Modulation of Wound Response and Soft Tissue Ingrowth in Synthetic and Allogeneic Implants With Platelet Concentrate

Anthony P. Sclafani, MD; Thomas Romo III, MD; Gennady Ukhainsky, MD, DDS; Steven A. McCormick, MD; Jason Litner, MD; Sherwin V. Kevy, MD; May S. Jacobson, PhD

Objective: To evaluate the modulation of wound healing and soft tissue ingrowth in synthetic and allogeneic implants with platelet gel. Attempts to influence wound healing with exogenous growth factors are highly dependent on the timing and dosing of treatment. Platelet gel made from autologous platelet concentrate (PC) and activated with calcium thrombin is increasingly used to enhance healing of surgical and chronic wounds, based on the assumption that proteins found in the blood can promote healing.

Methods: Adult New Zealand white rabbits underwent phlebotomy, and the blood was used to produce nonconcentrated autologous blood clot, platelet-poor plasma (PPP), and PC for each animal. Disks of porous high-density polyethylene (PHDPE) and acellular dermal graft (ADG) were implanted into each animal in a subcutaneous location. Implants of each type were treated with isotonic sodium chloride solution, PPP, PPP followed immediately with PC, or autologous blood clot (by means of manual impregnation). Animals were killed at 2, 7, 14, and 21 days after implantation. Implants were harvested with surrounding soft tissue and examined by means of light microscopy for evidence of acute and chronic inflammatory cells and vascular and fibroblast invasion.

Results: A platelet gel with platelet concentrations averaging 5.8 times greater than those of peripheral blood significantly improved wound healing and soft tissue ingrowth in surgically implanted grafts. Early inflammatory infiltrates were enhanced in PHDPE and ADG implants by PC and autologous blood clot compared with control implants, as evidenced by significantly increased neutrophil and macrophage counts at day 2. Compared with controls, statistically significant increases in fibroblast and endothelial cell counts were noted at day 7 in PC-treated implants (fibroblasts, 61% increase [P<.001] in PHDPE implants and 52% increase [P<.001] in ADG implants; capillaries, 95% increase [P<.05] in PHDPE and 97% increase [P<.001] in ADG implants). Lymphocyte counts were increased by PC in PHDPE and ADG implants (71% [P<.001] and 100% [P<.05], respectively). There were no statistically significant differences in any cell count variables beyond 7 days.

Conclusions: Treatment with PC prepared at 5 times the baseline platelet count significantly accelerated maturation of experimental wounds. By 14 days, the degree and quality of wound cellularity were equivalent among all treatment groups. Rapid wound healing was expected with this surgical model, which was chosen to observe the biological effects on early wound healing of a platelet gel in a noncompromised wound. Treatment with PC may be useful in scenarios in which enhancement and acceleration of early wound healing is desired.

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The natural wound response of the body both removes and deposits material. Debris and necrotic tissue undergo enzymatic and phagocytic debridement, and the wound bed is prepared for the subsequent deposition of reparative tissues. The presence of a foreign body complicates and usually delays this process and establishes a scenario in which a significantly abnormal wound response can occur.

It is well known that the presence of a foreign body in a wound lowers the threshold necessary for wound infection and achieves significant importance with the increasing use of synthetic and biological implant materials. Previous work has described the higher susceptibility to infection of a porous implant before soft tissue ingrowth and incorporation and the increasing tolerance of these porous materials to exposure with increasing soft tissue ingrowth. Similarly, allogeneic implants currently used for soft tissue augmentation and reconstruction also undergo a period of microscopic resorption, followed by incorporation by host fibroblasts, blood vessels, and collagen deposition. If the rapidity and thoroughness of the incorporation of these materials could be manipulated, accelerated, and enhanced, significant clinical improvement would be expected.

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Author Affiliations are listed at the end of this article.
We believe that enhancement of the wound response with various proteins would improve the ultimate viability of synthetic porous implants and the degree of persistence of biologic implants. A previous report from Sabini et al demonstrated the effect of pretreatment of porous high-density polyethylene (PHDPE) (Medpor; Porex Surgical, Newman, Ga) implants with basic fibroblast growth factor or autologous blood clot (ABC) in a rat model. The study showed that a single application of basic fibroblast growth factor induced no increase in collagen deposition or fibroblast invasion of the implant pores, whereas there was a significant effect on these variables in implants manually impregnated with ABC. The cocktail of bioactive growth factors (such as platelet-derived growth factor [PDGF], transforming growth factor β [TGF-β], vascular endothelial growth factor, and epidermal growth factor [EGF]) contained in the clot was thought to be the cause of this effect. We have chosen to examine a proprietary system (Harvest SmartPReP system; Harvest Technologies Corp, Norwell, Mass) for rapidly producing a high concentration of viable platelets and white blood cells that, when activated, have been shown to release elevated concentrations of these proteins. The platelet concentrate (PC) preparation can be used to treat an implant and its recipient bed. It is postulated that this increase in proteins is capable of significantly enhancing soft tissue ingrowth in synthetic implants and biologic porous materials.

Since the original description of fibrin glue prepared using donor plasma, many approaches to tissue adhesives have evolved. Cryoprecipitate-based fibrin glue has yielded promising results, but its use has been limited by the potential for infectious disease transmission. Commercially prepared fibrin sealant products such as Tisseel (Baxter HealthCare Corp, Deerfield, Ill) have greatly reduced but not entirely eliminated this potential. All of these preparations, however, are primarily tissue adhesives and do not significantly enhance the wound response.

Wound healing is a complex process involving a wide variety of cells, proteins, and endogenous factors. All of these proteins are naturally transported to the injury site in the circulating blood and are found specifically in the plasma, white blood cells, and platelets. We postulate that increasing the concentration of these various proteins through increased concentration of platelets and white blood cells in the clot will enhance the healing rate.

Activated platelets release into their local cellular environment many factors such as von Willebrand factor, TGF-β, platelet factor 4, interleukin 1, EGF, and PDGF. Insulin-like growth factor and fibronectin are present in plasma. Platelet-derived growth factor has been shown to modulate fibroblast cell migration and proliferation and is a chemotactant for neutrophils and monocytes. Results of clinical studies have shown that PDGFs have the potential to enhance healing in chronic wounds, and several PDGFs have been shown to be absent in chronic, nonhealing wounds. Topical application of EGF has been reported to enhance epidermal regeneration. Platelet-derived growth factor, EGF, and TGF-β have all been shown to enhance healing in chronic animal wounds. Vascular endothelial growth factor has been shown to participate in angiogenesis by stimulating mitosis of endothelial cells. Fibronectin has also been shown to enhance wound repair.

A clot formed from a platelet-rich gel may be superior to a natural clot in promoting wound healing. The platelet-rich gel produced by the SmartPReP system contains 4 to 6 times more platelets, 3 times more leukocytes, and fewer erythrocytes. Platelets inside this clot are bioactively equivalent to transfusable platelets, and growth factor levels have been shown to increase linearly with platelet concentration. We postulated that the SmartPReP system can produce a product that can enhance wound healing by creating a favorable environment for cell migration and tissue proliferation. We investigated the basic wound-healing processes induced by a PC produced using the SmartPReP system and examined the effect of this system in a biological model. The blood products produced with the SmartPReP system were used to treat subcutaneous implants of nonvascularized synthetic (Medpor) and xenogeneic (AlloDerm; LifeCell Corp, Branchburg, NJ) implants. These materials acted as scaffolding for wound healing. Medpor implants provided an opportunity to view the biological processes induced by the SmartPReP PC in the absence of a biologic matrix, whereas the same processes were examined in the presence of a proteinaceous matrix (AlloDerm).

**METHODS**

**SUBJECTS**

Adult female, ex-breeder New Zealand white rabbits (Hare-Marland, Hewitt, NJ) weighing at least 4.5 kg were habituated for a minimum of 5 days before any treatment. All animals were housed separately and provided with water and rabbit chow ad libitum. Animals were anesthetized before any procedure with intramuscular injections of a mixture of ketamine hydrochloride (100 mg/kg) and xylazine hydrochloride (7.5 mg/kg).

**IMPLANTATION**

The animals’ dorsa were shaved and prepped with a surgical scrub (Techni-Care; Care-Tech Laboratories Inc, St Louis, Mo). Disks of acellular dermal graft (ADG) (AlloDerm), approximately 1 cm thick, and PHDPE ultrathin sheets (Medpor), 0.85 mm thick, were created using sterile 8-mm dermatologic punches. Once created, the ADG disks were rehydrated in 2 sequential baths, and the PHDPE implants in a single bath of 0.9% isotonic sodium chloride solution, unless otherwise specified.

Incisions were made through the skin, approximately 3 to 4 cm from the dorsal midline in 4 separate paraspinal locations on the left and right sides. Blunt dissection beneath the skin was performed to create medial and lateral pockets, each 1.5 cm wide (producing a total of 8 pockets on each side of each animal). The surgical beds were treated as described in the “Experimental Sites” subsection of the “Methods” section, and the implants were treated and placed in the bed. Two implants were placed through each incision, and the implants in each pair were treated identically. The wound was then closed with 4-0 nylon sutures; one cutaneous suture was placed in addition to the deep surface of the wound to ensure separation of each medial and lateral implant.
EXPERIMENTAL SITES
Each animal was implanted with 4 sets of PHDPE implants (right side) and 4 sets of ADG implants (left side). Group 1 implants were soaked/hydrated with isotonic sodium chloride solution only and served as control implants. Group 2 implants were soaked in 2 separate baths of platelet-poor plasma (PPP) before implantation. Group 3 implants were also rehydrated in PPP. The hydrated graft was placed within the wound site and approximately 0.8 mL of PC activated with calcium thrombin in a 10:1 ratio was delivered onto the graft. After 10 seconds, the wound was closed. Excess plasma was expressed from the wound after each application. In group 4 animals, approximately 3 to 4 mL of autologous blood was drawn into a syringe without anticoagulant and expressed into a sterile container where it was allowed to clot. The graft material was then placed in the clotting blood and remained in the clotting blood for at least 3 minutes to allow the blood to impregnate the interstices of each implant before placement.

PREPARATION OF PC AND PPP
After induction of anesthesia, essence of wintergreen was applied to a shaved, prepared dorsal rabbit ear, venipuncture was performed with a 19-gauge needle, and 36 mL of blood was collected into a syringe containing 4 mL of an anticoagulant (anticoagulant citrate phosphate dextrose). Another 3 mL was collected with a separate syringe, placed into a sterile container, and allowed to clot (ABC), and an additional 0.5 to 1.0 mL was transferred into a separate tube for platelet count. The 40 mL of blood–anticoagulant citrate dextrose mixture was centrifuged through a standardized, proprietary process for separation of the blood into platelet-rich plasma and PPP (Harvest SmartPReP system). We used 0.5 to 1.0 mL of the PC for determination of the platelet concentration. The PPP was placed in a separate sterile container to be used for pretreatment of groups 2 and 3 implants. The PC was then placed in 1 side of a double-lumen syringe with a spray tip; the other lumen contained a solution of 1000-U/mL bovine thrombin in 100mM calcium chloride. These were mixed and sprayed in a 10:1 ratio onto the appropriate areas in group 3 implants.

ANIMAL MAINTENANCE
All animals were fitted postoperatively with Elizabethan collars to prevent manipulation of the wound sites. After implantation, pain was controlled with twice-daily subcutaneous injections of buprenorphone (0.02 mg/kg) for the first 2 postoperative days. One milliliter of the combination product, consisting of penicillin G benzathine, penicillin G procain, and procaine hydrochloride (Flo-Cillin) was administered subcutaneously immediately before surgery and again on postoperative day 2. Animals were killed at designated times with a 100-mg intraperitoneal injection of pentobarbital sodium followed by an additional 50-mg intracardiac injection after loss of consciousness.

IMPLANT HARVEST
Animals were divided into 4 time groups. Time A animals were killed 2 days after implantation; time B animals, 7 days after; time C animals, 14 days after; and time D animals, 21 days after.

The animals' backs were shaved and full-thickness samples of skin with any underlying muscle and the implant were removed and preserved in 10% formalin. Thin sections of each implant were stained with hematoxylin-eosin. All specimens were observed at low and high magnification for the presence or absence of acute or chronic inflammatory cells, neovascularization, and fibroblast invasion. The number of cells per high-power field were counted in 3 separate areas in the center of each implant and averaged.

DATA ANALYSIS
Data were analyzed by means of 1-way analysis of variance; a Tukey-Kramer multiple comparisons test was performed in all cases where P<.05 (GraphPad InStat; GraphPad Software Inc, San Diego, Calif). Lowess curve graphs were generated with the use of GraphPad Prism (GraphPad Software).

RESULTS
Four animals died during the study; necropsy results showed that the deaths were unrelated to the experiment. The remaining animals survived until the scheduled killing. Rabbits weighed 4.6 to 5.6 kg; the 40.5 mL of blood withdrawn from each animal thus represented 8.7% to 10.6% of total animal blood volume and not significant blood loss.

Inadequate anticoagulation of the specimen precluded accurate platelet counts in 11 animals. In addition, the results of the platelet counts of whole blood or PC samples in 5 animals were grossly inconsistent with most of the other samples. If these outliers are excluded from consideration, the whole blood platelet count was 304 000±95 000 per microliter, and the PC platelet count was 1 753 000±579 000 per microliter. The PC platelet counts increased to 5.78±0.78 times greater than that of whole blood.

Clinically, all implants became progressively more attached to surrounding tissue peripherally with increasing time. The PHDPE and ADG showed clinical differences between treatment groups at 7 days; little to no difference was seen at later times.

Histologically, increasing tissue ingrowth and fibrous encapsulation were seen in both implant types with increasing time. There were no statistically significant differences in either implant material at any time between controls and implants treated with PPP. When specifically examined for counts of fibroblasts, macrophages/giant cells, capillaries, lymphocytes, and neutrophils, a general temporal sequence was seen; in PHDPE implants, peaks were noted in neutrophil and macrophage counts at 2 days, capillary and lymphocyte counts at 7 days, and fibroblast counts at 14 days. Evaluation of repopulation of ADG was hindered by an increasingly intense lymphocytic infiltrate, which became significantly more intense than that seen in PHDPE implants after 7 days; this infiltrate was also associated with a rise in giant cell counts.

In PHDPE implants, macrophage counts were increased compared with those of controls at 2 days when implants were treated with PC or ABC (86% or 92%, respectively [P<.001]). Similarly, neutrophil counts were significantly increased compared with those of controls at 2 days when treated with PC or ABC (48% [P<.05] or 76% [P<.001], respectively). No differences were noted in these cells after this time point.
Table. Summary of Statistically Significant Histological Data

<table>
<thead>
<tr>
<th>Treatment Cell Type (Postoperative Day)</th>
<th>ABC</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Cell Count, Mean ± SD*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase Compared With Controls, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHDPE Implants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (2)</td>
<td>34.10 ± 8.32</td>
<td>59.90 ± 13.20</td>
</tr>
<tr>
<td>Macrophages/giant cells (2)</td>
<td>12.60 ± 4.03</td>
<td>24.20 ± 4.44</td>
</tr>
<tr>
<td>Fibroblasts (7)</td>
<td>44.33 ± 4.38</td>
<td>55.00 ± 13.73</td>
</tr>
<tr>
<td>Capillaries (7)</td>
<td>21.67 ± 7.47</td>
<td>33.12 ± 20.02</td>
</tr>
<tr>
<td>Lymphocytes (7)</td>
<td>30.33 ± 4.92</td>
<td>37.62 ± 9.75</td>
</tr>
<tr>
<td>ADG Implants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (2)</td>
<td>32.60 ± 9.13</td>
<td>60.20 ± 18.29</td>
</tr>
<tr>
<td>Macrophages/giant cells (2)</td>
<td>11.50 ± 4.14</td>
<td>23.30 ± 5.38</td>
</tr>
<tr>
<td>Macrophages/giant cells (7)</td>
<td>12.88 ± 5.08</td>
<td>16.33 ± 6.80</td>
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<tr>
<td>Fibroblasts (7)</td>
<td>40.88 ± 6.56</td>
<td>53.89 ± 12.24</td>
</tr>
<tr>
<td>Capillaries (7)</td>
<td>17.25 ± 3.33</td>
<td>24.67 ± 10.10</td>
</tr>
<tr>
<td>Lymphocytes (7)</td>
<td>25.62 ± 4.69</td>
<td>44.33 ± 23.55</td>
</tr>
</tbody>
</table>

Abbreviations: ABC, autologous blood clot; ADG, acellular dermal graft; NS, not significant; PC, plasma concentrate; PHDPE, porous high-density polyethylene.

*Indicates average cell counts per high-power field in implants for neutrophils, macrophages/giant cells, capillaries, fibroblasts and lymphocytes treated with isotonic sodium chloride solution (control), ABC, and PC. Data were analyzed with 1-way analysis of variance.

At 7 days, fibroblast and capillary counts were increased compared with those of controls in PHDPE implants when treated with PC (61% [P < .001] and 95% [P < .05], respectively); again, no differences were noted at other time points. Lymphocytes were also statistically more commonly observed in implants treated with PC than in controls at 7 days (increase of 71% [P < .001]) (Table). Treatment with ABC failed to significantly increase fibroblast, capillary, or lymphocyte cell counts at any time.

Evaluation of the ADG implants was impaired by the progressive integration of the implant into adjacent dermis, in addition to the lymphocytic infiltration. Neutrophil and macrophage counts were, however, significantly increased compared with those of controls at 2 days when treated with PC or ABC (neutrophils, 59% [P < .05] or 85% [P < .001], respectively; macrophages, 101% or 108% [both, P < .001], respectively).

At 7 days after implantation and treatment, mean fibroblast, capillary, and lymphocyte cell counts were increased compared with those of controls in PC-treated ADG implants (52% [P < .001], 97% [P < .001], and 100% [P < .05], respectively). Treatment with ABC increased only fibroblast counts at 7 days only (32% [P < .05]) (Table). No statistically significant differences were noted at any other time points.

**COMMENT**

Identification of methods to enhance or hasten wound healing is a goal of significant potential benefit. Wounds in high-risk settings (eg, type 1 diabetes mellitus, tobacco use, previously irradiated tissue, and synthetic implants) would benefit from enhancing early wound healing. Other, more typical wounds would also benefit from accelerating the wound response in terms of minimizing patient discomfort and disability.

The field of human growth factor science has attracted considerable interest, but direct clinical applications have been slow to develop. There is a complex relationship between these growth factors, and application of a particular growth factor at a single time point may not adequately replicate the normal sequence and concentration of growth factors.

When a PC is prepared and activated using thrombin, a number of bioactive factors are released in the wound. These include fibronectin, fibrinogen, thrombospordin, von Willebrand factor, PDGF, TGF-β, vascular endothelial growth factor, platelet-derived angiogenesis factor, and insulinlike growth factor I. The levels of these proteins vary with time, with TGF-β and PDGF peaking early; these factors function as mitogens and chemoattractants for a number of cells, some of which can secrete additional growth factors.

We have examined the effect on wound healing of both components of whole blood processed using the SmartPrep system. These treatments were compared with control treatment (isotonic sodium chloride solution) and ABC, a scenario that represents adding platelets and their attendant proteins (of unclear magnitude) at levels greater than baseline to the graft. These treatments were evaluated in the following 2 settings: wound response in a PHDPE implant and an ADG. In the PHDPE, the implant represents a nonbiologic, avascular scaffold for promotion of granulation tissue, whereas the ADG provides a (predominantly) collagen scaffold for angiogenesis and cellular migration.

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Figure 1. Cellular response curves over time in control wounds and in autologous blood clot (ABC)– (A) and plasma concentrate (PC)–treated (B) porous high-density polyethylene implants. Solid lines indicate experimental values; interrupted lines show control data. HPF indicates high-power field; asterisks, P<.001; and daggers, P<.05.
The formation of the ABC resulted in the natural release of proteins from platelets and white blood cells into the graft environment; these would be supplemented by proteins present in plasma. Because a large volume of whole blood (relative to the volume of the graft) was allowed to clot ex vivo, and the resultant preparation was applied to the grafts, it is reasonable to assume that ABC-treated wounds have concentrations of growth factors slightly higher than those of peripheral blood. The observed difference between ABC (representing some modest increase compared with the baseline level of platelets) and PC (representing a 3.8-fold increase of platelet levels) is consistent with the dose-response study of Haynesworth et al\(^ {16} \) and would argue for the clinical use of consistently high platelet concentrations in PC.

From our results, we see that the general pattern of cellularity in the treated wounds was similar to that of controls. In general, peaks in neutrophil and macrophage counts occurred at 2 days, and capillary counts reached maximum levels at 7 days in PHDPE and ADG implants. Some differences in implant type and treatment existed.

Treatment of PHDPE implants with PPP failed to enhance counts of cellularity at any time. Treatment of PHDPE implants with ABC increased the early neutrophil and macrophage counts. The PC-treated implants also showed significant enhancement in fibroblast, capillary, and lymphocyte counts at postoperative day 7 (Table). The ADG implants showed similar changes; the only additional findings were the increase in fibroblast counts in ABC-treated implants compared with controls and increased giant cell counts in PC-treated implants at 7 days (Table). Of significance was an increasingly intense lymphocytic infiltrate seen in all ADG implants, regardless of treatment. This most likely represents the beginning of a chronic inflammatory reaction to the xenograft and is clearly not due to the treatment. However, superimposed on this response is the effect of PC on ADG at 7 days, a finding similar to that seen in PHDPE implants.

The findings seen in this study confirm that application of ABC or a PC preparation can enhance early wound cellularity. The autologous blood clot contains serum levels of fibrinogen and fibronectin. However, the clot formation resulted in the natural release of proteins from platelets and leukocytes into the graft environment. Because the 3-mL volume of the clot was greater than that of the graft material, the resultant preparation as applied to the grafts contained an excess of these released proteins. It is therefore reasonable to assume that ABC-treated wounds have concentrations of growth factors slightly higher than those of peripheral blood.

The PC also contains baseline serum levels of fibrinogen and fibronectin; however, in our study platelet counts were concentrated to 5.78 times the baseline level. The additional effects seen in PC-treated implants (compared with PPP-treated implants) of increased fibroblast, capillary, and lymphocyte counts can be attributed to the higher platelet concentration. Kevy and Jacobson\(^ {14} \) have shown that levels of vascular endothelial growth factor, PDGF, TGF-\( \beta \), and EGF in platelet release are linearly related to platelet concentration. The application of activated PC provides a uniform increase in PDGF levels and maintains the normal growth factor proportions.

The normal relative peaks in cellular activity were preserved in wounds treated with PC (Figure 1). However, ABC- and PC-treated wounds showed higher peak levels of neutrophils and macrophages at 2 days. Only PC-treated wounds showed statistically significant increases in counts of fibroblasts, capillaries, and lymphocytes at 7 days. All significant differences between treated and untreated implants were lost by postoperative day 14 (Figure 2).
The wounds treated with PC were essentially supercharged during the early wound response, showing significantly enhanced early cellularity. However, the cellularity of the mature wound does not appear to differ significantly from those of untreated controls. These findings are curiously analogous to those of Sandulache et al; these researchers transplanted a variety of autogenic, allogenic, and xenogenic fetal or adult fibroblasts into experimental wounds. They found increased tensile strength compared with control wounds for a number of cell types at days 7 and 14; however, by day 28, no differences were noted compared with controls. In our short-term study, the elevated levels of growth factors in PC (present at the onset of wound healing, ie, at implantation) increased the numbers of cells involved early in the process of wound healing but did not appear to change the phenotype or relative pattern of cellular infiltrate in the wound at day 7; by day 14, there was no difference between control and PC-treated wounds. The growth factors in the PC act in concert (for a greater effect than single growth factor treatment) but at a single point in time. The effect of these growth factors is seen on early wound-healing mediators; at later times (14 and 21 days), the cellular amplification is lost, precluding any runaway, uncontrolled, or neoplastic response. Any long-term effects of these PC growth factors would necessarily be related to their effectiveness in stimulation of other secondary mitogens and chemotactants. Marx et al have shown greater bone density at 6 months after treatment with PC. The precise cause of this long-term benefit is unknown.

The reported trend toward decreased edema and ecchymosis in face-lift flaps treated with PC requires a larger series for further evaluation. It is unclear which cells affected by PC could account for any observed clinical findings. Given the findings presented in this study, we believe that there are clinical scenarios that warrant the use of an activated, high-level PC. Wounds that are known to be at high risk for delayed or impaired healing and those in which uncomplicated healing is imperative may benefit from PC treatment. Wounds in patients with diabetes or peripheral vascular disease and those in which uncomplicated healing is imperative may benefit from PC treatment. Wounds in patients with diabetes or peripheral vascular disease and in the setting of synthetic implants could derive significant benefit from application of PC.

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Author Affiliations: Division of Facial Plastic Surgery (Dr Sclafani) and Departments of Otolaryngology (Drs Ukrainsky, McCormick, and Litner) and Pathology (Dr McCormick), The New York Eye & Ear Infirmary, and Department of Otolaryngology, Manhattan Eye, Ear & Throat Hospital and Lenox Hill Hospital (Dr Romo), New York, NY; Department of Otolaryngology, New York Medical College, Valhalla (Drs Sclafani and Romo); and Center for Blood Research Laboratories, Children’s Hospital (Drs Kevy and Jacobson), and Department of Pediatrics, Harvard Medical School (Dr Kevy), Boston, Mass.

Correspondence: Anthony P. Sclafani, MD, The New York Eye & Ear Infirmary, 310 E 14th St, Sixth Floor, N Bldg, New York, NY 10003 (asclafani@nyee.edu).

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