compared to 9/19 before treatment.	PRP injection may provide relief of LBP caused by FJS within 1 week to 3 months of treatment. Study confounded by small sample size, subjective pain metrics and lack of placebo-control.
Wu et al. (2017)	Randomized, controlled, prospective trial	46 patients (19 male, 27 female) ≥ 18 years old (mean age = 52) with back pain and (i) clinical signs of FJS and (ii) imaging positive for degenerative changes. Did not include patients with neurological deficits or radiculopathy.	Randomized into PRP (A) and anesthetic (B) groups. 0.5 mL PRP or anesthetic into the facet joint. VAS (at rest, flexion), RDQ, ODI, and MacNab criteria surveyed before treatment, immediately following treatment and 1 week, 1 month, 2 months, and 3 months post-treatment.	Groups A and B showed sustained, significantly reduced VAS after 1 week. Group B significantly outperformed A at 1 week and 1 month of follow-up. Group A improvement in VAS significantly greater at 3 months of follow-up. VAS trend was mirrored by RDQ and ODI. MacNab satisfaction of B peaked at 80% at 1 month, but declined to 50% at 6 months. Group A MacNab satisfaction steadily rose to 80% at 6 months of follow-up. No complications arose as the result of treatment	In all metrics (pain, function and satisfaction), Group B outperformed A in the short run (< 3 months). Group A showed favorable outcomes steadily increasing with progressing follow-up dates. While anesthetic/corticosteroid injection may provide more relief from FJS initially, PRP injection may serve as a superior long-term therapeutic. Study confounded by lack of negative control.

PRP platelet-rich plasma, *VAS* visual analog scale, *ODI* Oswestry Disability Index, *LBP* low back pain, *RDQ* Roland-Morris disability questionnaire, *FJS* facet joint syndrome

this study. Longer follow-up periods may also be useful in detecting symptom rebound or stable therapeutic effect.

In a subsequent randomized, controlled prospective study, Wu et al. compare the efficacy of injected PRP with that of injected anesthetic/corticosteroid solution. Patients with back pain and clinical signs of FJS and imaging positive for degenerative changes were recruited for this study. Both PRP and corticosteroid demonstrated significantly reduced VAS relative to baseline after 1 week and sustained this response through 6 months. Interestingly corticosteroid, significantly outperformed PRP at 1 week and 1 month of follow-up, though PRP offered greater improvement at 3 and 6 months. No complications arose as a result of treatment.

Wu et al. (2017) provide robust preliminary evidence in support of PRP as a viable, long-term therapeutic in the setting of FJS. While anesthetic/corticosteroid injection may provide more relief from FJS initially, PRP injection showed steady increases in pain, function, and satisfaction metrics that could extend past 6 months of follow-up. The large sample size and the addition of a randomized control offer a substantial improvement to the design of Wu et al. (2016), results are still confounded by lack of negative control and rigid inclusion criteria. These confounders are likely the result of a small recruitment pool and may be addressed in future multi-institutional trials. The findings of studies assessing the efficacy of PRP for the treatment of facet joint arthropathy related pain are summarized in Table 3.

Conclusion

Despite considerable advances in recent decades, low back pain remains highly prevalent and difficult to treat. Platelet-rich plasma may be a safe and effective therapy for patients with chronic low back pains secondary to degenerative conditions of the spine and the lower back. Limited small studies have demonstrated PRP to be beneficial in application to degenerative disc disease, sacroiliac joint-related pain, and facet joint arthropathy. Further large clinical trials are required however to better assess safety and efficacy of this treatment in the future.

Compliance with Ethical Standards

Conflict of Interest Ivan Urits, Omar Viswanath, Annemarie C. Galasso, Emily R. Sottosani, Keenan M. Mahan, Christopher M. Aiudi, and Vwaire J. Orhurhu declare no conflict of interest.

Alan D. Kaye discloses that he is on the Speakers Bureau for Depomed, Inc., and Merck.

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.

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