Protocol

Orthopedic Applications of Platelet-Rich Plasma

(20198)

Medical Benefit		**Effective Date**: 10/01/15	**Next Review Date**: 07/19
Preauthorization	No	**Review Dates**: 07/15, 07/16, 07/17, 07/18	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With tendinopathy	Interventions of interest are: • Platelet-rich plasma injections	Comparators of interest are: • Nonpharmacologic therapy (e.g., exercise, physical therapy) • Analgesics • Anti-inflammatory agents	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With non–tendon soft tissue injury or inflammation (e.g., plantar fasciitis)	Interventions of interest are: • Platelet-rich plasma injections	Comparators of interest are: • Nonpharmacologic therapy (e.g., exercise, physical therapy) • Analgesics • Anti-inflammatory agents	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With osteochondral lesions	Interventions of interest are: • Platelet-rich plasma injections	Comparators of interest are: • Nonpharmacologic therapy • Analgesics • Anti-inflammatory agents • Surgery	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With knee or hip osteoarthritis	Interventions of interest are: • Platelet-rich plasma injections	Comparators of interest are: • Exercise • Weight loss (if appropriate) • Analgesics • Anti-inflammatory agents • Surgery	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With anterior cruciate ligament reconstruction	Interventions of interest are: • Platelet-rich plasma injections plus orthopedic surgery	Comparators of interest are: • Orthopedic surgery alone	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With hip fracture	Interventions of interest are: • Platelet-rich plasma injections plus orthopedic surgery	Comparators of interest are: • Orthopedic surgery alone	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: • With long bone nonunion	Interventions of interest are: • Platelet-rich plasma injections plus orthopedic surgery	Comparators of interest are: • Recombinant human bone morphogenetic protein-7 plus orthopedic surgery	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: • With rotator cuff repair	Interventions of interest are: • Platelet-rich plasma injections plus orthopedic surgery	Comparators of interest are: • Orthopedic surgery alone	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: • With spinal fusion	Interventions of interest are: • Platelet-rich plasma injections plus orthopedic surgery	Comparators of interest are: • Orthopedic surgery alone	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: • With subacromial decompression surgery	Interventions of interest are: • Platelet-rich plasma injections plus orthopedic surgery	Comparators of interest are: • Orthopedic surgery alone	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: • With total knee arthroplasty	Interventions of interest are: • Platelet-rich plasma injections plus orthopedic surgery	Comparators of interest are: • Orthopedic surgery alone	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity

DESCRIPTION

The use of platelet-rich plasma (PRP) has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. 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.

SUMMARY OF EVIDENCE

Primary Treatment for Tendinopathies

For individuals with tendinopathy who receive PRP injections, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews with meta-analyses. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Findings from meta-analyses of RCTs have been mixed and have generally found that PRP did not have a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Primary Treatment for Non–Tendon Soft Tissue Injury or Inflammation

For individuals with non–tendon soft tissue injury or inflammation (e.g., plantar fasciitis) who receive PRP injections, the evidence includes three small RCTs, multiple prospective observational studies, and a systematic review. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review, which identified three RCTs on PRP for plantar fasciitis, did not pool study findings. Results among the three RCTs were inconsistent. The largest RCT showed that treatment using PRP compared with corticosteroid injection resulted in statistically significant but temporary improvements in AOFAS American Orthopaedic Foot and Ankle Society Ankle-Hindfoot Scale scores, indicating improved outcomes. Confirmation of these results in larger double-blind RCTs would be needed to permit greater certainty on the efficacy of PRP in plantar fasciitis. The evidence is insufficient to determine the effects of the technology on health outcomes.

Primary Treatment for Osteochondral Lesions

For individuals with osteochondral lesions who receive PRP injections, the evidence includes an open-labeled quasi-randomized study. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The quasi-randomized study found a statistically significant greater impact on outcomes in the PRP group than in the hyaluronic acid group. Limitations of the evidence base include lack of adequately randomized studies, lack of blinding, lack of sham controls, and comparison only to an intervention of uncertain efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Primary Treatment for Knee or Hip Osteoarthritis

For individuals with knee or hip osteoarthritis (OA) who receive PRP injections, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Three RCTs have compared PRP with placebo while most trials have compared PRP with hyaluronic acid for knee OA. A meta-analysis of three trials comparing PRP with placebo showed a significant improvement in functional scores. However, only one of the trials was considered at low risk of bias. Comparisons between PRP and hyaluronic acid have shown inconsistent results. A meta-analysis including only low risk of bias trials showed no difference between the two treatments in functional scores. Also, using hyaluronic acid as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for OA is not robust. The single RCT evaluating hip OA reported statistically significant reductions in visual analog scale scores for pain, with no difference in functional scores. Additional studies comparing PRP with placebo and with alternatives other than hyaluronic acid are needed to determine the efficacy

of PRP for knee and hip OA. Studies are also needed to determine the optimal protocol for delivering PRP. The evidence is insufficient to determine the effects of the technology on health outcomes.

Adjunct to Surgery

For individuals with anterior cruciate ligament reconstruction who receive PRP injections plus orthopedic surgery, the evidence includes two systematic reviews of multiple RCTs and prospective studies. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Only one of the two systematic reviews conducted a meta-analysis; it showed that adjunctive PRP treatment did not result in a significant effect on International Knee Documentation Committee scores, a patient-reported, knee-specific outcome measure that assesses pain and functional activity. Individual trials have shown mixed results. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with hip fracture who receive PRP injections plus orthopedic surgery, the evidence includes an open-labeled RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The single open-labeled RCT failed to show a statistically significant reduction in the need for surgical revision with the addition of PRP treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with long bone nonunion who receive PRP injections plus orthopedic surgery, the evidence includes three RCTs. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. One trial with a substantial risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between those who received PRP plus allogenic bone graft and those who received only allogenic bone graft. While the trial showed a statistically significant increase in the proportion of bones that healed in patients receiving PRP in a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. The second RCT, which compared PRP with recombinant human bone morphogenetic protein-7, also failed to show any clinical or radiologic benefits of PRP over morphogenetic protein. The third RCT reported no difference in the number of unions or time to union in patients receiving PRP injections s no treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with rotator cuff repair who receive PRP injections plus orthopedic surgery, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with spinal infusion who receive PRP injections plus orthopedic surgery, the evidence includes two controlled prospective studies. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The two studies failed to show any statistically significant differences in fusion rates between the PRP arm and the control arm. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with subacromial decompression surgery who receive PRP injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. A single small RCT failed to show a reduction in self-assessed or physician-assessed spinal instability scores with PRP injections. However, subjective pain, use of pain medications, and objective measures of range of motion showed clinically significant improvements with PRP. Larger trials are required to confirm these benefits. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with total knee arthroplasty who receive PRP injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The RCT showed no significant differences between the PRP and untreated control groups in bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, or Knee Society Score and Knee Injury and Osteoarthritis Outcome Score. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Use of platelet-rich plasma is considered **investigational** 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
  - Plantar fasciitis
  - Osteochondral lesions
  - Osteoarthritis
- Adjunctive use in the following surgical procedures:
  - Anterior cruciate ligament 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, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of platelet-derived growth factor, transforming growth factors that function as a mitogen for fibroblasts, smooth muscle cells, osteoblasts, and vascular endothelial growth factors. Recombinant platelet-derived growth factor has also been extensively investigated for clinical use in wound healing.

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma (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 various 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 (see the Prolotherapy Protocol). However, prolotherapy differs in that it involves the injection of chemical irritants intended to stimulate inflammatory responses and induce the release of endogenous growth factors.

PRP is distinguished from fibrin glues or sealants, which have been used 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® (Haemacure Corp) are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This protocol does not address the use of fibrin sealants.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Blood products such as PRP are included in these 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, the FDA has not attempted to regulate activated PRP.

A number of PRP preparation systems are available, many of which were cleared for marketing by the FDA through the 510(k) process for producing platelet-rich preparations intended to be mixed with bone graft materials to enhance the bone grafting properties in orthopedic practices. The use of PRP outside of this setting (e.g., an office injection) would be considered off-label. The Aurix System™ (previously called AutoloGel™; Cytomedix) and SafeBlood® (SafeBlood Technologies) are two related but distinct autologous blood-derived preparations that can be used at the bedside for immediate application. Both AutoloGel™ and SafeBlood® have been specifically marketed for wound healing. Other devices may be used during surgery (e.g., Medtronic Electromedics, Elmd-500 Autotransfusion system, the Plasma Saver device, the SmartPReP® [Harvest Technologies] device). The Magellan™ Autologous Platelet Separator System (Medtronic Sofamor Danek) includes a disposable kit for use with the Magellan™ Autologous Platelet Separator portable tabletop centrifuge. GPS®II (BioMet Biologics), a gravitational platelet separation system, was cleared for marketing by FDA through the 510(k) process for use as 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 activated platelets and associated proteins, increasing variability between studies of clinical efficacy.

RELATED PROTOCOLS

Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions

Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non–Orthopedic Conditions

Intra-Articular Hyaluronan Injections for Osteoarthritis

Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Prolotherapy

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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