JECT. 2005;37:381–386
The Journal of The American Society of Extra-Corporeal Technology

Use of Platelet Gel and Its Effects on Infection in Cardiac Surgery

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Abstract: The use of plasmapheresis in cardiac surgery has failed to show an unequivocal benefit. However, the further processing of plasmapheresed blood to obtain a platelet-rich concentrate, termed platelet gel, may reduce patient susceptibility to infection through poorly understood mechanisms related to a combination of platelets, white blood cell content, and expedited wound healing. The purpose of the study was to retrospectively evaluate the incidence wound infections in patients undergoing cardiac surgery. Platelet gel (PG) patients (n = 382) received topical administration of a mixture of platelet concentrated plasma, 10% calcium chloride (5 mL), and bovine thrombin (5000 units). A control group (NoPG, n = 948) operated on concurrently with the treatment group did not receive PG, but otherwise received similar wound care. A historical control (HC, n = 929) included patients operated on before the availability of PG. After Institutional Review Board approval, 20 factors reported in the literature to predispose individuals for increased infection were recorded along with infections classified either as superficial or deep sternal according to the Society of Thoracic Surgeon criteria. All data were obtained from our institutional contribution to the Society of Thoracic Surgeon database. All adult (>19 years of age) patients undergoing cardiac surgery at our institution between October 2002 and June 2005 were included in this study (n = 2259). The incidence of superficial infection was significantly lower in the PG group (0.3%) compared both with the NoPG (1.8%) and HC (1.5%) groups (p < .05). There was a similar relationship found when comparing deep sternal wound infections (PG, 0.0% vs. NoPG, 1.5%; p < .029 and PG vs. HC, 1.7%; p < .01). In conclusion, the application of PG in patients undergoing cardiac surgery seems to confer a level of protection against infection, although the mechanisms of action remain to be elucidated. **Keywords:** platelet gel, cardiac surgery, infection. *JECT. 2005;37:381–386*

Wound infection can be a devastating complication after cardiac surgery. Reoperation, prolonged intensive care unit stay, and increased mortality have been associated with sternal infections, raising the cost of cardiac surgery while decreasing patient quality of life (1,2). The expenditure for a single sternal infection has been estimated in the United States at $20,103 (3). Many surgical interventions have been designed or modified to reduce the incidence of wound complications, but the heterogeneity of this patient population makes their efficacy difficult to predict.

During the past several years, there has been a renewed interest in the application of plasmapheresis in surgery, which has resulted from an increasing knowledge in the area of regenerative medicine with the application of autologous harvested growth factors. The term platelet gel has been used to describe the application of a concentrated platelet-rich plasma fraction to various procedures both within and outside of surgery. The primary clinical applications of platelet gel are an effort to improve wound healing by increasing the availability of specific proteins, called growth factors, which are involved in the migration and proliferation of cells to the site of injury (4). These peptides are contained within the intracellular milieu of platelets, and on activation, are released into the extracellular environment where they upregulate a number of pathways involved in tissue healing. Although there is a paucity of research in the benefits of platelet gel as an anti-infective measure, the theoretical basis for reducing infection is compelling and includes improved wound healing through platelet-derived growth factor release, antimicrobial activity of the residual white blood cells, and the release of antimicrobial peptides by the platelets themselves (5). Therefore, it is not unreasonable to expect that improved wound healing from the release of platelet-derived growth factors would be expected to reduce the

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The senior author has stated that authors have reported no material, financial or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

occurrence of infection in patients undergoing cardiac surgery and serves as the basis for this study.

MATERIALS AND METHODS

After Institutional Review Board approval, three groups were created from all adult (>19 years of age) patients who underwent cardiac surgery at a single tertiary care center (Geisinger Medical Center, Danville, PA). The perioperative and surgical care of these patients was similar with little deviation from standards of care that were established by a single group of four cardiac surgeons. This included similar antibiotic therapy and similar glucose management. The treatment group (PG) consisted of patients that underwent intraoperative plasmapheresis for the production of platelet gel by the phlebotimization of between 120 and 300 mL of whole blood, which was processed by one of the techniques described below. The PG group received a topical administration of a mixture of platelet concentrate, 10% calcium chloride (5 mL), and bovine thrombin (5000 U) to all surgical sites of each patient. For cases involving coronary surgical revascularization, endoscopic vein harvesting was used for the removal of all leg veins while a small number of patients (<3%) had a single radial artery removed performed through an open technique. Platelet gel was administered to the vein and artery harvest sites through dual applicator tips (2–7 in in length) applied liberally to the subcutaneous areas just before skin approximation, and then on the cutaneous incision. Platelet gel was applied to the chest after approximation of the sternal borders with stainless steel wires. The fascia was closed with an additional application of platelet gel, as well as one final coating on the skin. Once applied, the concentrate was undisturbed for a minimum of 2 minutes before proceeding with the successive steps toward closure or the application of dressings.

Two additional patient groups were created. The first consisted of control group (NoPG), which was patients who were operated on concurrently with the treatment group. They received similar wound care and were operated on during the same time period (October 2002 through June 2005). A historical control (HC) group was included to control for the differential use of platelet gel between surgeons. Patients in this group were operated on during an 18-month period immediately before the use of platelet gel. A subgroup of patients from each of these groups was examined for factors reported to predispose individuals to increased risk for wound infection. The primary endpoints for the study included both superficial and deep sternal wound infections, along with the rates of urinary tract and systemic infections. All criteria were defined by the Society of Thoracic Surgeons (STS) database criteria, and the data taken for analysis came from this same source.

Platelet Gel Preparation

Three different commercially available devices were used for the production of platelet gel. All were based around a separation technique that uses a dual-speed centrifuge. The majority of procedures (~70%) were performed using the plasma sequestration kit for the Continuous Autotransfusion System (CATS, Terumo Cardiovascular, Ann Arbor, MI). Fresh whole blood (300 mL) was collected, before skin incision and heparinization, into a 600-mL collection bag to which 60 mL of citrate phosphate dextrose had been added. The blood was processed according to standard operating instructions modified to collect the initial 30 mL of the platelet-rich concentrate from the sequestration process. The platelet-rich concentrate was placed on a platelet rocker and kept at room temperature until application. Of the remaining 30% of procedures, an equal number was performed using either the Smart Prep II Platelet Separator (Harvest Technologies, Plymouth, MA) or the Angel Platelet Separation Device (COBE Cardiovascular, Arvada, CO). When the Smart Prep II system was used, 108 mL of whole blood was collected, whereas 162 mL was collected when the Angel was used. Anticoagulation of the collected blood was similar for both devices with the use of acid citrate dextrose with a whole blood to anticoagulant ratio of 9:1. Standard operating instructions were followed for both Smart Prep II and Angel systems, with 20 mL of platelet concentrate collected from each patient.

Thrombin was used as the agonist for platelet activation and was prepared by reconstituting lyophilized bovine thrombin with 5 mL of 10% $CaCl_2$ within 30 minutes of intended use. The solution was transferred aseptically to the sterile field and placed in a commercial application kit (Micromedics, Minneapolis, MN) along with the platelet concentrate. A dual syringe technique was used with the platelet concentrate drawn into a 10-mL syringe while the bovine thrombin/$CaCl_2$ solution was drawn into a 1-mL syringe. The platelet gel was created by mixing the platelet concentrate with the reconstituted thrombin in a ratio of 10 parts concentrate to 1 part thrombin/$CaCl_2$. Quality assurance of the platelet gel was performed according to the methods described by Stammers et al. (6).

Statistics

All data were loaded onto a personal computer in spreadsheet format. Univariate analysis was conducted using SAS version 8.0 and included chi-square test, Fishers exact test, and two-sample *t* test, where appropriate. Adjustment for error from multiple comparison testing was performed using Bonferroni *p* value adjustments. All tests were two-sided, and statistical significance was accepted at $p \leq .05$.

RESULTS

A total of 2259 patients were included in this study, with 382 patients in the PG group, 948 in the NoPG group, and

929 patients in the HC group. Because of the infrequent occurrence of infection in this patient population, no effort was made to subcategorize patients according to either lesion or operative results. However, a random number of patients were selected from each group for comparison of 20 parameters that have been shown to increase the risk for infection. Results of this comparison are shown in Table 1 and show significant differences in patients undergoing reoperation, surgery distribution among surgeons, operative status, type of procedure, blood product use, or use of internal mammary artery. There were similar incidences of leg (2.2% vs. 2.4% and 2.3%, p = not significant), urinary tract (1.5% vs. 1.7% and 1.7%, p = not significant), and systemic infection (3.0% vs. 2.0% and 2.2%, p = not significant). Because of the design of this study, all patients undergoing cardiac surgery, requiring either the use of the heart lung machine or as a standby in the case of beating heart surgery, were included. Although there was a diverse case mix, there was no difference in the distribution of cases requiring cardiopulmonary (Figure 1).

The platelet yield was determined through quantitative determination of samples in five patients from each of the commercial platelet concentrating systems used in this study. There were no differences in either the platelet yield or the platelet-concentrating effects between any of the devices used (Figure 2).

The incidence of superficial infection was significantly lower in the PG group (0.3%) compared with the NoPG (1.8%) and HC (1.5%) groups ($p < .05$; Figure 3). This was also found when comparing deep sternal wound infections between groups (PG, 0.0% vs. NoPG, 1.5%; $p < .029$ and PG vs. HC, 1.7%; $p < .01$).

DISCUSSION

The reported incidence of wound infection varies widely, which is most likely the result of different inclusion criteria,

Table 1. Demographic and risk factors for sternal infection.

n	Sample size	HC 244	NoPG 297	PG 134
Age	Mean (SD)	65 (13)	64 (13)	64 (14)
	<55 years (%)	50 (20%)	55 (19%)	29 (22%)
	≥75 years (%)	53 (22%)	65 (22%)	33 (25%)
Sex	Male (%)	156 (64%)	192 (65%)	89 (66%)
Pre-op LOS	Mean (SD)	1.3 (2.4)	1.6 (3.2)	1.0 (2.0
	≥4 days (%)	27 (11%)	32 (11%)	11 (8%)
BSA	Mean (SD)	1.94 (0.25)	1.99 (0.25)	2.00 (0.28)
Smoker	Current (%)	28 (11%)	48 (16%)	22 (16%)
	Ever (%)	97 (40%)	131 (44%)	62 (46%)
Diabetic	Yes (%)	66 (27%)	100 (34%)	46 (34%)
	On insulin (%)	17 (7%)	29 (10%)	16 (12%)
Renal failure	Yes (%)	18 (7%)	22 (7%)	11 (8%)
Infectious endocarditis	Yes (%)	15 (6%)	8 (3%)	5 (4%)
Chronic lung disease	Yes (%)	24 (10%)	29 (10%)	10 (7%)
Immunosuppression	Yes (%)	1 (<1%)	0 (0%)	1 (1%)
PVD	Yes (%)	30 (12%)	47 (16%)	22 (16%)
Redo sternotomy	Yes (%)	47 (19%)	22 (7%)	13 (10%)*†‡
Surgeon	A (%)	75 (31%)	118 (40%)	1 (1%)*†‡
	B (%)	54 (22%)	78 (26%)	33 (25%)
	C (%)	56 (23%)	89 (30%)	8 (6%)
	D (%)	59 (24%)	12 (4%)	92 (69%)
Status	Emergent (%)	16 (7%)	7 (2%)	0 (0%)*†‡
	Urgent (%)	40 (16%)	82 (28%)	32 (24%)*†
Type of procedure	No CAB or valve (%)	19 (8%)	16 (5%)	2 (1%)*†‡
	CAB, No valves (%)	58 (24%)	181 (61%)	79 (59%)
	Single valve, No CAB (%)	54 (22%)	34 (11%)	24 (18%)
	CAB and single valve (%)	70 (29%)	42 (14%)	14 (10%)
	Multiple valves, No CAB (%)	29 (12%)	17 (6%)	9 (7%)
	CAB and multiple valves (%)	14 (6%)	7 (2%)	6 (4%)
Number of valves	0 (%)	77 (32%)	197 (66%)	81 (60%)*†‡
	1 (%)	124 (51%)	76 (26%)	38 (28%)
	2 (%)	43 (18%)	24 (8%)	15 (11%)
IMA use	Yes (%)	109 (45%)	196 (66%)	85 (63%)*†‡
Blood product use	Yes (%)	140 (57%)	125 (42%)	63 (47%)*†
Ventilator time ≥48 hours	Yes (%)	32 (13%)	27 (9%)	15 (11%)
Reoperation	Yes (%)	29 (12%)	23 (8%)	8 (6%)

*Overall $p \leq .05$.
†Historical control vs. NoPG $p \leq .05$ (Bonferroni adjusted).
‡Historical control vs. PG $p \leq .05$ (Bonferroni adjusted).
§NoPG vs. PG $p \leq .05$ (Bonferroni adjusted).

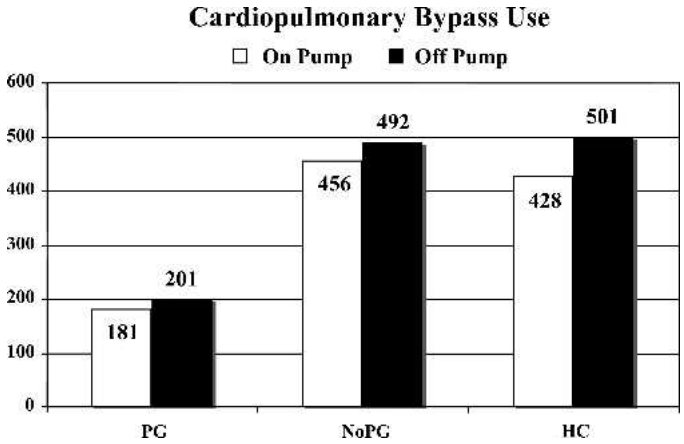

Figure 1. Distribution of cases between groups that required cardiopulmonary bypass. HC, historical control; NoPG, no platelet gel; PG, platelet gel.

different reporting strategies, and different actual occurrences. However, all reports are less than 8%, with most well below 4% (7). Very large sample sizes are required to study outcomes with such low occurrences where the effects of bias and confounding variables may be more pronounced.

Platelets share structural and functional similarities with granulocytes known to participate in antimicrobial host defense. On stimulation by thrombin, platelets release a variety of antimicrobial peptides, including platelet factor 4, RANTES, connective tissue activating peptide 3, platelet basic protein, thymosin β-4, fibrinopeptide B, and fibrinopeptide A (5). Although these peptides have been shown to be effective against a variety of organisms, especially *Escherichia coli* and *Staphylococcus aureus*, the significance of platelet gel application remains to be elucidated. In addition to platelet antimicrobial activity, platelet gel preparations contain leukocytes, typically in baseline or above concentrations, depending on the method of separation (6). These leukocytes also contain growth factors, but perhaps more importantly, have well-known antimicrobial activities.

Expedited healing can potentially reduce the risk of infection. If the wound heals faster, subcutaneous structures are exposed to the environment for a shorter time, reducing the opportunity for an invasion from extrinsic sources. The antimicrobial action of white blood cells and platelets, both found in the platelet gel, may reduce the potential for infection to develop. However, these activities remain theoretical, and the actual clinical impact of application of concentrated and activated platelets remains to be resolved. The purpose of this study was to retrospectively review the occurrence of wound infections after cardiac surgery and the application of platelet gel to wounds created as a result of cardiac surgery.

This study suffers from its design as a retrospective analysis. Furthermore, two of the four surgeons were the primary appliers of this treatment, whereas two used the technique sparingly. However, the perioperative care was similar for all surgeons, and the management of patients in the intensive care unit was achieved according to identical standing orders. Although a prospective randomized trial would be ideal, the ability to conduct one is low, and the number of patients necessary to achieve even a modest reduction in infection rate would be high. The value of observational studies is being appreciated more as funding for larger trials is growing scarce, whereas advanced statistical models are seeing increased use to improve the grade of evidence obtained (8,9). The more advanced statistical techniques require even larger sample sizes, and to accrue the required number of subjects could delay dissemination of results to the point that they become irrelevant. Indeed, the power of the available evidence must be weighed against two factors. The first factor is the clinical mandate of "above all, do no harm." The second factor relates to the mandate from capitated health plans to be fiscally responsible.

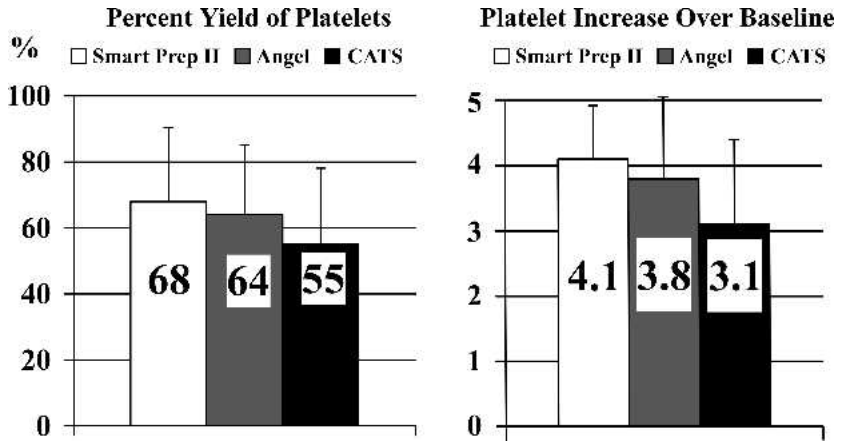

Figure 2. Platelet yield and concentrating effect for the platelet concentrating devices used in this study. Smart prep II, Harvest Technologies; Angel, COBE Cardiovascular; CATS, Terumo Cardiovascular.

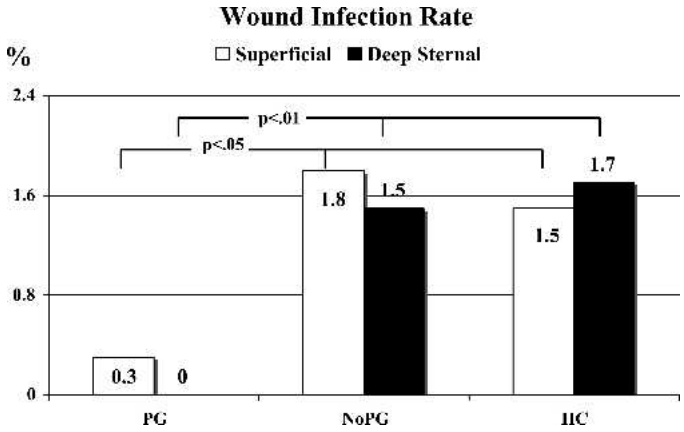

Figure 3. Overall rate of superficial and deep sternal wound infections. HC, historical control; NoPG, no platelet gel; PG, platelet gel.

The relative risk of platelet gel is low compared with the consequences of infections, especially those that involve the sternum. The harvesting of platelets from platelet-rich plasma represents an autologous source of biological agents that can be collected and processed in a point-of-care fashion. The largest potential risk is the use of bovine thrombin. Exposure to topical bovine thrombin during surgery may result in the development of antibodies to multiple protein and carbohydrate antigens (10). Indeed, Schoenecker et al. (11) found that all patients studied ($n = 82$) had antibovine thrombin antibodies, and sensitizing the serum can result in cross-reactivity with other bovine preparations and other xenoantigens, but not with human hemostatic preparations. The authors concluded that bovine thrombin should not be used in patients sensitized by prior exposure to these elements. In addition, life-threatening coagulopathies may develop because of anti-Factor V antibodies, developed from bovine Factor V–contaminated thrombin preparations (12). Although bovine thrombin preparations remain standard today, the development of autologous thrombin preparations should eliminate these potential risks. We are presently involved in the development of autologous thrombin protocols to supplant the use of bovine thrombin.

Economically, platelet gel use in cardiac surgery imposes low additional cost with any of the devices used in this study, with the CATS autotransfusion device being the most economic to use because this device is routinely used for all of our cardiac patients. The addition of plasmapheresis disposables to the main processing kit adds less than $100 to the procedure and yields the added bonus of sequestering some autologous hemostatic components for use at the end of the procedure. However, it did require the most volume to process so it may not be applicable in all patients.

Our interest in plasmapheresis for patients undergoing cardiac surgery developed in the early 1990s (13,14). The process that produced a platelet-rich plasma fraction was summarized in two meta-analyses (15,16). Rubens et al. (15) felt that the procedure was effective in reducing transfusion rates, although the benefit was smaller in the higher-quality studies reviewed (15). Mahoney (16) found that the process saved $2500 to $4400, despite a higher initial expenditure on disposable components. Rubens et al. suggested that further study was needed, but recent data are limited despite increased demands on the blood supply.

The early results of platelet gel application to the sternal wound suggests that our efforts should continue. All three groups were different in terms of risk factors for sternal infection, although the PG and NoPG groups were the most similar. Despite the differences, the actual infection rates were identical in both the HC and NoPG groups but were significantly lower in the treatment group. The application of platelet gel did not confer additional risk or expense sufficient to discontinue the practice and requires further prospective analysis to ascertain its benefit for improving outcomes.

Future studies should include large samples and measures of product quality. Ideally, a consensus can be reached on three main issues: a uniform measure of infections, both superficial and sternal, and potentially wound dehiscence; applicable measures of platelet gel quality should be used (3,6); and a detailed report of any adverse events should be provided. If multiple teams report on sufficiently large samples, meaningful conclusions can be made concerning the use of platelet gel application as an anti-infective strategy. Until those occur, the results of this study provide an intriguing stimulus to continue the use of platelet gel in patients undergoing cardiac surgery.

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