PLATELET-DERIVED GROWTH FACTORS FOR TREATMENT OF WOUNDS

Policy Number: DERMATOLOGY 010.9 T2
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APPLICABLE LINES OF BUSINESS/PRODUCTS

This policy applies to Oxford Commercial plan membership.

NON-COVERAGE RATIONALE

Autologous platelet rich plasma (e.g., Procuren®, AutoloGel®, or SafeBlood®) is unproven for the treatment of wounds.

The better designed studies do not demonstrate that autologous platelet rich plasma such as Procuren, AutoloGel or SafeBlood improves health outcomes in patients with wounds. The remaining studies have design flaws that do not allow confidence in analyzing final study results. The clinical utility of autologous platelet rich plasma remains to be determined in larger well-designed controlled clinical trials comparing their use with standard wound care.

BACKGROUND

Platelet Rich Plasma: Platelet-rich plasma (also known as platelet-enriched plasma, platelet-rich concentrate, autogenous platelet gel, or platelet releasate) is being evaluated as an enhancement for soft-tissue healing by placing supraphysiologic concentrations of autologous platelets at the site of tissue damage. AutoloGel and SafeBlood are autologous preparations in which blood is
drawn from the patient and centrifuged to create platelet-rich plasma that is applied to the wound. Procuren®, an autologous product that has been used as treatment in the past for chronic wound healing, but it is no longer manufactured or commercially available.

**CLINICAL EVIDENCE**

**Platelet Rich Plasma:**
Carter et al. (2011) conducted a systematic review and meta-analysis to evaluate the use of platelet-rich plasma (PRP) for the treatment of cutaneous wounds compared to standard wound care. Twenty-four studies met inclusion criteria. These studies included 3 systematic reviews, 12 randomized controlled trials, 2 prospective cohort studies, 3 prospective comparative studies, and 4 retrospective reviews. The results of the meta-analysis suggested that PRP therapy can positively impact wound healing and associated factors such as pain and infection in cutaneous wounds. Limitations of the studies included heterogeneous patient populations, lack of long-term follow-up, and pooling of data on different types of PFG products and regimens. Several of the studies included in the meta-analysis had conflicting results.

Litmathe et al. (2009) performed a prospective, double-blind study in 44 high-risk patients for wound healing complications (e.g., obesity, diabetes, smokers, peripheral vascular disease, heart failure) after cardiac surgery. The study group was treated with autologous platelet gel (APG). The control group underwent conventional wound treatment. The incidence of major and minor wound complications at the thoracotomy, as well as in the area of saphenous vein harvesting, was not pronounced in either of the groups. The authors concluded that despite promising results in other fields of surgery, APG shows no beneficial effect in high-risk patients undergoing cardiac surgery.

Saad Setta et al. (2011) investigated the efficiency of platelet releasate on the healing of chronic diabetic ulcers in comparison with platelet-poor plasma (PPP). This study included 24 patients with chronic diabetic ulcers. They were systematically randomized into two groups: PRP group (n = 12) and PPP group (n = 12). The results showed that healing in PRP group was significantly faster. The authors concluded that PRP enhances healing of chronic diabetic foot ulcers. These findings require confirmation in a larger study.

Lawlor et al. (2011) evaluated whether incision application of platelet-rich plasma (PRP) decreased postoperative wound complications in vascular surgery patients. A prospective, randomized trial randomized 81 incisions in 51 patients who underwent femoral artery exposure for elective revascularization procedures or endovascular abdominal aneurysm repairs. Using the ASEPSIS wound classification system, the researchers found no difference in incidence of wound infection. Wound complications occurred in 9 (23%) of 40 of PRP group and 9 (22%) of 41 of non-PRP. Severe wound complications developed in 5 (13%) PRP and 6 (5%) of non-PRP. In multivariate analysis, there were no predictors for wound infection. According to the researchers, platelet-rich plasma did not decrease the incidence of groin wound complications in these patients.

A prospective, randomized, controlled, blinded multicenter study initially included 72 patients with diabetic foot ulcers who were treated with autologous platelet-rich plasma gel or control (saline gel). Thirty-two patients were excluded from the final protocol because of protocol violations and failure to complete treatment. Significantly more wounds healed in patients treated with platelet-rich plasma gel (13 out of 16 or 81.3%) than patients treated with control gel (8 out of 19 or 42.1%) (Driver et al., 2006). Study limitations include small sample size, study supported by manufacturer, protocol violations occurring during the study period, and high rate of patient dropouts.

A prospective, randomized, controlled trial was conducted to evaluate autologous platelet concentrate used during blepharoplasty surgery in 33 patients. The study showed that although there were statistically significant differences in edema using autologous platelet gel, trends towards improvement in postoperative ecchymosis and edema were not significant (Vick et al., 2006). Study limitations include small sample size, no external controls, and lack of blinding.
Within a prospective randomized study, Buchwald et al. (2008) evaluated whether intraoperative use of autologous platelet gel on the leg during a coronary artery bypass graft (CABG) could reduce the incidence of postoperative wound healing disturbances. The application group (AG) included 35 patients and was compared to a control group (CG) that also had 35 patients. The platelet gel, as well as the thrombin required to activate the platelets, was prepared from autologous patient blood during the operation. Wound healing was photographically documented after surgery, and the patients were contacted by telephone on day 50 after surgery to obtain information on wound healing status. During the primary clinical stay, no statistically significant differences were recorded in the number of hematomas, postoperative leg swelling, or pain level. Large-area hematomas were less frequent in the application group. In the follow-up 51 days after surgery, 17.6% (6/34) of the patients from the AG and 31.4% (11/35) of the patients from the CG showed leg wound healing disturbances. The investigators concluded that despite optimum application of the autologous platelet gel to the wound, no clinically relevant differences were found between the groups, either during the primary clinic stay or in the follow-up period.

In a controlled study by Stacey et al. (2000), 86 patients with chronic venous ulcers were randomly assigned to receive autologous platelet lysate or placebo. The results of the study demonstrated no major difference in healing outcome between the treatment and control groups.

Kirsner et al. (2010) evaluated 2517 patients with diabetic neuropathic foot ulcers who received advance biological therapies such as Apligraf, Regranex, or Procuren. Advanced biological therapy was used on average within 28 days from the first wound clinic visit. Wounds treated with bilayered living cell therapy (Apligraf) first were 31.2% more likely to heal, and healed faster than wounds first treated with recombinant growth factor therapy and were 40.0% more likely to heal than those first treated with platelet releasate.

Kazakos et al. (2008) conducted a study to assess the benefits of using autologous platelet-rich plasma (PRP) gel in the treatment of acute limb soft tissue wounds. Fifty-nine patients with acute wounds (open fractures, closed fractures with skin necrosis and friction burns) were randomized into two groups. Group A (32 patients) were treated with conventional dressings and Group B (27 patients) were managed with local application of PRP gel. The rate of wound healing rate was significantly faster in Group B at week 1, 2 and 3. The investigators concluded that PRP gel treatment can be a valuable and effective aid in the management of acute trauma wounds. The value of this study is limited by the small sample size.

Almdahl et al. (2010) evaluated if spraying of wounds after open long saphenous vein harvesting with platelet-rich plasma might reduce the frequency of harvest site infections. A total of 140 patients undergoing first-time coronary artery bypass grafting were randomized into two groups of 70 patients. Both groups had standard surgical leg wound closure and care except topical application of platelet-rich plasma as adjunctive treatment in the active treatment group. End points were wound infection and cosmetic result at 6 weeks. The follow-up was 100% complete. Nine patients (13%) in the treatment group and eight (11%) in the control group experienced harvest site infection. The overall cosmetic result was also similar between the groups, but the top score was borderline and more frequent in the treatment group. The investigators concluded that topical application of autologous platelet-rich plasma on vein harvest wounds did not reduce the rate of surgical site infection.

Córdoba-Fernández et al. (2010) analyzed the use of autologous platelet gel in the surgical treatment of ingrown toe nails in a within-patient clinical trial. Thirty-five healthy volunteers (70 feet) underwent surgical treatment for bilateral ingrown hallux nails. Recovery time (days), postoperative pain (analog chromatic scale), and inflammation (digital circumference) at 48 hours postoperative were the outcomes of interest. Recovery time and postoperative pain were less in the experimental group, although the differences of means were not statistically significant. The investigators concluded that local application of APG in surgical ingrown toenail wounds may produce a slight increase in acute inflammatory phase dermal wound healing, but it does not cause a statistically significant reduction in recovery times or postoperative pain.
Villela and Santos (2010) systematically reviewed evidence regarding the use of platelet-rich plasma (PRP) for the topical treatment of chronic leg ulcers. The systematic review of the literature was performed according to the steps recommended by the Cochrane Collaboration with studies published until July 2008. Among 18 selected studies, 7 (39%) of these studies were randomized clinical trials. Five of the seven randomized clinical trials studied ulcers of diabetic etiology. The results of meta-analysis showed that PRP favors the healing process (95% CI: 2.94-20.31). According to the reviewers, the present systematic review and meta-analysis show that there is scientific evidence regarding favorable outcomes of the use of PRP for the treatment of diabetic ulcer. The reviewers stated that the sample size of the studies analyzed was small.

In a Cochrane review, Martinez-Zapata et al. (2012) evaluated whether autologous platelet-rich plasma (PRP) promotes the healing of chronic wounds. Nine eligible randomized controlled trials (RCTs) were included in the review, with a total of 325 participants of whom 44% were women. The median number of participants per RCT was 26 (range 10 to 86). Four RCTs recruited people with mixed chronic wounds (there were participants with wounds caused by more than one etiology and participants who had wounds of several etiologies in the same trial), three RCTs recruited people with venous leg ulcers and two RCTs considered foot ulcers in people with diabetes. The median length of treatment was 12 weeks (range eight to 40 weeks). Only one study was at low risk of bias; three studies were at high risk of bias and the risk of bias was unclear in the remaining studies. The proportion of completely healed chronic wounds was reported in seven RCTs that compared PRP with standard treatment or placebo, with no statistically significant difference between the groups, in diabetic foot ulcers, in venous leg ulcers and in mixed chronic wounds. The total area epithelialized at the end of the intervention was reported in three RCTs of mixed chronic wounds. There was no statistically significant difference among the groups. The percentage of wound area healed was reported in two RCTs of mixed chronic wounds, and results were statistically significant in favor of the PRP group. Wound complications such as infection or necrosis were reported in three RCTs, and there was no statistically significant difference among groups. Adverse effects were reported in three studies and there was no statistically significant difference among study participants treated with PRP and those not given PRP. The authors concluded that there is currently insufficient evidence to suggest that autologous PRP is of value for treating chronic wounds. The authors also concluded that current evidence is based on a small number of RCTs, most of which are either at high or unclear risk of bias. According to the authors, well-designed and adequately powered clinical trials are needed to evaluate the use of autologous platelet-rich plasma for healing of chronic wounds.

A meta-analysis of treatment of chronic diabetic wounds found that platelet releasate, an autologous product, and becaplermin have improved healing rates over standard care, and becaplermin was more effective than platelet releasate after 20 weeks of treatment. Baseline effectiveness for standard care, becaplermin, platelet releasate, and wound care center care were 30.9%, 43.0%, 36.8%, and 35.6% respectively. Data for this meta-analysis was obtained from published clinical trials, meta-analyses, and data on 26,599 patients with wounds (Kantor and Margolis, 2001).

Frykberg et al. (2010) conducted a prospective case series to evaluate how a physiologically relevant concentration of an autologous platelet-rich plasma (PRP) gel affects initial wound healing trajectories of chronic, nonhealing wounds of various etiologies. Using convenience sampling methods, 49 patients with 65 nonhealing wounds (mean duration 47.8 weeks) were prescribed PRP gel. The most common wounds were pressure ulcers (n = 21), venous ulcers (n = 16) and diabetic foot ulcers (n = 14). Mean wound area and volume were 19 cm2 and 36.2 cm3, respectively. Following a mean of 2.8 weeks with 3.2 applications, reductions in wound volume (mean 51%, SD 43.1), area (39.5%, SD 41.2), undermining (77.8%, SD 28.9), and sinus tract/tunneling (45.8%, SD 40.2) were observed. For all wound etiologies, 97% of wounds improved. According to the investigators, the results of this study suggest the application of this PRP gel can reverse nonhealing trends in chronic wounds. These findings require confirmation in a statistically robust randomized controlled trial.
Marquez De Aracena Del Cid et al. (2009) evaluated the efficiency of the subconjunctival application of autologous regenerative factor-rich plasma (RFRP) in a study of 35 patients with different degrees of ocular alkali burns. The patients were classified into moderate and relevance groups according to the severity of the burn. A control group underwent conventional topical medical treatment. A further group was added to the severe chemical burn group, which received autohemotherapy. The clinical evolution of the lesions and the period in which the pathology prevented the patient from working were studied; monitoring was carried out until the patient had healed. In the moderate chemical burns, there was a significant reduction in corneal and conjunctival epithelization times, sick leave duration, and healing time when the patients were treated with RFRP in comparison to the control group. With regard to the severe burns, significant reduction in time to corneal scarring in those treated with RFRP in comparison to traditional treatment was reported. RFRP showed, at least as effective and less side effects than the autohemotherapy. The limitation of this study is small sample size.

Spyridakis et al. (2009) evaluated 52 patients with pilonidal sinus disease who underwent open excision and secondary closure of the surgical wound (n = 22) or additional local postoperative infusion of platelet-derived growth factors (n = 30). Duration of total wound healing and time to return to normal activities were evaluated. Wound-healing rates were much greater for the platelet group. Complete healing of the surgical wound required 24 days for the platelet group while the respective time for the control group was more than 30 days. According to the investigators, the study provides evidence that the use of platelet-derived growth factors directly to the surgical wound enhances the healing process resulting in faster recovery of patients surgically treated for pilonidal sinus disease. Study limitations include lack of blinding or randomization.

A study by Mazzucco et al. (2004) evaluated patients with dehiscent sternal wounds and patients with necrotic skin ulcers who were treated with autologous platelet gel and retrospectively compared with patients having similar lesions but undergoing traditional treatment. In patients with dehiscent sternal wounds, the healing rate and hospital stay were significantly reduced. Patients with necrotic skin ulcers required a shorter time to have surgery. Study limitations include lack of blinding or randomization, use of historical controls, and non-reporting of inclusion/exclusion criteria.

Margolis et al. (2001) conducted a retrospective cohort study of 26,599 patients from the Curative Health Services database who were treated with platelet releasate or standard wound therapy. The authors determined that more diabetic neuropathic foot ulcers treated with platelet releasate healed by 32 weeks than ulcers treated with standard wound therapy (50% versus 41% respectively). The study did not control for glycemic control or microbiologic status of the wound and commencement of treatment was not standardized.

de Leon et al. (2011) investigated clinical outcomes in chronic nonhealing wounds following the short-term use of a platelet-rich plasma (PRP) gel (AutoloGel System). The study design was a large, observational case series using a multicenter registry database (all wounds included), which compared different populations within the database. Thirty-nine centers contributed to the registry. The target population included 285 chronic wounds (patient n = 200). Wound etiologies included diabetic, pressure, or venous ulcer; dehisced, surgical, or traumatic wound; and wounds of other etiologies. Clinical relevance was determined by analyzing outcomes in wounds that responded to treatment. A positive response occurred in 96.5% of wounds within 2.2 weeks with 2.8 treatments. In 86.3% of wounds, 47.5% area reduction occurred, and 90.5% of wounds had a 63.6% volume reduction. The authors concluded that in chronic wounds recalcitrant to other treatments, utilization of PRP gel can restart the healing process. The lack of a comparison group limits the conclusions that can be reached from this study.

In a diabetic inpatient clinical guideline, the National Institute for Health and Clinical Excellence (NICE) recommends that autologous platelet-rich plasma gel and platelet-derived growth factor (PDGF) should not be offered as treatment for diabetic foot problems unless part of a clinical trial (NICE, 2012).
The AutoloGel Process Centrifuge is one of several devices cleared for marketing by FDA for point-of-care preparation of platelet-rich plasma (PRP) from a sample of a patient's blood (see listings under product code JQC for additional devices). However, the AutoloGel System is currently the only autologous PRP product cleared by the FDA specifically for treatment of chronic wounds. See the following Web site for more information:

In April 2003, the FDA approved the use of the GPS™ Platelet Separation Kit. The GPS™ separation kit aids separation of the patient's own blood components by density through the use of the GPS™-Thermo International Equipment Company (IEC) centrifuge. The GPS separation kit permits platelet rich plasma to be rapidly prepared from a small volume of the patient's blood that is drawn at the time of treatment. The GPS Platelet Separation Kit is designed for use in the clinical laboratory or intraoperatively at point of care, for the safe and effective preparation of platelet poor plasma and platelet concentrate from a small sample (50-60 ml) of whole blood. See the following Web site for more information:

**Additional Products**
Platelet-enriched plasma, platelet-rich concentrate, autologous platelet gel, platelet releasate, Magellan® Autologous Platelet Separator, Platelet Separator SmartPReP® Centrifuge System, Fibrinet Autologous Fibrin & Platelet System, CASCADE® Autologous Platelet System, Gravitational Platelet Separation System, Mini GPSII, SmartPReP® 2 APC® system, Vitagel Surgical Hemostat

**APPLICABLE CODES**

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the Member’s plan of benefits or Certificate of Coverage. This list of codes may not be all inclusive.

**Non-Reimbursable CPT Code**

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<th>CPT Code</th>
<th>Description</th>
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<tr>
<td>0232T</td>
<td>Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed</td>
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*CPT® is a registered trademark of the American Medical Association.*

**Non-Reimbursable HCPCS Codes**

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<tr>
<td>G0460</td>
<td>Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment</td>
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<tr>
<td>S9055</td>
<td>Procuren or other growth factor preparation to promote wound healing</td>
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**REFERENCES**

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by the UnitedHealthcare Medical Technology Assessment Committee. [2013T0523G]


POLICY HISTORY/REVISION INFORMATION

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<td>- Updated list of applicable (non-reimbursable) HCPCS codes to reflect quarterly code edits; added G0460 (effective 08/02/2012)</td>
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