Platelet-Rich Plasma in Orthopaedic Surgery

A Critical Analysis Review

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Abstract

» Platelet-rich plasma has shown great promise and potential to stimulate biologic activity in difficult-to-heal musculoskeletal tissue. However, the optimal formulation, method of administration, and dosing for different tissues have yet to be determined.

» Within a given platelet-rich plasma preparation technique, there is a high degree of inter-subject and intra-subject variability in the composition of platelet-rich plasma produced. This likely contributes to the inconsistent results reported in the current platelet-rich plasma literature.

» Current evidence best supports the use of platelet-rich plasma as a treatment for osteoarthritis of the knee. Evidence on the use of platelet-rich plasma as a treatment or adjunct for rotator cuff repair, lateral epicondylitis, hamstring injuries, anterior cruciate ligament (ACL) reconstruction, patellar tendinopathy, Achilles tendinopathy, and fractures is inconsistent or only available from low-powered studies. To our knowledge, no comparative studies examining platelet-rich plasma treatment for partial ulnar collateral ligament tears in the elbow currently exist.

» Current evidence suggests that different platelet-rich plasma formulations are needed for different tissues and pathologies. Ultimately, improved understanding of the underlying structural and compositional deficiencies of the injured tissue will help to identify the biologic needs that can potentially be targeted with platelet-rich plasma.

Platelet-rich plasma, an autologous blood concentrate, has gained popularity among physicians as a treatment modality for orthopaedic injuries. The biologic rationale for its use involves the local delivery of growth factors, inflammation modulators, and cell adhesion molecules that are released from a concentrated pool of degranulating platelets. These bioactive proteins, which include platelet-derived growth factor, insulin-like growth factors I and II, fibroblast growth factor, vascular endothelial growth factor, and transforming growth factor-beta, are all thought to facilitate and enhance the healing of injured tissue. As a result, platelet-rich plasma is believed to augment the natural healing process by increasing the concentration of these cytokines at the site of injury. The autologous nature and thus the safety of platelet-rich plasma make it an attractive treatment option. Categorized as a minimally manipulated tissue and autologous blood product, platelet-rich plasma has avoided the regulatory hurdles of extensive preclinical and clinical trial testing, resulting in its

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widespread use despite the lack of consistent evidence supporting its efficacy. This article provides a critical analysis of the available literature on platelet-rich plasma treatment in orthopaedic surgery, with a focus on recent Level-I and II studies.

Platelet-Rich Plasma Preparation

Because the optimal platelet-rich plasma composition for treating different orthopaedic pathologies remains unknown, there remains substantial variability in the methods of platelet-rich plasma production among commercial systems[1,2]. Prior studies have demonstrated differences in platelet, leukocyte, and growth factor content depending on separation technique[3]. To complicate matters further, within a given separation technique, there is a high degree of inter-subject and intra-subject variability in the composition of platelet-rich plasma produced[4]. This likely contributes to the inconsistency of results reported in the literature. Special attention has been devoted to the leukocyte concentration within platelet-rich plasma, with leukocyte-rich platelet-rich plasma associated with a higher concentration of pro-inflammatory mediators such as interleukin-1 and tumor necrosis factor-alpha[5]. As a result, some have suggested that leukocyte-reduced platelet-rich plasma is more suitable for intra-articular treatment, although there is currently no clinical evidence to substantiate this recommendation. Ultimately, more research is needed to determine the optimal platelet-rich plasma formulation (leukocyte and platelet number, other plasma proteins), activation status (when and how to initiate platelet degranulation), need for a carrier vehicle (fibrin matrix or collagen-based scaffold), and dosing regimen (single injection compared with serial injection and intraoperative injection compared with delayed injection)[6]. Because of the heterogeneity of currently utilized platelet-rich plasma formulations, a validated classification system characterizing the composition is useful for the comparison of studies. Mishra et al.[7] proposed a system that classifies platelet-rich plasma by leukocyte content, platelet number, and activation (Table I), which will be used to describe the noncommercial platelet-rich plasma preparations in this review.

Rotator Cuff Repair

Adjunctive use of platelet-rich plasma during arthroscopic rotator cuff repair has been extensively studied within the platelet-rich plasma literature, with multiple randomized controlled trials (RCTs) and meta-analyses on the topic. However, the heterogeneity of these studies, with regard to platelet-rich plasma composition, means of administration, tear size, and repair technique (single-row or double-row), makes it difficult to compare results. Despite the number of variables, the overwhelming majority of studies have shown no difference in clinical outcomes after rotator cuff repair in patients who received platelet-rich plasma augmentation compared with controls[8-13]. Saltzman et al.[12] performed a systematic review of 7 meta-analyses, each with a Quality of Reporting Meta-analyses (QUORUM) score of >15, evaluating platelet-rich plasma use at the time of the arthroscopic rotator cuff repair surgical procedure. When compared with control patients, patients who received platelet-rich plasma at the time of rotator cuff repair did not report improved clinical outcome scores, including the Constant score[14], University of California Los Angeles (UCLA) score[14], American Shoulder and Elbow Surgeons (ASES) score[14], and Simple Shoulder Test[15], after a minimum 12-month follow-up. In a meta-analysis of 11 Level-I or II studies, Warth et al.[8] showed a significantly decreased improvement in the Constant score when platelet-rich plasma was injected over the tendon surface compared with application at the tendon-bone interface ($p = 0.046$); however, this difference did not reach the minimal clinically important difference.

The effect of platelet-rich plasma on retear rates after arthroscopic rotator cuff repair is more controversial. Of the studies that assessed the integrity of the cuff repair at least 6 months postoperatively, the majority demonstrated no difference in retear rates[8,11,12,16-20]. Nevertheless, some studies have shown that, in certain settings, platelet-rich plasma applied at the tendon-bone interface decreased retear rates[21-23]. In the meta-analysis by Warth et al.[8], retear rates were significantly decreased when

TABLE I Platelet-Rich Plasma Classification System by Mishra et al.[7]

Type or Subtype	Leukocytes	Activated*
Type		
1	Increased	No
2	Increased	Yes
3	Minimal or none	No
4	Minimal or none	Yes
Subtype		
A	Platelets ≥5 times baseline†	
B	Platelets <5 times baseline	

*Users can choose to activate platelets endogenously or through the addition of an exogenous clotting factor (e.g., $CaCl_2$) to any commercially available system.
†Buffy coat-based systems (leukocyte-rich) typically produce highly variable platelet concentrations ranging from 3 to 8 times baseline (subtype A or B), whereas plasma-based systems (leukocyte-poor) typically produce platelet concentrations <5 times baseline (subtype B).

platelet-rich plasma was used for tears >3 cm in anterior-posterior length using a double-row repair technique ($p = 0.046$). Additionally, retear rates were decreased when platelet-rich fibrin matrices were used to supplement repairs compared with liquid-based platelet-rich plasma, although this result did not reach significance ($p = 0.054$). Saltzman et al. performed a subgroup analysis involving 4 meta-analyses and suggested that application of a platelet-rich fibrin matrix at the bone-tendon interface could potentially be an avenue for decreasing the retear rate in the setting of small and medium tears repaired with a double-row technique[12]. However, to our knowledge, no studies have thus far evaluated these variables in combination.

Elbow Ulnar Collateral Ligament (UCL) Injuries

There is a paucity of data on the use of platelet-rich plasma for treating partial ulnar collateral ligament (UCL) tears of the elbow, with the current literature, to our knowledge, consisting of only 2 case series[24,25]. Podesta et al.[24] examined 34 overhead-throwing athletes with partial UCL tears treated with a single platelet-rich plasma injection (Arteriocyte Magellan) and physical therapy. At a mean follow-up of 70 weeks, the authors reported a mean time to return to play of 12 weeks, significant improvements in Kerlan-Jobe Orthopaedic Clinic[26] and Disabilities of the Arm, Shoulder and Hand (DASH)[14] outcomes scores ($p < 0.001$), and decreased dynamic medial elbow joint space widening. One patient had treatment that failed and underwent UCL reconstruction at 31 weeks after injection. Dines et al.[25] reviewed 44 baseball players with partial UCL tears treated with platelet-rich plasma injections (Arthrex ACP [Autologous Conditioned Plasma]) and physical therapy. Sixteen patients had 1 injection, 6 patients had 2 injections, and 22 patients had 3 injections. Similarly, the mean time to return to play was 12 weeks. The major limitation of these studies is the lack of a control group. Comparative studies are needed to evaluate whether platelet-rich plasma injections can actually stimulate the healing of partial UCL injuries.

Lateral Epicondylitis

Several RCTs have compared platelet-rich plasma injection with various controls for the treatment of symptomatic lateral epicondylitis[27-32]. Most of the studies used type-1A platelet-rich plasma in their treatment (leukocyte-rich, with platelet concentration >5 times the baseline). In a double-blind, multicenter study consisting of 230 patients, Mishra et al.[31] compared tendon needling with and without platelet-rich plasma (Biomet GPS III). No significant differences were found at 12 weeks, but the platelet-rich plasma group reported superior improvement in pain with resisted wrist extension at 24 weeks. There were no differences in the Patient-Rated Tennis Elbow Evaluation[33] between groups. Rehabilitation was not standardized across the trial centers, a weakness acknowledged by the authors. In a single-blind study of 28 patients, Thanasas et al.[34] compared treatment with a single injection of platelet-rich plasma (Biomet GPS III) with that of autologous blood. Both treatment groups underwent physical therapy. Pain reduction was superior in the platelet-rich plasma group compared with the autologous blood group at 6 weeks, but this difference dissipated at 12 and 24 weeks. In a double-blind study of 50 patients, Montalvan et al.[32] performed 2 injections of either platelet-rich plasma (Arthrex ACP) or saline solution at an interval of 4 weeks. No differences in subjective pain scores and pain with isometric wrist extension were found between groups at all time points within the final 12-month follow-up. Conversely, 2 RCTs on the same patient population compared treatment with platelet-rich plasma injections (Biomet GPS III) with treatment with corticosteroid injections and found superior reductions in pain and improvements in DASH scores with platelet-rich plasma at 6 months and 1 year[27,29]. Patients treated with platelet-rich plasma continued to progressively improve, and those treated with corticosteroid declined at 12 weeks. Overall, the available evidence suggests that platelet-rich plasma injections may provide some benefit in the long term, but ultimately, more studies are needed to clearly delineate the effects of platelet-rich plasma from the natural course of tendon healing and symptom resolution.

Hamstring Injuries

Platelet-rich plasma injection near the proximal myotendinous hamstring origin has been theorized to help to speed the recovery process after acute hamstring injury. Several RCTs have examined the treatment of grade-2 hamstring injuries with platelet-rich plasma injection, with time to return to play as the primary outcome measure[35-37]. Hamilton et al.[35] compared treatment with a single platelet-rich plasma injection (Biomet GPS III) with that with a platelet-poor plasma injection or no injection control in a study of 90 professional athletes. All participants underwent a standardized rehabilitation program. Although the platelet-rich plasma group returned to play 5.7 days sooner than the platelet-poor plasma group, there was no difference in the time to return to play between the platelet-rich plasma group and the control group. Furthermore, there was no significant difference in the reinjury rate 6 months after returning to competition among all treatment groups. In another double-blind study, Reurink et al.[37] compared treatment with 2 injections of either platelet-rich plasma (Arthrex ACP) or saline solution in 80 athletes. The first injection was given within 5 days of injury and the second injection was given 5 to 7 days later. There were no differences between treatment groups with regard to time to return to play, reinjury rate, subjective scores, strength testing, and magnetic resonance imaging (MRI) measures. In contrast, A Hamid et al.[36] compared a single platelet-rich plasma injection

(Biomet GPS III) combined with a rehabilitation program with rehabilitation alone in a smaller study of 24 athletes. Return to play and pain severity or interference, which was assessed with the Brief Pain Injury-Short Form (BPI-SF)[38], were examined. The platelet-rich plasma group returned to play sooner (26.7 days) than controls (42.5 days), but there was no difference in pain scores between groups. More research, perhaps with the use of leukocyte-rich platelet-rich plasma that has shown promise in the treatment of lateral epicondylitis, is required.

Anterior Cruciate Ligament (ACL) Reconstruction

Although ACL reconstruction has traditionally been considered a successful procedure that allows patients to return to the same-level competition, the ultimate function of the graft is dependent on a complex biologic process of cellular repopulation and revascularization, followed by progressive matrix remodeling and maturation. In addition to these processes within the midsubstance of the ACL graft, healing also needs to occur between the graft and the bone tunnel. Several RCTs have evaluated the use of platelet-rich plasma as a surgical adjunct in ACL reconstruction in an attempt to accelerate graft remodeling and maturation[39-41]. Faster graft maturation as measured by MRI signal intensity has been demonstrated in several studies using supplementary platelet-rich plasma during ACL reconstruction[39,42,43]. Sánchez et al.[44] evaluated patients who underwent ACL reconstruction with and without adjunct platelet-rich plasma (BTI prgf) and obtained biopsy specimens from grafted tendons during a second-look arthroscopy between 6 and 24 months postoperatively. Both gross morphology and histologic evaluation of the grafts demonstrated improvements in graft remodeling and more newly formed connective tissue enveloping the graft in patients treated with platelet-rich plasma. The authors theorized that this connective tissue envelope is eventually integrated in the remodeled tendon graft. However, the biomechanical and clinical implications of these findings are unclear.

The effect of adjunctive platelet-rich plasma applied to the graft-tunnel interface has been evaluated, with most studies indicating that it does not significantly affect tunnel healing or widening[39,45-48]. In a double-blind study, Vogrin et al.[46] compared ACL reconstruction using hamstring graft with and without platelet-rich plasma (Arteriocyte Magellan). Vascularization was assessed by MRI. Although no differences between groups was seen in the intra-articular portion of the ACL grafts, increased vascularization was observed in patients treated with platelet-rich plasma at the graft-tibial tunnel interface at 4 to 6 weeks. However, no differences were observed at later time points.

Additionally, the majority of studies have not indicated any clinical improvement in knee stability or outcome scores with the use of adjunctive platelet-rich plasma during ACL reconstruction[39,41,47]. In a Level-I study, Nin et al.[41] randomized 100 patients to patellar tendon allograft ACL reconstruction with and without a platelet-enriched gel (noncommercial protocol, type 2A). Gels were sutured into the allograft and were applied in the tibial tunnel. At a mean follow-up of 2 years, there were no significant differences between groups in any clinical and radiographic parameters, including the visual analog scale (VAS) for pain, International Knee Documentation Committee (IKDC) score[49], anterior laxity measured by the KT-1000 arthrometer (MEDmetric), and appearance on radiographs and MRI.

Patellar Tendinopathy

To our knowledge, there have been only 2 RCTs comparing platelet-rich plasma with control interventions for refractory patellar tendinopathy. In a double-blind study of 23 patients, Dragoo et al.[50] compared a single platelet-rich plasma injection (Biomet GPS III) with dry needling combined with eccentric exercise. At 12 weeks, the treatment failed in 3 patients in the control group; these 3 patients subsequently crossed over into the platelet-rich plasma group. Outcome measures included the Victorian Institute of Sports Assessment (VISA)[51], VAS, Tegner activity scale[52], Lysholm knee scale[52], and 12-Item Short Form Survey (SF-12). The platelet-rich plasma group had greater improvement in VISA scores than the control group at 12 weeks but not at ≥26 weeks. Conversely, the control group had greater improvement in Lysholm scores than the platelet-rich plasma group at ≥26 weeks. There were no differences between groups in any other outcome measure. In another RCT of 46 patients, Vetrano et al.[53] compared 2 platelet-rich plasma injections (Kaylight MyCells) given 2 weeks apart with 3 sessions of focused extracorporeal shock-wave therapy. Both patient groups underwent an exercise program. Outcome measures included the VISA, VAS, and modified Blazina scale[53]. The platelet-rich plasma group showed superior improvement compared with the extracorporeal shock-wave therapy group with regard to VISA and VAS scores at 6 and 12 months and the modified Blazina scale score at 12 months. In a prospective, nonrandomized cohort study, Filardo et al.[54] examined 15 patients who had undergone nonoperative or surgical treatment that had failed; these patients subsequently underwent 3 platelet-rich plasma injections (noncommercial protocol, type 2A) at 15-day intervals. These patients were compared with a control group who had not undergone any prior treatment. No significant differences between groups were observed in either pain or VISA scores at 6 months after intervention. Larger-scale studies are needed to determine whether platelet-rich plasma injections are an appropriate treatment modality for patellar tendinopathy.

Knee Osteoarthritis

The currently available Level-I or II studies comparing intra-articular platelet-rich plasma injections with hyaluronic acid injections or placebo controls for knee osteoarthritis have shown promising results with the use of

platelet-rich plasma[55-61]. Its mechanism of action seems to be through immunomodulation and production of anti-inflammatory mediators rather than direct modification of the cartilage[58,60]. Thus, much like a corticosteroid injection, symptomatic relief after platelet-rich plasma injection may be consistent but only temporary. A meta-analysis by Riboh et al.[57] revealed superior Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores in patients treated with leukocyte-reduced platelet-rich plasma compared with those treated with hyaluronic acid, although no such difference was found in patients treated with leukocyte-rich platelet-rich plasma. Recently, Smith[56] conducted a U.S. Food and Drug Administration (FDA)-sanctioned, double-blind RCT comparing 3 weekly platelet-rich plasma injections (Arthrex ACP) with saline solution injections in 30 patients. Improvement in WOMAC scores in the platelet-rich plasma group was superior to that in the placebo group from 2 weeks to 1 year after intervention. At 1 year, WOMAC scores for the platelet-rich plasma group improved by 78% from the baseline scores, whereas scores for the placebo group improved by only 7%. In an RCT of 65 patients, Simental-Mendía et al.[58] compared treatment with 3 injections of platelet-rich plasma (noncommercial protocol, type 4B) at 2-week intervals with treatment with acetaminophen (500 mg every 8 hours) over 6 weeks. The platelet-rich plasma group reported greater improvements in all subscores of the WOMAC (stiffness, pain, and functional capacity) compared with those treated with acetaminophen at 6, 12, and 24 weeks. Finally, in a study by Patel et al.[55], 78 patients (156 knees) were treated with a single injection of platelet-rich plasma (noncommercial protocol, type 4B), 2 injections of platelet-rich plasma spaced 3 weeks apart, or a single injection of normal saline solution. Both platelet-rich plasma groups reported significant improvement in all WOMAC subscores ($p < 0.05$), and the control group reported no improvement. There were no significant differences between groups that received 1 injection or 2 injections. In another RCT, Filardo et al.[62] compared 3 weekly injections of platelet-rich plasma (noncommercial protocol, type 2A) with injections of hyaluronic acid in 192 patients with knee osteoarthritis. Subjective outcomes measured included IKDC subjective scores, Knee injury and Osteoarthritis Outcome Score (KOOS), EuroQol VAS, and Tegner scores. Both treatment groups reported significant improvements in function and symptoms according to all subjective scores used ($p < 0.0005$), but comparative analysis demonstrated no differences between groups at any follow-up time point. Additionally, the platelet-rich plasma group reported more pain and swelling immediately after the injection; this pain was possibly related to the leukocyte-rich composition of the platelet-rich plasma used. Despite the heterogeneity among studies, the majority of published data suggest superior symptomatic relief with the use of leukocyte-reduced platelet-rich plasma in patients with early knee degenerative changes compared with hyaluronic acid or placebo, and its use may be considered in this population.

Achilles Tendinopathy

A few small RCTs have evaluated the effects of platelet-rich plasma injection treatment for chronic midsubstance Achilles tendinopathy[63-66]. In the largest RCT to date, to our knowledge, 54 patients received eccentric exercise therapy in combination with a single platelet-rich plasma (Biomet GPS III) or saline solution injection[63]. Although VISA scores and tendon structure and neovascularization as measured by color Doppler ultrasonography improved in both groups after 12 weeks, there were no significant differences between groups. In a pilot study of 20 patients, Kearney et al.[64] compared platelet-rich plasma injection (EmCyte GenesisCS) with an eccentric loading program. Outcome measures included the VISA and EuroQol-5D (EuroQol-5 Dimensions). No significant differences were noted between groups during the first 6 months after injection, although the sample size was small. Krogh et al.[65] compared treatment with a single platelet-rich plasma (Biomet GPS II) injection with that with a saline solution injection in 24 patients. After 3 months, no differences were observed between groups in the VISA score or pain at rest, while walking, and when the tendon was squeezed. However, the majority of patients dropped out of the study at 3 months. Future well-designed RCTs with larger sample sizes are needed to ultimately conclude if platelet-rich plasma deserves a role in the treatment of chronic Achilles tendinopathy.

Fractures and Delayed Unions or Nonunions

Platelet-rich plasma has demonstrated osteogenic properties in several in vitro and preclinical studies, as shown in a review by Iqbal et al.[66]. As a result, several RCTs have examined the use of platelet-rich plasma in the setting of acute traumatic fractures or iatrogenic osteotomy[67-70]. However, in the majority of these studies, platelet-rich plasma was used in conjunction with other augments (e.g., bone graft, bone marrow concentrate), making it difficult to ascertain the relative contribution of platelet-rich plasma. In a study of 30 patients with distal radial fractures, Namazi and Mehbudi[69] compared a single intra-articular injection of platelet-rich plasma (Arthrex ACP) immediately after percutaneous pinning fixation with percutaneous fixation alone. The platelet-rich plasma group reported better improvement in pain and activity scores compared with the control group at 3 and 6 months. Wrist flexion and extension motion was also better in the platelet-rich plasma group compared with the control group at 3 months, although there were no significant differences between groups at 6 months. Griffin et al.[68] evaluated the use of platelet-rich plasma (EmCyte GenesisCS) applied during closed reduction and cannulated screw fixation of 200 patients with femoral neck fractures. Platelet-rich plasma was injected through the cannulated screws into the fracture site prior to final tightening and

compression. A regression analysis adjusting for sex, fracture displacement, dementia, and age revealed no significant effect of platelet-rich plasma on the rate of reoperation compared with controls. Additionally, there were no significant differences in radiographic nonunion or osteonecrosis between groups. Dallari et al.[67] conducted a trial of 33 patients undergoing high tibial osteotomy randomized to 3 groups: lyophilized bone chips with platelet gel (noncommercial protocol, type 1A) (Group A), lyophilized bone chips with platelet gel and bone marrow stromal cells (Group B), and lyophilized bone chips alone (Group C). In comparison with Group C, Groups A and B demonstrated significantly increased osteoblasts and osteoid areas, as well as increased bone apposition on the chips on histomorphometric analysis ($p \leq 0.03$). Radiographs also revealed a significantly higher rate of osseointegration in Groups A and B than in Group C ($p < 0.005$). However, meaningful clinical improvement was not evaluated.

The majority of studies evaluating the use of platelet-rich plasma for delayed unions or nonunions of long bones consist of small case series[71-73]. In the lone RCT of 120 patients, Calori et al.[74] compared augmentation with platelet-rich plasma (noncommercial protocol, type 1A) with augmentation with recombinant bone morphogenetic protein 7 (BMP-7) applied during the revision surgical procedure of long bone nonunions. Revision of the fixation construct and supplemental use of bone graft occurred in the majority of patients in each group. Significantly higher clinical and radiographic union rates and shorter healing times were observed in the BMP-7 group compared with the platelet-rich plasma group ($p = 0.016$). Currently, there is limited clinical evidence supporting the use of platelet-rich plasma in bone-healing applications.

Conclusions

Platelet-rich plasma therapies have the ability to locally deliver high concentrations of biologic factors essential to the healing process to augment musculoskeletal tissue repair. Many of these platelet-derived growth factors have been shown to improve tendon and

TABLE II Summary of Clinical Studies on Platelet-Rich Plasma Use in Orthopaedic Surgery

Condition or Procedure	Clinical Summary
Rotator cuff repair	A meta-analysis of 8 Level-I studies and 3 Level-II studies showed no differences in overall gain in outcome scores or retear rates[8]. More studies are needed to evaluate whether platelet-rich fibrin matrix applied at the tendon-bone interface decreases retear rates.
UCL injuries	There are currently no comparative studies, to our knowledge.
Lateral epicondylitis	Six months after the use of Biomet GPS III (type 1A), 1 RCT showed superior improvement in pain with resisted wrist extension when compared with dry needling[31], 1 RCT showed early pain reduction but no later differences when compared with autologous blood injection[34], and 2 RCTs (on same patient population) showed superior reduction in pain and improvement in DASH scores when compared with corticosteroid injections[27,29]. Future studies should clearly delineate the effects of platelet-rich plasma from the natural course of tendon healing and symptom resolution.
Hamstring injuries	Two RCTs showed no differences in return to play, reinjury rate, or subjective scores when compared with saline solution injection[35,37]. One RCT showed earlier time to return to play when compared with rehabilitation alone[36].
ACL reconstruction	Two RCTs showed accelerations in graft remodeling and maturation[39,40]. However, the biomechanical and clinical implications are unclear. Five RCTs showed no improvement in tunnel healing or decreased tunnel widening[39,42,45,47,48]. Five RCTs showed no differences in knee stability or outcome scores[39-41,45,47].
Patellar tendinopathy	One RCT showed no differences in VISA, VAS, Lysholm knee scale, and Tegner activity scale scores when compared with dry needling at 6 months[50]. One RCT showed superior improvement in VISA, VAS, and modified Blazina scale scores when compared with extracorporeal shock-wave therapy at 12 months[53].
Knee osteoarthritis	With the use of leukocyte-poor platelet-rich plasma, 3 RCTs showed superior outcome scores when compared with hyaluronic acid or saline solution injection[55,56,59].
Achilles tendinopathy	Four RCTs showed no differences in outcome scores when compared with saline solution injection or rehabilitation alone[63-65].
Fractures and delayed unions or nonunion	One RCT showed superior pain and activity scores in patients undergoing percutaneous fixation of distal radial fractures[69]. Two RCTs showed no differences in reoperation rate, radiographic nonunion, or osteonecrosis in patients undergoing closed reduction and cannulated screw fixation of femoral neck fractures[68,70]. One RCT showed inferior clinical and radiographic union rates and longer healing times in the treatment of long bone nonunions when compared with supplemental use of BMP-7[74].

bone healing in animal studies[66,75]. Although there is a general belief that platelet-rich plasma has great promise and potential to stimulate biologic activity in difficult-to-heal musculoskeletal tissue, translating these therapies into clinically meaningful treatment has thus far been met with mixed success.

The inconsistent results from clinical studies (Table II) can partially be attributed to the lack of understanding of the optimal platelet-rich plasma formulation for different tissues and pathologies. It may be naive of us to think that the same type of platelet-rich plasma would work for a degenerative rotator cuff tear or a hamstring muscle strain or as an adjunct for articular cartilage repair. These are all very different tissues with different biologic requirements. In fact, in the current platelet-rich plasma literature, studies demonstrating a positive effect for lateral epicondylitis were more likely to use a leukocyte-rich formulation[27,29,31], whereas those demonstrating a positive effect for knee osteoarthritis were more likely to use a leukocyte-reduced formulation[55,56,58]. Even within a specific tissue, there are likely very different biologic requirements depending on patient-related factors (age, smoking status, underlying medical conditions) and acute injury compared with chronic injury.

Improved understanding of the underlying structural and compositional deficiencies of the injured tissue will help to identify the biologic needs that can potentially be targeted with platelet-rich plasma. We need continued research to further delineate the cellular and molecular mechanism(s) of degeneration and repair of various orthopaedic tissues, including meniscus, tendon, cartilage, muscle, and bone. Improved understanding of the basic pathophysiology of these tissues will come from use of more appropriate animal models, as well as examination of tissue samples from patients with well-characterized phenotypes. In addition to understanding the abnormalities at the microstructural and molecular levels, we also need further information about the nociceptive factors that actually lead to symptoms. This information will provide insight into the biologic factors that we can try to target with the next generation of platelet-rich plasma. This type of information will help to define how or if platelet-rich plasma can be both symptom-modifying and structure-modifying.

In addition to understanding the pathophysiology of the tissues being treated, the other side of the equation is to further characterize the numerous components in platelet-rich plasma. In addition to the numerous cytokines and other factors contained in the alpha granules and dense granules of platelets, there are a number of proteins and other active biologic mediators in the plasma component. The content, concentration, and biologic activity of these various mediators likely differ between different platelet-rich plasma preparations. As we learn more about the myriad components in platelet-rich plasma, we can ultimately attempt to refine it by adding or subtracting factors to tailor its use for specific clinical needs. For instance, if there is a paucity of available cells in the tissue, just adding platelet-rich plasma may not be enough. Rather, including an exogenous cell source or cell recruitment factors may also be required. Similarly, filtering out unwanted factors may be necessary to optimize the healing milieu or to drive undifferentiated cells down desired pathways within certain tissues. Given the inter-subject and intra-subject variability in platelet-rich plasma composition with our current separation techniques, slight manipulations of the product may be required to achieve a consistent therapeutic effect.

Further progress in this field will come from studies that correlate the biologic activity and components of platelet-rich plasma with clinical outcome. Because of the tremendous inter-individual variability in platelet-rich plasma preparations, the optimal way to further study this area would be to characterize the platelet-rich plasma delivered to a specific patient. The challenge is in defining the relevant factors to measure in a given platelet-rich plasma sample. The field would benefit from identification of sentinel markers of the biologic activity of platelet-rich plasma that could be measured efficiently and cost-effectively in a given aliquot of platelet-rich plasma. This information

TABLE III Grades of Recommendation for Platelet-Rich Plasma Treatment*

Condition or Procedure	Grade
Rotator cuff repair	C
UCL injuries	I
Lateral epicondylitis	C
Hamstring injuries	C
ACL reconstruction	C
Patellar tendinopathy	C
Knee osteoarthritis	B
Achilles tendinopathy	C
Fractures and delayed unions or nonunions	C

*Grade A indicates good evidence (Level-I studies with consistent findings) for or against recommending intervention. Grade B indicates fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention. Grade C indicates conflicting or poor-quality evidence (Level-IV or V studies) not allowing a recommendation for or against intervention. Grade I indicates that there is insufficient evidence to make a recommendation.

about the actual platelet-rich plasma delivered to a specific patient could then be correlated with that patient's clinical outcome, thus providing deeper insight into the mechanism of action, potential, and limitations of platelet-rich plasma therapy for various orthopaedic conditions.

In summary, the lack of standardization among studies with regard to platelet-rich plasma preparation, administration, and concomitant therapy limits the ability to draw definitive conclusions from the currently available data. Our recommendations for the use of platelet-rich plasma treatment in orthopaedic surgery are summarized in Table III. More refined and optimized approaches using platelet-rich plasma may well have a positive effect for certain orthopaedic conditions. However, further critical review and rigorous clinical studies are required to identify the best way to use this potentially effective modality. Further characterization of the underlying pathophysiology and biologic requirements of the tissues being treated as well as of the components of platelet-rich plasma may ultimately allow more careful matching of a specific platelet-rich plasma preparation to the pathology being treated.

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