Orthopedic Applications of Platelet-Rich Plasma

Summary
This policy addresses the use of platelet-rich plasma (PRP) as a treatment of musculoskeletal conditions, including but not limited to primary treatment of plantar fasciitis, tendinopathies such as lateral epicondylitis (ie, tennis elbow) and adjunctive use in orthopedic surgical procedures. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

The evidence base on the efficacy of PRP treatment consists of numerous small controlled trials for a wide variety of orthopedic conditions. Recent literature indicates an increasing number of randomized controlled trials (RCTs), and a search of the clinical trials database (available at ClinicalTrials.gov) reveals that many more RCTs are in progress. Current results of PRP trials are mixed, with some trials reporting improvement with PRP and other trials reporting no improvement. It is uncertain whether the mixed results are due to variability in the conditions studied and outcomes measured; to differences in platelet separation technique, concentration or activation; or to differences in the timing and frequency of administration. Additional studies are needed to resolve these issues.

Related Policies
2.01.16 Recombinant and Autologous Platelet-Derived Growth Factors as a Primary Treatment of Wound Healing and Other Non-Orthopedic Conditions
2.01.26 Prolotherapy
7.01.100 Bone Morphogenetic Protein
8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)

Policy
*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Use of platelet-rich plasma is considered not medically necessary for all orthopedic indications. This includes, but is not limited to, use in the following situations:

- Primary use (injection) for the following conditions:
  - Achilles tendinopathy
  - Lateral epicondylitis
  - Osteochondral lesions
Adjunctive use in the following surgical procedures:
- ACL reconstruction
- Hip fracture
- Long-bone nonunion
- Patellar tendon repair
- Rotator cuff repair
- Spinal fusion
- Subacromial decompression surgery
- Total knee arthroplasty

Background
A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors (PDGFs), epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of PDGF, transforming growth factors that function as a mitogen for fibroblasts, smooth muscle cells, osteoblasts, and vascular endothelial growth factors. Recombinant PDGF has also been extensively investigated for clinical use in wound healing (see Policy No. 2.01.16).

Autologous platelet concentrate suspended in plasma, also known as PRP, can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing the various growth factors. The polymerization of fibrin from fibrinogen creates a platelet gel, which can then be used as an adjunct to surgery with the intent of promoting hemostasis and accelerating healing. In the operating room setting, PRP has been investigated as an adjunct to a variety of periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a type of transforming growth factors, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries. Alternatively, PRP may be injected directly into various tissues. PRP injections have been proposed as a primary treatment of miscellaneous conditions, such as epicondylitis, plantar fasciitis, and Dupuytren contracture. Injection of PRP for tendon and ligament pain is theoretically related to prolotherapy (discussed in Policy No. 2.01.26). However, prolotherapy differs in that it involves injection of chemical irritants that are intended to stimulate inflammatory responses and induce release of endogenous growth factors.

PRP is distinguished from fibrin glues or sealants, which have been used for many years as a surgical adjunct to promote local hemostasis at incision sites. Fibrin glue is created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel® (Baxter) and Hemaseel® are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This policy does not address the use of fibrin sealants.
Blood products such as PRP are regulated by the Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating human cells, tissues, and cellular and tissue-based products. The regulation process for these products is described in the U.S. Food and Drug Administration’s (FDA) 21 CFR 1271 of the Code of Federal Regulations. Under these regulations, certain products including blood products such as PRP are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, FDA has not attempted to regulate activated PRP.

There are numerous PRP preparation systems on the market today with FDA clearance. Many of these systems have 510(k) clearance for producing platelet-rich preparations intended to be used to mix with bone graft materials to enhance bone grafting properties in orthopedic practices. The Aurix System™ (previously called AutoloGel™ from Cytomedix) and SafeBlood® (SafeBlood Technologies) are two related but distinct autologous blood-derived preparations that can be prepared at the bedside for immediate application. Both AutoloGel and SafeBlood have been specifically marketed for wound healing. Other devices may be used in the operating room setting, such as Medtronic Electromedics, Elmd-500 Autotransfusion system, the Plasma Saver device, or the Smart PreP device. The Magellan Autologous Platelet Separator System (Medtronic) includes a disposables kit designed for use with the Magellan Autologous Platelet Separator portable tabletop centrifuge. BioMet Biologics received marketing clearance through FDA’s 510(k) process for a gravitational platelet separation system (GPS®II), which uses a disposable separation tube for centrifugation and a dual cannula tip to mix the platelets and thrombin at the surgical site. Filtration or plasmapheresis may also be used to produce platelet-rich concentrates. The use of different devices and procedures can lead to variable concentrations of active platelets and associated proteins, increasing variability between studies of clinical efficacy.

**Rationale**

At the present time, there are a large number of techniques available for the preparation of platelet-rich plasma (PRP) or PRP gel. The amount and mixture of growth factors produced by different cell-separating systems are variable, and it is also uncertain whether platelet activation before injection is necessary. A number of systematic reviews of the evidence on PRP have been published; these will be the focus of the evidence review. Individual RCTs will be reviewed in some instances, eg, if a systematic review is not available or if there is an individual RCT that is likely to influence the policy but was not included in a systematic review.

**Mixed Indications**

A 2012 systematic review addressed a wide variety of orthopedic indications. This publication included 23 randomized trials and 10 prospective cohort studies that compared PRP with placebo, corticosteroids, or a standard procedure. For most of the studies, the outcome measures differed, but 6 RCTs (n=358) and 3 prospective cohort studies (n=88) reported results of PRP using a visual analog score (VAS) and were combined for analysis. These studies assessed injuries to the acromion, rotator...
cuff, lateral humeral epicondyle, anterior cruciate ligament (ACL), patella, tibia, and spine. Follow-up ranged from 6 weeks to 24 months. Of 22 RCTs that evaluated functional outcomes, 6 showed a functional benefit of PRP, 15 showed no difference between PRP and the control, and 1 showed a significant functional advantage for the control group. Interpretation of this systematic review is limited by the combination of a wide variety of conditions, as well as the lack of standardization of platelet-separation techniques and outcome measures in the primary literature.

PRP as a Primary Treatment of Tendinopathies
There are a large number of small RCTs that evaluate treatment of tendinopathies at various locations. In 2014, Andia et al published a systematic review of PRP in the treatment of painful tendinopathies.9 They included 13 prospective controlled trials (12 RCTs, 1 controlled study that was not randomized) with data from 636 patients included in the meta-analysis. The number of studies on various tendinopathies included 7 studies on chronic elbow tendinopathy, 2 on supraspinatus, 3 on patellar, and 1 study on Achilles tendinopathy. Nearly all studies used leukocyte-rich PRP, and the PRP preparation protocol was the same in about half of the studies. The number of injections ranged from 1 (9 studies) to 3 (1 study). Control interventions included physical therapy (1 study), extracorporeal shock wave therapy (1 study), corticosteroid (3 studies), autologous blood (3 studies), saline (3 studies), and dry needling (2 studies). Risk of bias was considered to be low in 4 studies, unclear in 3, and high in 6. Meta-analysis found that PRP was not better than control interventions in reducing pain at 1 or 2 month follow-up. A small significant effect in pain reduction was found at 3 months (weighted mean difference [WMD], -0.61). At 1 year, the WMD between PRP and control interventions was significant at -1.56. Due to heterogeneity between studies, these findings had low power and precision.

The evidence on specific tendinopathies is reviewed next.

Achilles Tendinopathy
One RCT included in the systematic review by Andia et al was a single-center, randomized, double-blind, placebo-controlled trial of PRP injection in patients with chronic midportion Achilles tendinopathy published in 2010.10 Fifty-four patients were randomized to receive PRP or saline injection, and all patients performed eccentric exercises. The Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire evaluating pain score and activity level was completed at baseline and at 6, 12, and 24 weeks. The mean VISA-A score improved significantly after 24 weeks in both groups, and the between-group difference was not statistically significant. There were no significant differences on secondary measures of patient satisfaction and number of patients returning to their desired sport.

No additional trials of PRP for chronic Achilles tendinopathy were identified in a 2013 Cochrane review.11

Lateral Epicondylitis (Tennis Elbow)
Numerous RCTs have been published for treatment of lateral epicondylitis with PRP. A 2014 systematic review concluded that there is strong evidence that PRP is not effective for lateral epicondylar tendinopathy.12 Six studies were included in the review, 4 of which were considered to be of high quality based on the PEDro score. The authors reported that 3 of 4 high-quality studies and 2 low-quality studies showed no significant benefit when compared with a control group (corticosteroids,
autologous whole blood, saline, needling), while 1 high-quality study showed a beneficial effect of a PRP injection when compared with a corticosteroid injection.

PRP as a Primary Treatment of Nontendon Soft Tissue Injury or Inflammation

Plantar Fasciitis
There are at least 3 small RCTs on the treatment of plantar fasciitis. In 2014, Franceschi et al published a qualitative systematic review of the literature on PRP for chronic plantar fasciitis.13 Eight prospective studies were identified, 3 of which were randomized. The 3 single-blinded RCTs had a total of 90 patients and compared treatment with PRP with corticosteroids (n=60) or prolotherapy (n=30). The largest RCT (N=40) by Monto et al in 2014 compared PRP with corticosteroid injection and had follow-up to 24 months.14 There was an apparent difference in the age and baseline score of the two groups. Blinded assessment with American Orthopaedic Foot and Ankle Society (AOFAS) hindfoot score at 3, 6, 12, and 24 months showed a temporary improvement in the corticosteroid group with a return to near baseline levels (score, 58) by 12 months. In the PRP group the AOFAS score increased from 37 at baseline to 95 at 3 months and remained elevated through 24 months with a final score of 92 (difference of 46 from controls, p=0.001). Confirmation of these results in a larger double-blind RCT with other concentration systems would allow greater certainty regarding the efficacy of PRP in plantar fasciitis.

PRP as a Primary Treatment of Focal Cartilage Lesions and Osteoarthritis

Osteochondral Lesions
No RCTs on treatment of osteochondral lesions were identified. In 2012, Mei-Dan et al reported a quasi-randomized trial of 29 patients with 30 osteochondral lesions of the talus assigned to 3 intra-articular injections of hyaluronate or PRP.15 At 28-week follow-up, scores on the AOFAS Ankle-Hindfoot Scale improved to a greater extent in the PRP group (from 68 to 92) than the hyaluronate group (from 66 to 78). Subjective global function also improved to a greater extent in the PRP group (from 58 to 91) than the hyaluronate group (from 56 to 73). Interpretation of the composite measures of VAS pain and VAS function is limited by differences in the groups at baseline. Neither the patients nor the evaluators were blinded to treatment in this small study.

Osteoarthritis
There are at least 5 RCTs and several quasi-randomized trials published on treatment of osteoarthritis. A 2014 systematic review of PRP for degenerative cartilage pathology included 5 RCTs, 3 quasi-randomized controlled trials, and 8 single-arm prospective series (total N=1543 patients) comparing PRP with hyaluronic acid (HA; 4 RCTs, 2 quasi-randomized) or saline (1 RCT).16 Meta-analysis of functional outcomes found that the effectiveness of PRP was greater than that of HA and improved over 12 months. Fewer than 3 injections, single spinning, and lack of additional activators led to greater uncertainty in the treatment effects. PRP also had lower efficacy in patients with higher degrees of cartilage degeneration. Results were consistent when analyzing only RCTs, but asymmetry in funnel plots suggested significant publication bias. Additional study in high-quality RCTs with a larger number of patients, and with comparisons to alternatives other than HA, is needed to determine the efficacy of PRP for this common condition.
PRP as an Adjunct to Surgery

ACL Reconstruction
A large number of controlled trials have been published on PRP as an adjunct to anterior cruciate ligament (ACL) reconstruction. A 2013 Cochrane review of platelet-rich therapies for musculoskeletal soft tissue injuries identified 4 trials (203 patients) on PRP used in conjunction with ACL reconstruction. Pooled data found no significant difference in International Knee Documentation Committee (IKDC) scores between the PRP and control groups. A 2015 qualitative systematic review by Figuera et al included 11 RCTs or prospective cohort studies with a combined total of 516 patients. Four studies found significantly faster graft maturation while 3 found no significant difference. One study showed faster tunnel healing while 5 showed no benefit. One study showed better clinical outcomes and 5 showed no improvement in clinical outcomes when using PRP. The largest trial is by Nin et al who randomized 100 patients to undergo arthroscopic ACL reconstruction with or without PRP. The use of PRP on the graft and inside the tibial tunnel in patients treated with bone–patellar tendon–bone allografts had no discernable clinical or biomechanical effect at 2-year follow-up.

Hip Fracture
One RCT was identified for treatment of hip fracture. In 2013, Griffin et al reported a single-blind randomized trial of PRP for the treatment of hip fractures in patients aged 65 years and older. Two hundred patients underwent internal fixation of a hip fracture with cannulated screws and were randomly assigned to receive standard-of-care fixation or standard-of-care fixation with injection of PRP into the fracture site. The primary outcome measure was the failure of fixation within 12 months, defined as any revision surgery. The overall risk of revision by 12 months was 36.88% and the risk of death was 21.5%. There was no significant risk reduction (39.74% control, 34.15% PRP) or significant difference between groups in most of the secondary outcome measures. For example, mortality was 23% in the control group and 20% in the PRP group. The length of stay was significantly reduced in the PRP-treated group (median difference, 8 days). There is a potential for bias from the nonblinded treating physician in this measure.

Long-Bone Nonunion
A 2012 Cochrane review found only 1 small (N=21) RCT of PRP for long-bone healing. However, only studies where PRP was compared with no additional treatment or a placebo were included in the review; therefore, the authors did not include the larger RCT by Calori et al described next.

Calori et al compared application of PRP or recombinant human bone morphogenetic protein-7 (rhBMP-7) for the treatment of long-bone nonunions in an RCT with 120 patients and 10 surgeons. Inclusion criteria were posttraumatic atrophic nonunion for at least 9 months, with no signs of healing over the last 3 months, and considered as treatable only by means of fixation revision. Autologous bone graft had been used in a prior surgery in 23 cases in the rhBMP-7 group and in 21 cases in the PRP group. Computer-generated randomization was developed to create 2 homogeneous groups; there were generally similar numbers of tibial, femoral, humeral, ulnar, and radial nonunions in the 2 groups. Following randomization, patients underwent surgery for nonunion, including bone grafts according to the surgeon’s choice (66.6% of rhBMP-7 patients, 80% of PRP patients). Clinical and radiologic evaluations by 1 radiologist and 2 surgeons trained in the study protocol revealed fewer unions in the
PRP group (68%) compared with the rhBMP-7 group (87%). Clinical and radiographic healing times were also found to be slower by 13% to 14% with PRP.

**Patellar Tendon Harvest**
One small RCT evaluated PRP as an adjunct to patellar tendon repair. In 2012, de Almeida et al reported a small (N=27) randomized trial of the effect of PRP gel on the harvest site of the patellar tendon during ACL reconstruction. VAS for pain in the postoperative period was significantly lower in the PRP group compared with the control group (3.8 vs 5.1). At 6 months, assessment by magnetic resonance imaging showed a smaller gap in the patellar tendon in the PRP group (4.9 mm vs 9.4 mm), but there was no significant difference between groups for the Tegner questionnaire or isokinetic testing.

**Rotator Cuff Repair**
The literature on PRP for rotator cuff repair consists of a number of small double-blind RCTs that have evaluated the efficacy of PRP membrane or matrix combined with surgical repair of the rotator cuff. Most of these studies show no significant benefit of PRP. Pooling of data from these trials shows no statistically or clinically significant benefit of PRP.

For example, a 2013 Cochrane review that pooled data for long-term function from 6 trials of PRP applied with rotator cuff repair showed no statistically or clinically significant differences between the PRP and control groups. A 2015 systematic review included 8 RCTs with sample sizes ranging from 28 to 88 and a combined total of 464 patients. Meta-analysis showed no significant differences between the PRP and control groups in retear rate (relative risk=0.94; p=0.66), Constant score (mean difference, 1.12; p=0.38), or University of California at Los Angeles (UCLA) score (mean difference, -0.68; p=0.32). The strength of the evidence based on GRADE was considered to be low for retear, moderate for Constant score, and low for UCLA shoulder score.

**Spinal Fusion**
No randomized trials on PRP in spinal fusion were identified; however, 2 controlled but not randomized studies found no difference in fusion rates with use of a platelet gel or platelet glue.

**Subacromial Decompression Surgery**
One small RCT used PRP as an adjunct to subacromial decompression surgery. Everts et al reported a rigorously conducted, small (N=40) double-blinded RCT of platelet and leukocyte-rich plasma (PLRP) gel following open subacromial decompression surgery in a carefully selected patient population. Blood was drawn from all patients after induction of anesthesia to maintain blinding. PLRP with autologous thrombin was injected into both the subacromial intracapsular space and the subcutaneous layer covering the incision during wound closure. Postoperative examinations at 1, 2, 4, and 6 weeks were performed by independent evaluators; unique patient identifier codes were used to maintain patient and investigator blinding. Neither self-assessed nor physician-assessed instability were improved. Both subjective pain and use of pain medication were lower in the PLRP group across the 6 weeks of measurements. For example, at 2 weeks after surgery, VAS scores for pain were lower by about 50% in the PLRP group (close to 4 in the control group, close to 2 in the PLRP group), and only 1 patient (5%) was taking pain medication compared with 10 (50%) control patients. Objective measures of range of motion showed clinically significant improvement in the PLRP group across the 6-week
assessment period, while patients reported improvements in activities of daily living such as ability to sleep on the operated shoulder at 4 weeks after surgery and earlier return to work.

**Total Knee Arthroplasty**

One small RCT with 40 patients found no significant differences between the PRP and untreated control groups in bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, Knee Society Scores or Knee Injury and Osteoarthritis Outcome Score.\(^27\)

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in April 2015 identified a large number of ongoing and unpublished trials with PRP. One study that may influence this policy is listed in Table 1.

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<th>NCT No.</th>
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<td>Impact of Platelet Rich Plasma Over Alternative Therapies in Patients</td>
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<td></td>
<td>With Lateral Epicondylitis (IMPROVE)</td>
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NCT: national clinical trial.

**Summary of Evidence**

The evidence base on the efficacy of platelet-rich plasma (PRP) treatment consists of numerous small controlled trials for a wide variety of orthopedic conditions. Recent literature indicates an increasing number of randomized controlled trials (RCTs), and a search of the clinical trials database (available at ClinicalTrials.gov) reveals that many more RCTS are in progress. Current results of PRP trials are mixed, with some trials reporting improvement with PRP and other trials reporting no improvement. It is uncertain whether the mixed results are due to variability in the conditions studied and outcomes measured; to differences in platelet separation technique, concentration or activation; or to differences in the timing and frequency of administration. Additional studies are needed to resolve these issues.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**American Academy of Orthopaedic Surgeons**

The American Academy of Orthopaedic Surgeons (AAOS) 2013 guidelines were unable to recommend for or against growth factor injections and/or PRP for patients with symptomatic osteoarthritis of the knee.\(^28\) A recommendation of inconclusive is based on a single low-quality study and conflicting findings that do not allow a recommendation for or against the intervention. The AAOS recommendation is based on 3 studies that were published before May 2012.
National Institute for Health and Clinical Excellence

In 2009, the U.K.’s National Institute for Health and Clinical Excellence (NICE) issued guidance on use of autologous blood injection for tendinopathy. NICE concluded that the current evidence on the safety and efficacy of autologous blood injection for tendinopathy is inadequate in quantity and quality. NICE recommends this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.

In 2013, NICE issued guidance on use of autologous blood injection (with or without techniques for producing PRP) for plantar fasciitis. NICE concluded that the evidence on autologous blood injection for plantar fasciitis raises no major safety concerns but that the evidence on efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research. In addition, physicians should ensure that patients understand the uncertainty about the procedure's efficacy, be aware of alternative treatments, and be provided with clear written information.

U.S. Preventive Services Task Force Recommendations

Not applicable

Medicare National Coverage

There is no national coverage determination (NCD).

References


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<td>Policy created on the orthopedic applications of platelet-rich plasma that were previously described in Policy No. 2.01.16</td>
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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 18, 2015 and is effective October 15, 2015.

Signature on File
Deborah M. Smith, MD, MPH