BlueCross BlueShield of Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Recombinant and Autologous Platelet-Derived Growth Factors as a Primary Treatment of Wound Healing and Other Miscellaneous Conditions

Policy Number: 2.01.16
Origination: 09/1999
Last Review: 09/2014
Next Review: 09/2015

Policy

BCBSKC will provide coverage for platelet-derived growth factors when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Recombinant platelet-derived growth factor (i.e., becaplermin) may be considered **medically necessary** when used as an adjunct to standard wound management for the following indications (for further information on patient selection criteria, see Considerations below.)

- Neuropathic diabetic ulcers extending into the subcutaneous tissue
- Pressure ulcers extending into the subcutaneous tissue

When Policy Topic is not covered

Other applications of becaplermin are considered **investigational**, including, but not limited to, ischemic ulcers, ulcers related to venous stasis, and ulcers not extending through the dermis into the subcutaneous tissue.

Use of autologous blood-derived preparations (i.e., platelet-rich plasma) is considered **investigational**. This includes, but is not limited to, use in the following situations:

- Treatment of acute or chronic wounds including nonhealing ulcers
- Adjunctive use in surgical procedures
- Primary use (injection) for other conditions such as epicondylitis (i.e., tennis elbow), plantar fasciitis, or Dupuytren's contracture

Considerations

This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy 2.01.16.

Becaplermin

Appropriate candidates for becaplermin gel for treatment of neuropathic ulcers should meet ALL of the following criteria:

1. Adequate tissue oxygenation, as measured by a transcutaneous partial pressure of oxygen of 30 mm Hg or greater on the foot dorsum or at the margin of the ulcer
2. Full-thickness ulcer (i.e., Stage III or IV), extending through dermis into subcutaneous tissues
3. Participation in a wound-management program, which includes sharp debridement, pressure relief (i.e., non-weight bearing), and infection control

Appropriate candidates for becaplermin gel for the treatment of pressure ulcers should meet ALL of the following criteria:

1. Full-thickness ulcer (i.e., Stage III or IV), extending through dermis into subcutaneous tissues
2. Ulcer in an anatomic location that can be off-loaded for the duration of treatment
3. Albumin concentration >2.5 dL
4. Total lymphocyte count >1,000
5. Normal values of vitamins A and C

Patients are typically treated once daily for up to 20 weeks or until complete healing. Application of the gel may be performed by the patient in the home.

Becaplermin is available in 2-, 7.5-, and 15-g tubes and is applied in a thin continuous layer, about 1/16 of an inch thick, i.e., the thickness of a dime. The amount of the gel used will depend on the size of the ulcer, measured in square centimeters. However, an average-sized ulcer, measuring 3 cm2, treated for an average length of time of 85 days, will require a little more than one 15-g tube. If the ulcer is treated for the maximum length of time of 140 days, 1.75 of the 15-g tubes would be required.

Autologous Blood-Derived Preparations (i.e., Platelet-Rich Plasma)

In July 2010, a new CPT category III code for **injections** of platelet-rich plasma became effective:
0232T: Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

The instructions issued with the code state that it is not to be reported with codes 20550, 20551, 20600-20610, 20926, 76942, 77002, 77012, 77021 and 86965. Code 0232T includes the harvesting and preparation of the platelet-rich plasma.

For situations other than injection (when 0232T would be reported), no specific CPT codes describe the preparation of autologous blood-derived products but CPT code 86999 (unlisted transfusion medicine procedure) can be used. It has been reported that providers have used CPT code 20926 (tissue graft, other) to describe the overall procedure. It is questionable whether platelet-rich plasma is appropriately considered a tissue graft.

The American Medical Association's Department of Coding instructs that placement of platelet-rich plasma into an operative site is an inclusive component of the operative procedure performed and not separately reported.

Description of Procedure or Service

This policy addresses the use of blood-derived growth factors, including recombinant platelet-derived growth factors and platelet-rich plasma (PRP), as a treatment of wounds or other musculoskeletal conditions, including but not limited to adjunctive use in surgical procedures and treatment of diabetic ulcers, ulcers related to venous stasis, lateral epicondylitis (i.e., tennis elbow), plantar fasciitis, or Dupuytren's contracture.

Background

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors (PDGF), 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, and osteoblasts), and vascular endothelial growth factors. Recombinant PDGF 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 and results in the polymerization of fibrin from fibrinogen, creating a platelet gel. The platelet gel can then be applied to wounds or may be used as an adjunct to surgery to promote hemostasis and accelerate 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 the tissue. PRP has also been proposed as a primary treatment of miscellaneous conditions, such as epicondylitis, plantar fasciitis, and Dupuytren's contracture. Injection of PRP for tendon and ligament pain is theoretically related to prolotherapy (discussed in policy No. 2.01.26). However, prolotherapy 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; Tissel (Baxter) and Hemaseal 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.

Regulatory Status

A recombinant PDGF product, becaplermin gel (Regranex®, McNeil Pharmaceutical) has been approved by the U.S. Food and Drug Administration (FDA). The labeled indication is as follows: "Regranex Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, Regranex Gel increases the complete healing of diabetic ulcers. The efficacy of Regranex Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers has not been evaluated." In 2008, the manufacturer added this black box warning to the labeling for Regranex, "An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of REGRANEX Gel in a post-marketing retrospective cohort study. REGRANEX Gel should only be used when the benefits can be expected to outweigh the risks. REGRANEX Gel should be used with caution in patients with known malignancy."

A number of commercially available centrifugation devices are used for the preparation of platelet-rich plasma. For example, AutoloGel™ (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 Electromedic, 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 the FDA's 510(k) process for a gravitational platelet separation system (GPSII), 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

Recombinant Platelet-Derived Growth Factor (Becaplermin Gel)

Diabetic Neuropathic Ulcers: This policy regarding the use of becaplermin gel was originally based on a 1999 TEC Assessment (1) that concluded that the evidence supports the conclusion that becaplermin treatment, in conjunction with good wound care, improves the health outcomes of patients with chronic neuropathic diabetic ulcers that meet the patient selection criteria defined here. Becaplermin gel plus good wound care resulted in a 43% complete wound-closure rate, compared to 28% for patients treated with good wound care alone. Becaplermin gel also appeared to reduce the average time to complete wound closure.

An industry-sponsored study assessed the effectiveness of recombinant platelet-derived growth factors (PDGF) on diabetic neuropathic foot ulcers in actual clinical practice. (2) Subjects (from a cohort of 24,898 patients in wound-care centers) whose wounds did not heal over an 8-week observation period were eligible for the study and were assessed over a period of 20 weeks or until they healed. Any individual with an open wound who was lost to follow-up was considered unhealed. Of the nearly 25,000 patients treated for foot ulcers, 2,394 (9.6%) received recombinant PDGF. A propensity score method with covariates to statistically model treatment selection was used to adjust for selection bias; results were stratified by 5 propensity score groups. Overall, the rate of healing was 26.5% in the control group and 33.5% in the patients treated with recombinant PDGF. The relative risk, controlling for the propensity to receive PDGF, was 1.32 for healing and 0.65 for amputation (6.4% vs. 4.9%, respectively). Analysis also indicated that those who received PDGF were more likely to be younger, male, and have older wounds, factors not known to affect wound healing. These results support clinical effectiveness of recombinant PDGF for treatment of diabetic neuropathic foot ulcers in actual clinical practice.

Pressure Ulcers: Results of a randomized study focusing on the use of becaplermin gel as a treatment of pressure ulcers was published in 1999. (3) The patient selection criteria for this study are summarized in the Policy Guidelines section but most importantly included full-thickness ulcers and an anatomic location where pressure could be off-loaded during treatment. This latter patient selection criterion may limit the number of patients with pressure ulcers who would be considered candidates for becaplermin therapy. Patients were randomized to 1 of 4 parallel treatment groups and received either a placebo or 1 of 3 doses of becaplermin. All patients received a standardized program of good wound care. In the 2 groups of patients treated with once daily doses of becaplermin (either 100 or 300 µg/g), the incidence of complete healing was significantly improved compared to the placebo group. There was no difference in outcome between the 100 and 300 µg/g group, suggesting that there is no clinical benefit in increasing the dose above100 µg/g. A third group of patients received becaplermin 100 µg/g twice a day. This group did not report an improved outcome compared to placebo, a finding that is unexplained.

Acute Traumatic Wounds: Topical recombinant PDGF has also been investigated for repair of work-related fingertip injuries. One study used alternate assignment to “randomize” 50 patients (fingertip wound area of 1.5 cm or more, with or without phalangeal exposure) to daily treatment with PDGF or surgical reconstruction. (4) Statistical analysis showed that the baseline characteristics of the two groups were similar for patient age, wound area (2.2–2.4 cm), and distribution of fingertip injuries across the digits. Assessment by an independent physician showed that in comparison with the surgical intervention, treatment with recombinant PDGF resulted in faster return to work (10 vs. 38 days, respectively) and wound healing (25 vs. 35 days, respectively) and a reduction in functional impairment (10% vs. 22%, respectively) and need for physiotherapy (20% vs. 56%, respectively). Fingertips treated with PDGF were also reported to have satisfactory esthetic results, while surgically treated fingertips were shorter and often unsightly. These results, if confirmed, could lead to improvement in health outcomes for patients with fingertip injury. However, the present study is limited by the small sample size, the method of randomization, and the potential for investigator bias (although the investigators did blind the examining physician from treatment allocation, the actual treatment may have been obvious). Additional RCTs are needed.

Adverse Effects: Growth factors cause cells to divide more rapidly. It is for this reason that the manufacturer continued to monitor studies begun before Regranex was approved in December 1997 for any evidence of adverse effects, such as increased numbers of cancers. In a long-term safety study completed in 2001, more deaths from cancer occurred in people who used Regranex than in those who did not use it. Following the report of the study completed in 2001, an additional study was performed using a health insurance database that covered the period from January 1998 through June 2003. This study used the database to identify two groups of patients with similar diagnoses, drug use, and use of health services, one of which used Regranex and one group that did not. The results of this study showed that deaths from cancer were higher for patients who were given 3 or more prescriptions for treatment with Regranex than those who were not treated with Regranex. No

single type of cancer was identified, but deaths from all types of cancer combined were observed. In 2008, the U.S. Food and Drug Administration (FDA) concluded that the increase in the risk of death from cancer in patients who used 3 or more tubes of Regranex was 5 times higher than in those patients who did not use Regranex. The risk of getting new cancers among Regranex users was not increased compared to non-users, although the duration of follow-up of patients in this study was not long enough to detect new cancers.

Conclusions: Results from randomized controlled trials show improved rates of healing with use of recombinant platelet-derived growth factor for diabetic neuropathic ulcers and pressure ulcers. The increase in rate of healing must be balanced with the potential for increased risk from cancer. Evidence is insufficient to determine whether becaplermin gel improves health outcomes when used to treat other types of wounds, including ischemic or chronic venous ulcers or acute traumatic wounds.

Autologous Blood-Derived Preparations (i.e., Platelet-Rich Plasma)

The policy on platelet-derived wound-healing formula was originally derived from a 1992 TEC Assessment, (5) which primarily focused on the Procuren process, referred to as a platelet-derived wound-healing formula. This preparation is no longer commercially available. At the present time, there are a large number of devices 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 prior to injection is necessary. (6-10)

Several systematic reviews of the evidence on PRP have been identified.

A 2009 systematic review identified 42 controlled trials on PRP, 20 of these were RCTs and included in the systematic review. (11) The 20 RCTs comprised 11 studies on oral and maxillofacial surgery, 7 on chronic skin ulcers, and 2 on surgery wounds. Four of the 11 studies on oral and maxillofacial (dental) surgery were combined to analyze the efficacy of PRP in patients with chronic periodontitis. The mean effect showed a greater reduction in patients in the PRP group for depth reduction of gingival recession of 0.54 mm. The mean effect for 3 studies assessing the clinical attachment level, was not significant, although the studies were heterogeneous. When only the 2 studies including patients at severe stages were considered, there was a 0.89 mm advantage for the PRP group. Of the 7 RCTs assessing PRP for skin ulcers, 6 could be combined for the measure of complete ulcer epithelialization. The observed relative risk ratio of 1.40 was not significant between the experimental and control groups. Two low-quality RCTs assessed the use of PRP in surgery wounds; both studies tended to favor the PRP group but were not statistically significant. The authors concluded that PRP improved the gingival recession but not the clinical attachment level in chronic periodontitis. Results were inconclusive for the healing of skin ulcers, and there were little safety data. Non-randomized controlled studies were identified, but not reviewed, for chronic elbow tendinosis, muscle strains, lumbar spinal fusions, and other orthopedic procedures. A 2010 systematic review of autologous growth factor injections in chronic tendinopathy found no high-quality studies using PRP. (12)

An industry-funded systematic review included 21 studies on PRP gel for cutaneous wound healing, 12 of which were RCTs. (13) There were 3 main types of wounds, including open chronic wounds, acute surgical wounds with primary closure, and acute surgical wound with secondary closure. Study quality was found to vary considerably, with 3 studies rated as high quality and 6 rated as poor quality. Two additional studies could not be rated because they were published only as an abstract and letter. The primary outcome measure for this meta-analysis was complete wound healing. Overall, results from the RCTs are mixed, i.e. some trials report a benefit but others do not. Of 4 RCTs that evaluated complete healing of chronic wounds, 2 reported a statistically significant benefit for PRP, and meta-analysis of the 4 RCTs showed a significant combined effect of PRP for complete healing of chronic wounds. However, 2 of the 4 studies were rated as low quality and the other 2 could not be rated because they were presented only in abstract or letter form. Meta-analysis could not be conducted for complete healing of acute primary or secondary closure wounds. The meta-analysis of the effect of PRP on complete wound healing of chronic wounds is limited by the inclusion of poor quality studies. There are no high-quality RCTs that show an improvement in complete healing with PRP.

A 2012 systematic review included 23 randomized trials and 10 prospective cohort studies that compared PRP to placebo, corticosteroid, or a standard procedure. (14) 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. 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. No significant benefit of PRP was found for the 6 RCTs or the 3 prospective cohort studies. 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.

Key references on PRP for specific indications are described below.

Achilles Tendinopathy: A single center, randomized, double-blind, placebo-controlled trial of PRP injection in patients with chronic midportion Achilles tendinopathy was reported by de Vos et al. in 2010. (15) 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. The authors conclude that “in patients treated with an eccentric exercise program, a PRP injection compared with saline injection did not result in greater improvement in pain and activity.”

Acute Traumatic Wounds: Kazakos and colleagues reported a prospective controlled study of the treatment of acute traumatic wounds with platelet gel in 59 consecutive patients (27 PRP and 32 controls). (16) Conventional treatment consisted of topical washing and cleaning of the wounds, removal of the necrotic tissue, and dressing with Vaseline gauze every 2 days. In all patients with open tibial fractures, an external fixation system was applied. PRP gel, prepared with specialized tubes and a bench-top centrifuge, was applied to the wounds after surgical debridement and placement of the external fixation system. The time needed for preparation and application of the PRP gel was 52 minutes. PRP gel was then applied to the wounds once weekly in the outpatient clinic until there was adequate tissue regeneration (mean of 21 days) to undergo reconstructive plastic surgery. Control patients receiving conventional treatment required a mean of 41 days for adequate tissue regeneration. Pain scores were significantly lower in the PRP-treated patients at 2 and 3 weeks (VAS score of 58 PRP vs. 80 controls). Although these results are encouraging, additional study with a larger number of subjects is needed.

Anterior Cruciate Ligament (ACL) Reconstruction: Nin and colleagues randomized 100 patients undergoing arthroscopic patellar tendon allograft anterior cruciate ligament reconstruction; platelet-enriched gel was used in one group (n=50), and a non-gel group (n=50) served as control. (17) The use of platelet-derived growth factors (PDGF) 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.

Lateral Epicondylitis (Tennis Elbow): A double-blind randomized trial of PRP for lateral epicondylitis was reported by Peerbooms and colleagues in 2010, with 2-year follow-up reported by Gosens et al. in 2011. (18, 19) One hundred patients with chronic (longer than 6 months) epicondylitis were randomized, 49 to receive corticosteroid injection and 51 to receive PRP injection. Stretching and exercise protocols were followed by each group, and normal sport or recreational activities were allowed as tolerated 4 weeks after injection. Eight patients were lost to follow-up, and their last scores were carried forward. Success was defined as 25% reduction in pain on VAS or Disabilities of the Arm, Shoulder, and Hand (DASH) outcomes measure score after 1 year without a re-intervention. Initially, mean VAS was 70.1 in the PRP-treated patients and 65.8 in the corticosteroid group. DASH scores were 161.3 and 131.2, respectively ($p<0.001$). At 4 and 8 weeks after injection, outcomes on VAS and DASH scores were significantly better in the corticosteroid group. At 12 weeks, between-

group differences were not significant. After 1 year, 73% of PRP and 49% of corticosteroid-treated patients met criteria for success on pain VAS; 73% of the PRP group and 51% the steroid group were successful using DASH outcome measures (P=0.005). At 2 years, both VAS and DASH scores were significantly better in the PRP group (21.3 and 17.6, respectively) compared to the corticosteroid group (42.4 and 36.5). Success on the DASH was achieved by 73% of the PRP group and 39% of the corticosteroid group, while more patients in the corticosteroid group (47% vs. 14%) had deteriorated at 2 years. Additional studies are needed to evaluate PRP in this condition.

Long Bone Nonunion: 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. (20) Inclusion criteria were post-traumatic 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 two homogeneous groups; there were generally similar numbers of tibial, femoral, humeral, ulnar, and radial nonunions in the 2 groups. Following randomization, the patients underwent surgery for nonunion, including bone grafts according to the surgeon's choice (66.6% of rhBMP-7 and 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 13–14% with PRP.

Osteochondral Lesions: 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. (21) At 28-week follow-up, scores on the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale (AHFS) 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: A 2009 report from Europe described a prospective study of intra-articular injection of PRP in 100 consecutive patients affected by chronic degenerative cartilage lesions. (22) Patients had a history of pain or swelling of the knee for at least 4 months and imaging findings on radiograph or magnetic resonance imaging (MR) of degenerative changes in the joint; 58 knees presented with a degenerative chondral lesion, 33 with early osteoarthritis, and 24 had advanced osteoarthritis. Exclusion criteria included systemic disorders, axial malalignment, severe cardiovascular diseases, infections, or immunodepression. Three injections were administered at 21-day intervals. During the treatment period, rest or mild activities such as an exercise bike or mild exercises in a pool were indicated. Gradual resumption of normal sport or recreational activities was allowed as tolerated. Five patients were lost to follow-up, and 4 did not complete treatment (1 patient had swelling after the first treatment). Evaluation was conducted in 91 patients (91% follow-up) before and at the end of the 3 treatments and at 6 and 12 months after treatment. The International Knee Documentation Committee (IKDC) objective score improved from 46% (of normal and nearly normal knees) to 78% at the end of therapy, declining to 67% at 12-month follow-up. The IKDC subjective score improved from 41 to 63 after treatment, with a score of 61 at 12-month follow-up. Treatment was less effective in older, heavier, and more advanced osteoarthritis patients than in younger patients with less severe chondral damage. Controlled studies are needed to evaluate this relatively simple, low cost, and minimally invasive method of applying growth factors.

Plantar Fasciitis: The 2012 systematic review by Sheth et al. identified 3 studies that evaluated the effect of autologous blood injections. (14) No controlled trials have been identified that evaluated the effect of PRP for plantar fasciitis.

Rotator Cuff Repair: Castricini et al randomized 88 patients with a rotator cuff tear to arthroscopic repair without (n=45) or with (n=43) augmentation with platelet-rich fibrin matrix. (23) At average follow-up of 20.2 months (range, 16-30 months), both groups demonstrated statistically significant improvement in the primary endpoint (Constant Scores evaluating pain, activities of daily living, range of movement, and power), but the between-group difference was not significant.

Randelli et al. randomized 53 patients in a double-blind study to activated PRP or to no treatment after arthroscopic rotator cuff repair. (24) VAS pain scores in the PRP group were lower than controls at baseline (4.8 vs. 6.4) through 30 days after surgery (1.1 vs. 2.4). At 3 months after surgery, the PRP group had higher scores on Constant scores (65.0 vs. 57.8) and the Simple Shoulder Test (8.9 vs. 7.1), University of California (UCLA, 26.9 vs. 24.2) and strength in external rotation (3.0 vs. 2.1). There was no difference in functional outcomes between the groups at 6, 12, and 24 months after surgery and no difference in the healing rate measured by magnetic resonance imaging (MRI) at 1 year or more after surgery. This study is limited by the difference in VAS between the groups at baseline.

Spinal Fusion: No randomized trials on PRP in spinal fusion were identified; however, 2 controlled studies found no difference in fusion rates with use of a platelet gel or platelet glue. (25, 26)

Subacromial Decompression Surgery: Everts and colleagues 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. (27) Blood was drawn from all patients after induction of anesthesia to maintain blinding. PLRP with autologous thrombin was injected into both the subacrominal 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 and close to 2 in the PLRP group) and only 1 patient (5%) was taking pain medication compared to 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.

Tonsillectomy: A double-blind RCT assessed the efficacy of PRP following tonsillectomy in 70 children, aged 4 to 15 years of age. (28) The PRP was prepared during the surgery and placed into the tonsil beds of half of the children, where it was directly visible. To compare pain symptoms and recovery, a daily diary was completed by either the patient or family member for 10 days after surgery. A FACES pain scale was used for the children aged 4 to 7 years, while a numbered pain scale was used for children older than 7 years. Diaries from 83% of the patients showed no differences in pain, medication doses, activity, and days eating solid foods between the two conditions.

Wound Closure: A study of PRP applied to saphenous vein harvest sites after wound closure found no difference in the incidence of wound infection or cosmetic result. (29)

Summary

Results from randomized controlled trials show improved rates of healing with use of recombinant platelet-derived growth factor for diabetic neuropathic ulcers and pressure ulcers. Evidence is insufficient to determine whether becaplermin gel improves health outcomes when used to treat other types of wounds, including ischemic or chronic venous ulcers or acute traumatic wounds.

For PRP treatment, there are numerous small controlled trials for a wide variety of conditions. The potential benefit of PRP has been of considerable interest and the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors is apparent. The oldest and most established evidence is in the area of dental surgery, which is outside the scope of medical policy. Recent literature indicates an increasing number of RCTs for other conditions, and a search of the clinical trials database (available online at: www.clinicaltrials.gov) reveals that many more RCTS are in progress. Current results of PRP trials are mixed. A recent systematic review found that a greater proportion of studies reported no benefit from PRP than studies that reported a benefit. It is unknown if 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. Therefore,

PRP as a primary treatment for acute or chronic wounds, or as an adjunct to surgical procedures, is considered investigational.

Practice Guidelines and Position Statements

In 2009, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) issued guidance on use of autologous blood injection for tendinopathy. (30) 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.

References

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Becaplermin for wound healing. TEC Assessments 1999; Volume 14, Tab 5.
2. Margolis DJ, Bartus C, Hoffstad O et al. Effectiveness of recombinant human platelet-derived growth factor for the treatment of diabetic neuropathic foot ulcers. Wound Repair Regen 2005; 13(6):531-6.
3. Rees RS, Robson MC, Smiell JM et al. Becaplermin gel in the treatment of pressure ulcers: a phase II randomized, double-blind, placebo-controlled study. Wound Repair Regen 1999; 7(3):141-7.
4. Senet P, Vicaut E, Beneton N et al. Topical treatment of hypertensive leg ulcers with platelet-derived growth factor-BB: a randomized controlled trial. Arch Dermatol 2011; 147(8):926-30.
5. Freedman BM, Oplinger EH, Freedman IS. Topical becaplermin improves outcomes in work related fingertip injuries. J Trauma 2005; 59(4):965-8.
6. DiGiovanni CW, Lin SS, Baumhauer JF et al. Recombinant human platelet-derived growth factor-BB and beta-tricalcium phosphate (rhPDGF-BB/beta-TCP): an alternative to autogenous bone graft. J Bone Joint Surg Am 2013; 95(13):1184-92.
7. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Growth factors for wound healing. TEC Evaluations 1992; Volume 7, Pages 352-77.
8. Crovetti G, Martinelli G, Issi M et al. Platelet gel for healing cutaneous chronic wounds. Transfus Apher Sci 2004; 30(2):145-51.
9. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg 2004; 114(6):1502-8.
10. Kevy SV, Jacobson MS. Comparison of methods for point of care preparation of autologous platelet gel. J Extra Corpor Technol 2004; 36(1):28-35.
11. Castillo TN, Pouliot MA, Kim HJ et al. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am J Sports Med 2011; 39(2):266-71.
12. Mazzucco L, Balbo V, Cattana E et al. Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, RegenPRP-Kit, Plateltex and one manual procedure. Vox Sang 2009; 97(2):110-8.
13. Sheth U, Simunovic N, Klein G et al. Efficacy of autologous platelet-rich plasma use for orthopaedic indications: a meta-analysis. J Bone Joint Surg Am 2012; 94(4):298-307.
14. Martinez-Zapata MJ, Marti-Carvajal AJ, Sola I et al. Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev 2012; 10:CD006899.
15. Martinez-Zapata MJ, Marti-Carvajal A, Sola I et al. Efficacy and safety of the use of autologous plasma rich in platelets for tissue regeneration: a systematic review. Transfusion 2009; 49(1):44-56.
16. de Vos RJ, van Veldhoven PL, Moen MH et al. Autologous growth factor injections in chronic tendinopathy: a systematic review. Br Med Bull 2010; 95:63-77.
17. Carter MJ, Fylling CP, Parnell LK. Use of platelet rich plasma gel on wound healing: a systematic review and meta-analysis. Eplasty 2011; 11:e38.
18. de Vos RJ, Weir A, van Schie HT et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. JAMA 2010; 303(2):144-9.
19. Moraes VY, Lenza M, Tamaoki MJ et al. Platelet-rich therapies for musculoskeletal soft tissue injuries. Cochrane Database Syst Rev 2013; 12:CD010071.

20. Kazakos K, Lyras DN, Verettas D et al. The use of autologous PRP gel as an aid in the management of acute trauma wounds. Injury 2009; 40(8):801-5.
21. Nin JR, Gasque GM, Azcarate AV et al. Has platelet-rich plasma any role in anterior cruciate ligament allograft healing? Arthroscopy 2009; 25(11):1206-13.
22. Griffin XL, Achten J, Parsons N et al. Platelet-rich therapy in the treatment of patients with hip fractures: a single centre, parallel group, participant-blinded, randomised controlled trial. BMJ Open 2013; 3(6).
23. de Vos RJ, Windt J, Weir A. Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review. Br J Sports Med 2014.
24. Peerbooms JC, Sluimer J, Bruijn DJ et al. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. Am J Sports Med 2010; 38(2):255-62.
25. Gosens T, Peerbooms JC, van Laar W et al. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. Am J Sports Med 2011; 39(6):1200-8.
26. Mishra AK, Skrepnik NV, Edwards SG et al. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. Am J Sports Med 2014; 42(2):463-71.
27. Krogh TP, Fredberg U, Stengaard-Pedersen K et al. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. Am J Sports Med 2013; 41(3):625-35.
28. Griffin XL, Wallace D, Parsons N et al. Platelet rich therapies for long bone healing in adults. Cochrane Database Syst Rev 2012; 7:CD009496.
29. Calori GM, Tagliabue L, Gala L et al. Application of rhBMP-7 and platelet-rich plasma in the treatment of long bone non-unions: a prospective randomised clinical study on 120 patients. Injury 2008; 39(12):1391-402.
30. Mei-Dan O, Carmont MR, Laver L et al. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. Am J Sports Med 2012; 40(3):534-41.
31. Chang KV, Hung CY, Aliwarga F et al. Comparative Effectiveness of Platelet-Rich Plasma Injections for Treating Knee Joint Cartilage Degenerative Pathology: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil 2014; 95(3):562-75.
32. Filardo G, Kon E, Di Martino A et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord 2012; 13:229.
33. Cerza F, Carni S, Carcangiu A et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med 2012; 40(12):2822-7.
34. Kon E, Buda R, Filardo G et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc 2010; 18(4):472-9.
35. de Almeida AM, Demange MK, Sobrado MF et al. Patellar tendon healing with platelet-rich plasma: a prospective randomized controlled trial. Am J Sports Med 2012; 40(6):1282-8.
36. Monto RR. Platelet-Rich Plasma Efficacy Versus Corticosteroid Injection Treatment for Chronic Severe Plantar Fasciitis. Foot Ankle Int 2014.
37. Castricini R, Longo UG, De Benedetto M et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. Am J Sports Med 2011; 39(2):258-65.
38. Rodeo SA, Delos D, Williams RJ et al. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: a prospective, randomized clinical study. Am J Sports Med 2012; 40(6):1234-41.
39. Weber SC, Kauffman JI, Parise C et al. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: a prospective, randomized, double-blinded study. Am J Sports Med 2013; 41(2):263-70.
40. Gumina S, Campagna V, Ferrazza G et al. Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: a prospective randomized study. J Bone Joint Surg Am 2012; 94(15):1345-52.
41. Randelli P, Arrigoni P, Ragone V et al. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. J Shoulder Elbow Surg 2011; 20(4):518-28.
42. Rha DW, Park GY, Kim YK et al. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. Clin Rehabil 2013; 27(2):113-22.
43. Carreon LY, Glassman SD, Anekstein Y et al. Platelet gel (AGF) fails to increase fusion rates in instrumented posterolateral fusions. Spine (Phila Pa 1976) 2005; 30(9):E243-6; discussion E47.
44. Tsai CH, Hsu HC, Chen YJ et al. Using the growth factors-enriched platelet glue in spinal fusion and its efficiency. J Spinal Disord Tech 2009; 22(4):246-50.

45. Everts PA, Devilee RJ, Brown Mahoney C et al. Exogenous application of platelet-leukocyte gel during open subacromial decompression contributes to improved patient outcome. A prospective randomized double-blind study. Eur Surg Res 2008; 40(2):203-10.
46. Sidman JD, Lander TA, Finkelstein M. Platelet-rich plasma for pediatric tonsillectomy patients. Laryngoscope 2008; 118(10):1765-7.
47. Almdahl SM, Veel T, Halvorsen P et al. Randomized prospective trial of saphenous vein harvest site infection after wound closure with and without topical application of autologous platelet-rich plasma. Eur J Cardiothorac Surg 2011; 39(1):44-8.
48. American Academy of Orthopaedic Surgeons. Treatment of osteoarthritis of the knee. 2013. Available online at: http://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf. Last accessed July, 2013.
49. National Institute for Health and Clinical Evidence (NICE). Interventional Procedure Guidance 279: Autologous blood injection for tendinopathy. 2009. Available online at: http://www.nice.org.uk/nicemedia/pdf/IPG279Guidance.PDF. Last accessed April, 2014.
50. National Institute for Health and Clinical Excellence. Autologous blood injection for plantar fasciitis. NICE interventional procedure guidance 437. 2013. Available online at: http://www.nice.org.uk/nicemedia/live/13883/62398/62398.pdf. Last accessed April 2014.
51. CMS Manual System. Autologous blood-derived products for chronic non-healing wounds. CAG-00190R3. 2012. Available online at: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=260. Last accessed April, 2014
52. CMS Manual System. Pub. 100-3 Medicare National Coverage Determinations, July 30, 2004.
53. CMS Manual System. Decision memo on autologous blood derived products for chronic non-healing wounds. CAG-00190R2. 2008. Available online at: https://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=208. Last accessed April, 2014.

Billing Coding/Physician Documentation Information

Becaplermin gel 0.01%, o.5gm (this is a pharmacy benefit)

Additional Policy Key Words

Policy# 2.01.16

Related Topics

N/A

Policy Implementation/Update Information

09/1999 New policy titled Growth Factors for Wound Healing – Becaplermin
09/2000 No policy statement changes.
09/2001 No policy statement changes.
09/2002 No policy statement changes.
09/2003 No policy statement changes.
09/2004 No policy statement changes.
09/2005 No policy statement changes.
09/2006 Policy updated to reflect BCBSA policy 2.01.16. Title changed from Growth Factors for Wound Healing – Becaplermin to Recombinant and Autologous Platelet-Derived Growth Factors as a Primary Treatment of Wound Healing and other Miscellaneous Conditions.
09/2007 Updated policy with reference numbers 9-12 policy statement unchanged
09/2008 No policy statement changes.
09/2009 Updated policy to reflect BCBSA policy 2.01.16. The following was added to the policy statement under the section When Policy Topic is Not Covered: “Autologous blood-derived preparations (i.e., platelet-rich plasma) are considered **investigational** in conjunction with another definitive surgical procedure to promote healing following surgery, such as but not limited to, total joint replacements or tendon repairs.” The following statement was added to the policy statement under the section Considerations: “The injection of the platelet rich plasma by the surgeon during a definitive surgical procedure is considered to be included

	in the surgical package based on the determination of the AMA's CPT Advisors noting that "the American Academy of Orthopaedic Surgeons Global Service Data book specifically states that local infiltration of most agents in included in the surgical procedure performed. Injecting plasma is not any different." Therefore the surgeon's submission of codes for the injection of the platelet rich plasma/tissue transplantation should be denied as subset to the primary procedure on the claim."
09/2010	Policy updated with literature search through September 2009; references 10, 15-21 added. PRP as an adjunct to surgical procedures added as investigational; other policy statements unchanged
09/2011	Updated to reflect BCBSA policy 2.01.16. Policy updated with literature search, reference numbers 11-14, 18, 19, 23, 24 added, policy statements unchanged.
09/2012	Policy updated with literature search through February 2012, references added and reordered; some references removed; policy statements unchanged
06/2013	Policy updated with literature search through March 8, 2013
09/2014	Policy updated with literature review through March 25, 2014; references 6, 19, 22-23, 26, 31, 36, and 48 added and reordered; policy statements unchanged

---