Safety of intra-articular platelet rich plasma injections for large joint osteoarthritis: a review article

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ABSTRACT

Platelet-rich plasma (PRP) use in intraarticular injections is thought to be potentially efficacious in the treatment of osteoarthritis (OA) and as an alternative to corticosteroid injections. However, little is known about the safety of PRP usage in the treatment of large joint osteoarthritis. In the 21 identified studies, there were primarily minor adverse effects include pain, redness, swelling, nausea, and dizziness. The limitations of this review include the relative paucity of well-designed studies that describe detailed adverse effects using safety as an outcome measure. Intraarticular injection of platelet-rich plasma has low risk of morbidity. This review describes the evidence for the short-term safety of intraarticular PRP injections and its derivations in the treatment of large joint OA (knee, hip, shoulder). Further investigation is needed to determine the short-term safety of PRP for use in the management of OA in the hip and shoulder, as well as the documentation of long-term safety in the shoulder, hip and knee.

Key Words
platelet-rich plasma, osteoarthritis, intraarticular injections, joint, safety

INTRODUCTION

Osteoarthritis (OA) is the most common cause of chronic pain and disability affecting an estimated 650 million people worldwide, or about 15% of all people in the world.[1] In North America and Europe, structural OA of the hands is reported in approximately 60% of adults who are age 65 and older, of the knee in 33%, and of the hip in 5%. OA is a complex disease involving all tissue components in the joint that results from a combination of risk factors, the most important being increasing age and obesity.[1] Current management of OA includes conservative therapies that are nonpharmacological including physical therapy, diet and exercise, weight loss, topical thermal and cryotherapy, and pharmacological including NSAIDs, opioid medications, and topical ointments such as lidocaine and capsaicin. When conservative therapy fails to alleviate symptoms of OA, a minimally invasive injection including viscosupplementation (VS) or corticosteroids can be used. With the different modalities offered in OA treatment, it is important to note that if all of these fail in providing relief, or if OA is severe enough, then arthroplasty is a common option.[2]

The American Academy of Orthopaedic Surgeons (AAOS) and American College of Rheumatology (ACR) formed national recommendations for using nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee that advised that intraarticular corticosteroid injections (CS) be administered no more than every 3 mo for patients with osteoarthritis whose symptoms were not controlled with full-dose acetaminophen. Furthermore, the national clinical guideline for care and management in adults from the United Kingdom's National Collaborating Centre for Chronic Conditions recommends intraarticular CS combined with weight loss and exercise for relieving pain in patients with osteoarthritis. It is important to note that within the ACR schema, there are only VS and CS provisions and no provisions for the role of regenerative medicine therapies such as platelet-rich plasma (PRP) therapy.

VS is a therapeutic modality where a solution of viscoelastic material is injected into the intraarticular space of the joint. The Food and Drug Administration (FDA) approved hyaluronic acid (HA) in the 1970s for use in eye surgeries and

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in 2007 for the treatment of knee OA. Although somewhat controversial, studies demonstrated improved duration pain relief and functional outcomes as compared to those of corticosteroid injections.[3] Although VS is still widely utilized in treating knee OA, the AAOS guidelines do not recommend that use. Treatment-related adverse effects have been well-documented, including septic arthritis, pseudoseptic reaction, and anaphylactic shock.[3]

Intraarticular CS has a well-documented history of systemic effects that includes acute changes in endocrine, metabolic, inflammatory markers and cytokines, hematologic, and vascular systems. Such serious side effects as suppression of the hypothalamic-pituitary-adrenal (HPA) axis, causing Cushing's Syndrome[4] and triggering of sickle cell crisis,[5] have been reported after a single injection. Importantly, intraarticular CS injections are also thought to have a destructive effect on soft tissues such as cartilage and tendon.[6]

PRP therapy has become a popular treatment in orthopaedic and sports-related injuries including osteoarthritis, tendinopathy, and muscle and ligamentous injuries.[7] Adverse effects from PRP injections include local pain, infection, allergic reaction, blood clot, and skin discoloration.[8]

PRP injections potentially have many advantages compared with VS and CS. Numerous studies and systematic reviews have sought to establish PRP's efficacy in the treatment of OA. Although many trials have demonstrated benefits in pain relief and functional outcomes, conflicting data exists.

At least seven studies have been performed comparing PRP to VS in treating knee OA. In three out of seven manuscripts, PRP was found to be superior to VS in pain relief and functional outcomes, and noninferior in one study.[9–15] To date, no review paper has sought to quantify the safety of intraarticular PRP in multiple large joints for osteoarthritis. This study sought to conduct a narrative review of such literature.

METHODS

An electronic search was performed using MEDLINE (PubMed) trials to identify English-language studies that reported on safety of PRP treatments. Selected studies reported on the safety in the context of the study. The following search terms were used in various combinations: PRP, platelet-rich plasma, osteoarthritis, safety, intraarticular, joint, adverse effect, hip, shoulder, and knee. The Cochrane library, OVID, and PubMed Central were used for completion of search criteria; however, all articles were collected from MEDLINE (PubMed). Retrieved articles were identified, evaluated, and abstracts read for relevance. Additionally, the safety of solely PRP was looked at; thus, any combination of PRP and another formula was not evaluated. This study also assessed specifically for safety, not efficacy.

RESULTS

A total of 21 articles were examined. Of those, 822 patients received a preparation of PRP (either autologous or homologous) and other patients received different regenerative medicine preparations including bone marrow aspirate concentrate (BMAC) or adipose derivatives of stromal vascular fraction (SVF), or a combination of PRP with bone marrow concentrate (BMC), HA, or adipose tissue-derived stem cells (ADSC).

A few studies did not quantify the number of "some cases" and "many patients" when describing only slight pain present during the first 2 to 3 days and mild transient sensation of heaviness in the injected joint, respectively.

Nine Randomized Control Trials Were Identified

Hip Studies

Battaglia *et al.*[16] investigated the clinical efficacy of PRP versus HA at 12 mo of follow-up in patients with hip OA. Ten patients experienced normal adverse effects that resolved in less than 72 hr, consisting of primarily moderate peri- and posttreatment pain. No major complication or adverse effect occurred, except that one patient experienced a pathological adverse effect (superficial hematoma) during first infiltration of the great saphenous vein branch with an abnormal course. The authors concluded that intraarticular PRP injections are as safe and efficacious as HA at 12-month follow-up.

Sanchez *et al.*[17] investigated the safety, effectiveness and symptomatic changes of intraarticular injections of PRP in patients with unilateral severe hip OA. One patient experienced normal adverse effects that resolved in less than 72 hr. Furthermore, most patients reported a transient sensation of heaviness in the injected joint; however, no septic complications were reported. One patient reported a mild rash after the second PRP injection that disappeared spontaneously. The authors concluded that PRP injections for pain relief were supported in safety and efficacy. They also showed improved function in a limited number of patients with OA of the hip.

Knee Studies

Smith[18] investigated the efficacy and safety of leukocyte-poor (LP)-PRP autologous conditioned plasma (ACP) injections for knee OA treatment through a feasibility trial that the FDA regulated. The study found that ACP is safe and provides quantifiable measures with respect to knee OA. No adverse events for ACP were reported. This indicated that the injection was safe for humans.

Al-Ajlouni *et al.*[19] investigated the safety of percutaneous intraarticular platelet lysates (PLs) injections and the short and intermediate influence on the Kellgren-Lawrence Grade 1 to 2 knee OA. Three adverse events occurred (intraarticular bleeding episodes): one after the second injection (which resolved in less than 72 hr) and two after the third injection. One episode was mild and settled with simple analgesia, and two episodes required overnight hospitalizations for observation. No additional adverse reactions (swelling, pain) or major complications (infection) were recorded. The authors noted that it was not known how much of this was due to technical causes or the PL itself. They concluded that intraarticular injection of autologous platelet lysates in patients with knee OA reduces

pain and restores function without provoking local or systemic adverse events.

Raeissadat *et al*.[20] investigated the efficacy comparing PRP and HA intraarticular injections in knee OA with Kellgren-Lawrence grades of 1 to 4. They concluded PRP injection is a safe therapeutic option in select patients with knee OA who have not responded to conventional treatment. Although authors mentioned probable adverse events to patients prior to the study, no adverse events were reported. Additionally, though the authors did not directly state PRP is safe, discussion and references indicated it was safe when compared to HA.

Paterson *et al*.[21] conducted a pilot feasibility and safety study of photo-activated (PA) -PRP injections compared with HA in knee OA that was confirmed by radiographs to be Kellgren-Lawrence grade 2 to 3. Two patients from the PA-PRP group experienced swelling and minor pain during the injection period, which was thought to be related to the injection technique; however, they completed the course and the symptoms resolved within the next week. No other adverse events were experienced during the intervention or follow-up period. The authors concluded the study demonstrated the feasibility of using PA-PRP injections and reported no serious adverse events. They concluded that PA-PRP might be a safe novel treatment for knee OA.

Bottegoni *et al*.[22] investigated the safety and effect of PRP intraarticular injections obtained from blood donors (homologous PRP) on early or moderate knee OA. No severe complications related to the infiltrations were observed during the treatment and follow-up period. Nine patients experienced normal adverse effects that resolved in less than 72 hr, which consisted of a transitory burning sensation immediately after injection or mild articular pain for a few days. The authors said that clinical studies showed PRP was safe, with no infections, worsened outcomes, or serious complications reported. Minor adverse events associated with repeated intraarticular injections of PRP have been moderate/mild effusions, pain, and swelling that lasted for a few days. The study concluded that homologous PRP has an excellent safety profile in selected elderly patients with knee OA who are not candidates for autologous PRP treatment.

Kon *et al*.[23] investigated the novel approach of PRP injections to treat degenerative lesions of the knee's articular cartilage. One patient experienced a persistent pain and swelling after injection, which resolved after 2 wk. The study concluded that autologous PRP intraarticular injections were safe and might be useful for treating early degenerative articular pathology of the knee, aiming to reduce pain and improve knee function and quality of life.

Say *et al*.[24] investigated the effects of using PRP and HA injections. Eight patients experienced normal adverse effects that resolved in less than 72 hr. The study concluded that the application of a single dose PRP was a safe, low-cost method for treating OA.

One Retrospective Trial was Identified

Abate *et al*.[25] investigated the efficacy and safety profile of PRP only versus a combination of HA and PRP in patients with mild to moderate knee OA. Three patients in the PRP-only group experienced normal/mild adverse effects (pain, heat, redness after injection) that resolved in less than 72 hr and did not require using any medication. Two patients in the PRP and HA group experienced this as well, but the possible effect of HA added to PRP was outside the scope of this narrative review. The authors concluded that a combination of PRP and HA was safe and effective in treating mild to moderate knee OA.

Other Pertinent Articles/Studies

Adverse events due to PRP have been well documented and often described as minor and transient. In a 2013 retrospective cohort study, 91 patients were injected with ADSCs with PRP for varying musculoskeletal pathologies. It found one patient experienced a localized rash around the injection site of the knee, while another patient experienced a hemorrhagic stroke. The authors said the stroke was a reaction to the synthetic HA that was injected as a scaffold material and likely was not caused by the joint limited injection site.[26] In a 2016 retrospective case series of 125 patients, ultrasound-guided BMC injections were followed by PRP injections at 8 wk. No patients reported worsening of symptoms following BMC or PRP procedures.[27] In a 2011 prospective pilot study of 91 patients, PRP was injected into knee degenerative cartilage lesions. One patient had a marked pain response with swelling that lasted for 2 wk. No other complications related to infiltrations or severe adverse events were reported during treatment and the 24-month follow-up period.[28] In a 2016 randomized comparison study of 120 patients with knee OA that compared PRP with HA and ozone gas, mild and very short-term side effects (pain, heat, redness) were noted in a few patients.[29] A 2012 prospective cohort study with a control group of 120 patients compared PRP and HA, finding no major adverse events or complications. Only temporary mild worsening of pain in knee joint after application of PRP was reported in six cases, all of which were resolved spontaneously after 2 days.[30] In a 2016 meta-analysis of 1055 patients comparing a placebo, HA, leukocyte-rich (LR)-PRP, and LP-PRP in treating knee OA, leukocyte concentration did not affect the incidence of local reactions to PRP injections. Knee pain and swelling afflicted all patients in both treatment groups, and only the subjective severity of the symptoms differed, which is highly susceptible to bias; actual incidence of local reactions was similar between groups. One study reported side effects that included syncope, dizziness, headache, gastritis, and tachycardia.[31]

DISCUSSION

Increasing evidence shows that PRP is safe and exhibits similar adverse reactions as HA injections. This review focused on studies that describe the use of PRP intraarticular injections in OA joints with discussion about safety of PRP use.

Evidence for intraarticular therapies in the management of knee OA is inconsistent and even controversial. Intraarticular

corticosteroids (CS) and HA are two common therapies frequently used, each with separate risks and benefits.

Comparing efficacy between HA and CS, the authors of a 2009 systematic review and meta-analysis suggested that CS is more effective than HA in the first 4 wk, whereas HA is more effective from 4 wk to 26 wk.[32] The history of CS injections has suggested that they increase risk of infection after total knee arthroplasty.[33] CS has a multimodal effect on genes because it affects proteins that upregulate catabolic pathways and downregulate anabolic pathways, and induce apoptosis of cells.[34]

CS is not alone in its propensity for chondrotoxicity. Local anesthetics (LA), which are commonly mixed with CS for intraarticular injections, also have been shown to have toxic effects on cartilage. Further, the combination of LA and CS might have synergistic effects of toxicity on soft tissues including chondrocytes and tenocytes.[35]

Complications from IA-CS Injection

Complications from intraarticular (IA)-CS injections include superficial and deep infections.[36,37] Furthermore, corticosteroids on articular cartilage have time- and dose-dependent deleterious effects. At low doses and short culture durations (less than 2 to 3 mg/dose or 8 to 12 mg/cumulative total dose in vivo), increased cell growth and recovery from damage has been observed. At higher doses and longer culture durations (greater than 3 mg/dose or 18 to 24 mg/cumulative total dose in vivo), corticosteroids have been associated with gross cartilage damage and chondrotoxicity.[38]

In a 2020 systematic review, authors reported that triamcinolone acetonide (TA) decreased cell viability significantly and caused cell apoptosis in cultured human rotator cuff derived cells. This deleterious effect was prevented by the simultaneous administration of PRP. The authors found that in some clinical situations, PRP may be useful as a protective agent for patients receiving TA injections.[39]

In a study by Wernecke *et al*.,[38] corticosteroid effects were examined on articular cartilage. The authors found an upregulation of cell-associated matrix aggrecan, type II collagen, and fibronectin. These findings indicated a beneficial effect of hydrocortisone on human chondrocyte metabolism because it stimulated cartilage macromolecule synthesis and inhibited degenerative enzymes. Furthermore, a significant downregulation of beneficial glycoprotein TIMP-3, a time- and dose-dependent depression of transcription of SOX9, COL-II, and aggrecan, and a time- and dose-inhibition of chondrocyte growth were reported in the study.

Chen *et al*.[40,41] applied a combination of PRP and HA on proinflammatory cytokines-induced chondrocyte for examining its regenerative and antiinflammatory effects and signaling cascades in advanced OA therapy. The authors demonstrated that this combination could rescue proinflammatory cytokines-induced degeneration through chondrogenic signaling recovery. Furthermore, intraarticular injection of PRP and HA can attenuate cartilage degeneration in anterior cruciate ligament transection (ACLT)-OA animal models. In this study, HA and PRP were shown to upregulate anabolic factors (CD44, TGF, Erk1/2, P-ERK1/2, SOX-9, Col II and AGN) and downregulate catabolic factors (COX2, MMP-1, MMP-3, CCL2, CCL3, CCL5, CCL20, CXCL1, CXCL2, CXCL5, CXCL16, CD40LG, LIF, TNFSF13B). Data from this study suggested that a combination of PRP and HA could efficiently suppress OA pathology-related chemokine and cytokine expressions.

To date, PRP and even botulinum toxin (BTA) do not have recommendation guidelines for intraarticular injections in osteoarthritis. Most randomized controlled trials of patients with knee OA support a slightly better symptomatic results of intraarticular PRP when compared to intraarticular HA, intraarticular corticosteroids, or even intraarticular saline, especially among patients in early stages of the disease. Unfortunately, the trials were not designed to demonstrate superiority of intraarticular PRP, so the results should be interpreted in that context. For instance, the strong placebo effect of IA injection can be a confounding factor. The mechanism of PRP and its joint biological effects are also unclear and are likely dependent on the composition of PRP and the varying concentrations of platelet along with differing amounts of growth factors. A pattern of safety was found to suggest low frequency of serious adverse events, including infections and allergic reactions; however, it was found that postinjection pain may be more common and even more severe with intraarticular PRP than other injections, though only for a short period.[3,42,43]

Preparation of PRPs also varies significantly depending on the type of system being used. In terms of platelet and leukocyte concentration, preparation can vary immensely in single-spin versus double-spin methods. Platelet concentration in PRP can differ widely across studies (from 300,000/mm^3 to over 1,500,000/mm^3.) Variations are due to differences in donors, blood volumes, agents used for platelet activation (thrombin or calcium chloride), number of centrifugations, and if the product was frozen. With this in mind, the discussion on pain and inflammation immediately after intraarticular injection of PRP could be due to the inflammatory effect that leukocytes cause, and could even be minimized with leukocyte-free PRP. Leukocyte influence on the action of LPRP action has not been entirely evaluated; however, supporters claim the inflammatory effect is beneficial, while others notice a negative effect in the form of solid enzyme release. Unfortunately, the validity of study results is a limitation because neither in-vitro nor the clinical results can be generalized to all PRP preparations because each PRP study varies widely in concentration, platelet activity, and type of joint therapy product utilized. It is also important to note that many studies involving PRP are compared to HA. With platelets, many growth factors like fibroblast growth factor-2 (FGF) have an action that in and of itself stimulates HA production by synovial cells. It would be beneficial to see a study on the true effects of FGF and the amount of HA that is being activated. If HA has an upper limit to its effects, a further discussion could involve whether the amount of FGF found in PRP is the reason it has similar and sometimes equivocal findings when compared to HA.[44–47]

In a study by Yang *et al*.[48] the authors demonstrated that PRP can protect chondrocytes from interleukin (IL)-1β-dependent apoptosis and can promote anabolism of

chondrocyte extracellular matrix. The effects of PRP on IL-1β, treated chondrocytes support the beneficial effects of PRP application in the treatment of arthritis.

Interleukin-1 (IL-1) is produced locally during inflammation, but not in normal tissue. The IL-1 family consists of IL-1α, IL-1β, and an endogenous IL-1 receptor antagonist (IL-1ra). In a study by Miller *et al*.,[49] patients with high synovial fluid IL-1ra and low IL-1β concentrations had a more rapid resolution of arthritis. Bresnihan *et al*.[50] found that systemic treatment of rheumatoid arthritis (RA) patients with IL-1ra for 24 wk showed a dose-dependent reduction in the number of swollen joints, overall patient scores, C-reactive protein, erythrocyte sedimentation rate, and number of new erosions. In a study by Alstergren *et al*.,[51] IL-1 inhibitors are increased to counteract the proinflammatory effects of IL-1β, and an increased amount of IL-1ra in temporomandibular (TMJ) synovial fluid was associated with very minimal painful mandibular movements, perhaps due to IL-1β receptor inhibition.[52]

Upregulation of cartilage catabolic cytokines and enzymes is thought to be a key mechanism of cartilage damage. Alpha 2 macroglobulin (A2M) is a serum protease inhibitor that slows all types of endoproteases. It is produced by chondrocytes and synoviocytes. Studies have shown A2M inhibits activities of ADAMTS-4, -5, -7, -12,[23,24] and this protease/A2M balance may play an important role in mediating cartilage destruction by catabolic factors. Zhu *et al*.[53] provides novel data indicating that A2M is a master inhibitor of many types of cartilage-degrading enzymes. It acts by blocking activity and decreasing gene expression and protein levels in the joint.

Contraindications and side effects from PRP administration are minimal. To date, no absolute medical contraindications to the use of PRP therapy have been identified. As per this review, there are few side effects from PRP, and it is a safe, autologous source of bioactive compounds with anabolic properties.

In one recent study, PRP was capable of inhibiting periodontal pathogens. Specifically, Porphyromonas gingivalis at 3 to 4 days and Aggregatibacter actinomycetemcomitans were inhibited whereas platelet-rich fibrin (PRF) did not have such an effect. The study mentioned the extra-added calcium chloride in activation of platelets found in PRP as a contributing factor in antibacterial activity. The absence of reported serious adverse events of intraarticular PRP is quite promising, especially the absence of reported cases of septic arthritis, a well-known complication of intraarticular injections. The antimicrobial effects are highly likely the confounding factor for the absence of serious adverse events.[45,54]

Platelets are a highly specialized member of the immune system. Platelets express a variety of surface proteins and receptors that detect and mediate responses to most classes of microbial pathogens and are known to provide important molecular and cellular coordination to bridge innate and adaptive host defense against infections.[55–57] Platelets also interact and respond to bacterial pathogens and elaborate multifunctional antimicrobial peptides and kinocidines.[55–57] There are proposed mechanisms in which platelets regulate complement activation and participate in clearing terminally activated platelets and microparticles from the circulation. A proposed sequence of events includes events associated with platelet-bacterial infection that proceeds through distinct and progressive phases: direct contact, morphogenesis, initial aggregation, and irreversible aggregation.[55–57]

Authoritative information from clinical trials is lacking and the fact that PRP is an autologous product, conceivably, would provide therapeutic tolerance. However, whether tolerance indicates safety is a question to be determined. PRP's osteointegrative role and ability to accelerate consolidation or osteointegration of fractures are hypothesized and these beneficial properties are not entirely supported by literature. Ongoing PRP studies in preclinical literature are attempting to determine the true properties of PRP, but those have yet to be fully elucidated.

All 21 studies that were examined are outlined in Supplement 1[58–68] (See Supplemental Digital File, which shows the studies involving PRP safety in large joint osteoarthritis, http://links.lww.com/COP/A60).

CONCLUSIONS

PRP is a novel therapeutic agent with minimal adverse effects and is generally tolerated in a majority of patients with shoulder, hip and knee OA. Many studies compare PRP, or some derivation of autologous blood-derived products, to that of saline or HA, and in most studies involving knee OA, it shows comparable outcomes and improvements in pain. Similar findings have been found in shoulder and hip OA. Its long-term profile has not been addressed.

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