Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes

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BACKGROUND: Platelet (PLT) transfusions are administered in cardiac surgery to prevent or treat bleeding, despite appreciation of the risks of blood component transfusion. The current analysis investigates the hypothesis that PLT transfusion is associated with adverse outcomes associated with coronary artery bypass graft surgery (CABG).

STUDY DESIGN AND METHODS: Data originally collected during double-blind placebo-controlled phase III trials for licensure of Trasylol (aprotinin injection) were retrospectively analyzed. Adverse outcome data of patients (n = 1720) that received, and did not receive, perioperative PLT transfusion were compared. Logistic regression analysis was used to assess the association of perioperative adverse events with PLT transfusion. Propensity scoring analysis was used to verify results of the logistic regression.

RESULTS: Patients receiving PLTs were more likely to have prolonged hospital stays, longer surgeries, more bleeding, re-operation for bleeding, and more RBC transfusions, and less likely to have full-dose aprotinin administration. Adverse events were statistically more frequent in patients that received one or more PLT transfusion. Logistic regression analysis showed that PLT transfusion was associated with infection, vasopressor use, respiratory medication use, stroke, and death. Propensity scoring analysis confirmed the risk of PLT transfusion.

CONCLUSIONS: PLT transfusion in the perioperative period of CABG was associated with increased risk for serious adverse events. PLT transfusion may be a surrogate marker for sicker patients and have no causal role in the outcomes observed. However, a direct contribution to outcomes remains possible.

The lack of evidence-based medicine supporting the transfusion decision is illustrated by the wide range of blood product use in coronary artery bypass grafting surgery (CABG). Use of RBC products ranges from 3 to 83 percent and use of PLTs ranges from 0 to 40 percent of procedures.[1,2] No consensus exists regarding the appropriate use of either RBC transfusion or PLT components.[1,3-5] As a result, physicians make transfusion decisions based upon their past teaching, enculturation, and "clinical judgment."

The risks of allogeneic transfusion extend beyond viral transmission and include allergy, alloimmunization, bacterial sepsis, GVHD, TRALI, renal failure, volume overload, and immunosuppression.[6-10] Indeed, the Advisory Committee on Blood Safety and Availability for the United States Department of Health and Human Services recently identified the three leading causes of transfusion-related

ABBREVIATIONS: CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; KIU = kallikrein-inhibiting units; NYHA = New York Heart Association; ICU = intensive care unit; PLT = platelets.

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fatalities as bacterial contamination of PLTs, hemolysis due to errors, and TRALI.[11]

Approximately 20 percent of CABG patients suffer abnormal bleeding, with PLT dysfunction thought to be the most common cause of this hemorrhage.[1-5,12,13] PLTs are commonly administered after CABG for the prevention or treatment of bleeding.

Aprotinin (Trasylol, Bayer Pharmaceutical Corporation, West Haven, CT) a 56-amino acid, nonspecific serine protease inhibitor is administered as a prophylactic agent to reduce bleeding, transfusion requirements, and the systemic inflammatory response associated with CABG surgery. Clinical evaluation of aprotinin for licensure by the USFDA included six carefully designed, implemented, and monitored studies in patients undergoing primary and reoperative CABG surgery. The combined data from this group of FDA Phase III evaluations represents a unique data set that not only contains information on CABG patients but specifically transfusions, with focus on preoperative risks, intraoperative events, and adverse outcomes. For the current retrospective analysis of these data, we hypothesized that administration of allogeneic PLT transfusions in the perioperative CABG patient independently increased the occurrence of adverse events (death, stroke, myocardial infarction, cardiac dysfunction, pulmonary dysfunction, and infection).

MATERIALS AND METHODS

Data from six randomized, double-blinded, placebo-controlled trials evaluating aprotinin use in CABG surgery were examined. Trials were conducted for licensure of Trasylol in the United States, January 1990 through May 1995 at 37 medical institutions (Denmark, 1; Israel, 2; United States, 34). Data from 37 patients participating in a pilot study were also included. Studies were prospectively randomized, blinded, and designed to collect data on adult patients undergoing either elective primary CABG or reoperation CABG. Patients undergoing valve procedures, combined procedures, or other unique cardiovascular surgeries were not included in the pivotal studies, although 16 patients from the pilot study had valve operation along with CABG. Male and nonpregnant female patients over 18 years of age and willing to give informed consent were included. Patients with a history of bleeding diathesis, with known hematologic abnormality, refusing blood transfusion, or with allergies to either bovine products or aprotinin were excluded. Cardiopulmonary bypass techniques and postoperative intensive care unit (ICU) procedures were those routinely used at each participating institution, as were intra- and postoperative blood conservation techniques. The heparin dose ranged from 300 to 400 IU per kg; the bypass indication for RBC transfusion was a Hct of 18 percent, whereas postoperative RBC transfusion Hct triggers ranged from 21 to 25 percent. Allogeneic blood transfusion was allowed if required by the clinical condition of the patient. Patients chosen for inclusion in this retrospective analysis were those who had received either placebo (saline, n = 861) or the "full-dose" aprotinin regimen (2×10^6 kallikrein-inhibiting units [KIU] intravenously after induction of anesthesia but before sternotomy followed by 5×10^5 KIU/hr for the duration of surgery plus 2×10^6 KIU added to the cardiopulmonary bypass machine pump priming fluid) (n = 859). Patient demographics, cardiac-specific and general medical history, details of surgery, and adverse event information were carefully collected on standardized case report forms. Adverse events were coded using standardized Coding Symbols for a Thesaurus of Adverse Reaction Terms terminology. Concomitant medications were coded using the WHO Drug Dictionary. All data were maintained as SAS data sets and analyzed using software (SAS Institute, Cary, NC).

In this database analysis, eight CABG-related adverse outcomes were examined. Myocardial infarction was defined as either a new Q-wave, development of a new and persistent left bundle branch block (electrocardiograms were read by a blinded independent laboratory), or on postmortem exam. Stroke, clinically identified by the investigator as a new persistent neurological deficit, was defined as any adverse event coding as cerebrovascular accident, cerebral embolism, cerebral hemorrhage, cerebral infarct, or cerebral ischemia. Death was recorded up to 30 days after surgery. Other potential adverse outcomes in cardiac surgery include pulmonary dysfunction, low cardiac output syndrome (congestive failure), and infection. Because definitions of these outcomes were not established per protocol, surrogate markers were determined by the authors. Cardiovascular stability was assessed by examining the use of inotropic, vasopressor, and antiarrhythmic agents administered. Inotrope therapies excluded the nondiscriminating, widely utilized agent dopamine. Persistent pulmonary dysfunction requiring drug therapy was considered to be physiologically driven, in contrast to blood gas analysis and time to extubation, variables possibly driven by institutional protocols. Therefore, pulmonary dysfunction was defined as the utilization of corticosteroids and bronchodilators. Infection was defined by a physician's note (adverse event report) defining a particular infection site (e.g., wound, pus, pneumonia). Urinary tract infections were excluded as they were considered related to technique of catheter insertion.

Continuous demographic and surgical outcome variables were compared between groups (PLTs or not) with a general linear model. Categorical demographic and surgical outcome variables were compared between groups with a logistic model. Both models adjusted for pretreatment with aspirin (yes/no), stratification by surgery (primary vs. reoperation) and study period (early vs. late in

drug development). The occurrence of adverse events and surrogate markers for adverse events were compared in PLT receiving and non-PLT receiving patients. A series of logistic regressions was used to assess the association of PLT transfusion with each of the eight adverse outcomes.

Initial analysis contained covariates for pretreatment with aspirin (yes/no), stratification by surgery (primary vs. reoperation), and study period (early vs. late in drug development), as well as PLT use. Results from these analyses are reported in Table 1.

The next step was to examine the association of pre-, intra-, and postoperative events and medical and personal risk factors with each of the eight adverse outcomes and to see if PLT use was still associated with the adverse outcomes after adjustment for these factors. Potential confounders were chosen based on clinical judgment and included: age, sex, race, weight, history of diabetes, history of unstable angina, previous history of coronary artery disease (CAD), history of hypertension, history of chronic obstructive pulmonary disease (COPD), history of congestive heart failure (CHF), New York Heart Association classification (identified as ≥II [NYHA II], ≥III [NYHA III], ≥IV [NYHA IV]), left ventricular ejection fraction less than 30 percent, left ventricular ejection fraction less than 50 percent, return to surgery for reexploration for surgical bleeding, return to surgery for reexploration for diffuse bleeding, return to surgery for any reason, left ventricular assist device, volume of reinfused shed mediastinal blood, RBC transfusion (yes/no), duration of surgery, total heparin dose, total protamine dose, minimum intraoperative Hct, and minimum intraoperative Hb. Potential confounders were added to the model used for initial analysis using stepwise regression (forward stepping regression with a backward elimination procedure, using an $\alpha = 0.10$).

Because transfusion was not randomly assigned in this patient population, and the concern that multivariate analysis may not adequately control for confounding and bias, selected outcomes were further analyzed using propensity scoring. The propensity for transfusion of PLTs was determined using stepwise logistic regression. All preoperative and intraoperative variables listed above were considered for inclusion. Two-way interactions and squared values of variables were also considered. Variables that remained in the model at the level of p less than 0.10 were then used to calculate a propensity score for each patient. This propensity score represented the probability that a patient would receive a transfusion. Stepwise regression analysis of the outcome variables, using the list of confounders above, was then repeated with just the propensity score forced to remain, to determine independent predictors. Because of the high correlation between use of aprotinin and the need for PLTs, use of aprotinin was included in the stepwise regression to determine propensity, but not in the modeling of adverse outcome. With propensity score and the PLT yes/no variables in the model, the PLT and no-PLT groups compared at a fixed level of propensity for PLT transfusion, akin to establishing comparable groups of patients who did and did not receive PLT transfusions.

TABLE 1. PLT transfusion experience, surgical characteristics, and adverse outcomes in CABG patients

	PLT transfusion		
Variable	Yes	No	p value
Number	284	1436	
Surgical characteristics*			
Thoracic drainage at 6-8 hr (cc)	820 ± 22	329 ± 13	<0.0001
Total thoracic drainage at 24 hr (cc)	2167 ± 86	1028 ± 46	<0.0001
Total heparin dose (IV)	479 ± 11	420 ± 6	<0.0001
Total protamine dose (mg)	371 ± 9	370 ± 5	NS
Intraoperative minimum Hct (%)	21.1 ± 0.3	22.5 ± 0.2	<0.0001
Intraoperative minimum Hb (gm/dL)	7.1 ± 0.1	7.48 ± 0.1	0.005
Reinfusion of shed blood (cc)	468 ± 28	235 ± 16	<0.0001
Full-dose aprotinin administration (%)	6.87	26.1	<0.0001
Length of surgery (hr)	5.0 ± 0.1	4.2 ± 0.1	<0.0001
Time in ICU (days)	5.6 ± 0.2	3.7 ± 0.1	<0.0001
Time in hospital (days)	12.5 ± 0.4	10.3 ± 0.3	<0.0001
Return to surgery for any reason (%)	19.0	2.4	<0.0001
Return to surgery for diffuse bleeding (%)	4.9	0.1	<0.0001
Return to surgery for surgical bleeding (%)	8.8	1.3	<0.0001
Adverse outcomes			
Postoperative infection	18.7	10.9	0.002
Antiarrhythmic agents	50.7	41.7	0.03
Vasopressors	68.7	53.7	<0.0001
Inotropes	54.9	31.8	<0.0001
Respiratory medications	52.5	33.5	<0.0001
Myocardial infarction	8.1	4.1	NS
Stroke	4.2	1.3	0.003
Death	7.7	1.4	<0.0001

* For all surgical characteristics (except return for reoperation), least square mean and standard error are presented. Adjustments for study period (early/late), stratification (primary/reoperative CABG), and pretreatment with aspirin were made. Within the group that received PLTs: primary CABG, n = 181; reoperative CABG, n = 103. Within the group that did not receive PLTs: primary CABG, n = 1203; reoperative CABG, n = 233.

RESULTS

Allogeneic PLT transfusion was administered to 284 of 1720 patients analyzed (14.4%). The distribution of the quantity of PLTs transfused was highly skewed in those patients who received PLTs (1 donor unit, 14.1%; 2-3 units, 6.7%; 4-23 units, 74.3%; >23 units, 4.9%). Unfortunately, the data-recording tool did not always delineate single donor platelet-pheresis units (presumably those with <5-6 units) versus pooled random donor units (those with ≥5-24 units). Gender, weight, and risk factors such as NYHA

TABLE 2. Demographics and medical history with respect to PLT transfusion in CABG patients*

Variable	PLT transfusion Yes	No	p value
Number	284	1436	
Age, years (mean ± SE)	64.9 ± 0.6	62.5 ± 0.3	0.0001
Weight, kg (mean ± SE)	83.1 ± 1.1	85.3 ± 0.6	NS
Male/female (%)	89/11	86/14	NS
Caucasian (%)	87.0	89.8	0.03
Prior myocardial infarction (%)	50.4	44.7	0.002
Unstable angina (%)	48.9	50.3	NS
CAD (%)	43.7	52.2	0.04
Hypertension (%)	42.3	49.2	NS
Noninsulin-dependent diabetes (%)	21.1	21.9	NS
COPD (%)	15.9	11.0	NS
CHF (%)	9.9	6.7	NS
NYHA ≥IV (%)	31.3	24.2	NS
Left ventricular ejection fraction ≤30 (%)	10.5	3.5	0.02

* Adjustments for study period (early/late), stratification (primary/reoperative CABG), and pretreatment with aspirin were made.

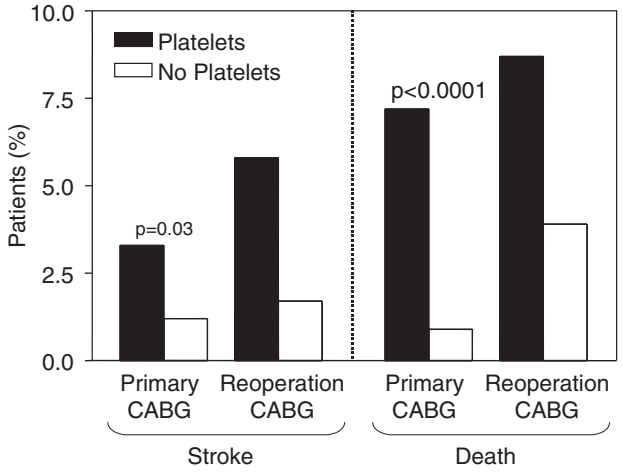

Fig. 1. Univariate association rates of stroke and death with PLT use in primary and reoperative CABG patients.

IV, unstable angina, hypertension, diabetes, a previous history of CAD, COPD, and CHF, were distributed evenly between the groups (Table 2). Adverse outcomes were not concentrated in specific study centers. Patients receiving PLT transfusions were more likely to be older, non-Caucasian, to have an ejection fraction less than 30 percent, no family history of CAD, previous history of CAD, and a prior myocardial infarction. Length of surgery, return for reoperation, chest tube drainage, heparin dose, reinfusion of shed mediastinal blood, days spent in ICU, and days spent in hospital were significantly less in patients who did not receive PLTs (Table 1). Patients who did not receive PLT transfusion were more likely to have been administered full-dose aprotinin. Minimum Hct and minimum Hb levels during surgery were significantly lower in patients who received PLTs. Eighty-eight percent of patients who received PLTs were also transfused with RBCs; patients who received three or more RBC transfusions tended to receive more PLT transfusions (data not shown).

A significant association between the administration of PLT transfusion and incidence of adverse outcomes was observed. Postoperative infection, stroke (Fig. 1), and death rates (Fig. 1) were all significantly higher in patients who were transfused with PLT (Table 1). The percentages of patients having stroke (0 donor units, 1.3%; 1 unit, 7.5%; 2-3 units, 10.5%; 4-23 units, 2.8%; >23 units, 7.0%) or mortality (0 donor units, 1.4%, 1 unit, 2.5%; 2-3 units, 5.3%; 4-23 units, 9.1%; >23 units, 50%) were elevated relative to those who did not receive PLT transfusion irrespective of the number of PLTs transfused. PLT transfusion was not associated with an increased risk of myocardial infarction. It is unclear from this data base if those patients who received 1 to 3 units of PLTs received single-donor PLT units. Therefore, data for total number of PLT units or donor exposures cannot be compared with those who received much larger numbers of units. Significant associations were identified between PLT transfusion and an increase in vasopressor, inotrope, antiarrhythmic, and respiratory medication use.

Stepwise logistic regression analysis adjusting for a number of pre-, intra-, and postoperative operative risk factors that may correlate with the likelihood of needing PLT transfusions was performed. PLT transfusion remained a predictor of postoperative infection, vasopressor utilization, respiratory medication use, stroke, and death (Fig. 2).

Using propensity scoring, the data were further evaluated for the safety risk associated with PLT transfusion, addressing specifically the outcomes of death and stroke. Three percent of patients required the insertion of an intra-aortic balloon pump during surgery. The incidence of death in these patients was much higher than in the rest of the sample, regardless of PLT transfusion. In the subset of patients not requiring intraoperative insertion of an intra-aortic balloon pump, PLT transfusion, as well as female gender, increasing age, previous history of CAD, COPD, or CHF, NYHA class greater than or equal to 4, increasing total heparin, and decreasing total protamine per hour of surgery were independent predictors of death. The risk of death associated with PLT use was significant (OR, 4.76; 95% CI, 1.65-13.73; p = 0.009). Independent predictors of stroke (at a p value of ≥0.05) when propensity score was included in the analysis were PLT use, administration of at least 300 mL of shed mediastinal drainage, female gender, decreasing weight, history of NIDDM, his-

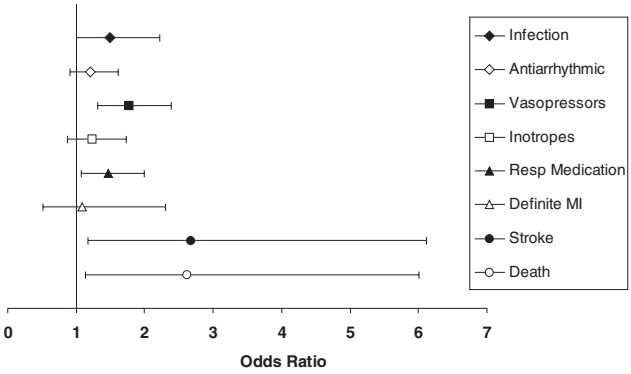

Fig. 2. Multivariate stepwise logistic regression analysis relating adverse outcomes to PLT administration in CABG patients. Data are not adjusted for administration of aprotinin. Association of PLT use and adverse outcomes are depicted with ORs (*x* axis) and 95-percent CIs (error bars). An OR greater than 1 indicates that PLT transfusion is associated with a higher rate of the adverse outcome. CIs that do not span 1 indicate that the association is significant.

tory of COPD, and return to surgery to repair a surgical bleed. The risk of stroke associated with PLT use was clinically meaningful (OR, 2.56; 95% CI, 0.99-6.67; p = 0.054). To remove the possible effects of patients who had excessive bleeding, the propensity score analysis for stroke and death were reanalyzed, removing those patients who returned to surgery for any reason or who received more than 24 PLT units, and very similar results were observed (data not shown).

DISCUSSION

The data show that allogeneic PLT transfusion is associated with a significant increase in the occurrence of critical adverse events in CABG patients. Stroke was at least threefold more likely to occur in patients who received a PLT transfusion. Death was more than five times as likely to occur in patients receiving a PLT transfusion. After adjusting for confounding variables, postoperative infection, use of vasopressors, use of respiratory medications, stroke, and death were still more prevalent in patients who received PLT transfusions.

Surgical procedures were not similar among patients who received PLT transfusion and no-PLT transfusion. Notably, the operation was almost 1 hour longer for patients receiving a PLT transfusion than for those not receiving one. Almost 20 percent of patients who received PLT transfusion returned to surgery for reexploration, whereas those who did not receive PLTs had approximately a 2-percent reoperation rate. Further, the amount of bleeding (thoracic drainage), length of time in the ICU, total hospital stay, and absence of aprotinin use were greater in the PLT transfusion group.

Although the initial FDA trials were randomized for aprotinin and placebo administration, they were not randomized for PLT use. PLT transfusion in these trials was based on independent physician decisions. Accordingly, patients receiving PLTs were more likely to have had a prior myocardial infarction and a poor (<30%) ejection fraction. However, none of the other risk factors analyzed were distributed differently between the two populations. Although these factors are not likely to represent all possible confounders, they were included along with age, gender, and race in multivariable regression outcomes.

The independent relationship of PLT transfusion and adverse events was reinforced by the observation that neither bleeding (thoracic drainage), reoperation for bleeding, nor length of surgery were consistent independent predictors of the same adverse events as PLT transfusion after accounting for other covariates. Despite the strength of the data in the current multivariate analysis, causality still cannot be established without a prospective randomized study because PLT transfusion may simply be a surrogate marker for sicker patients and have no causal role in the outcomes observed. Such a trial in the arena of cardiac surgery is unlikely because PLT transfusion utilization cannot be ethically randomized. Similarly, although increased bleeding, prolonged surgical procedure, and PLT transfusion may exist, cause and effect between these process variables and outcomes cannot be determined. Many patients who received PLTs also received RBC and FFP transfusions. This study does not delineate the relative contribution of each transfusion component upon adverse outcomes. Increased perioperative infection rates associated with PLT transfusion in this study have also been shown to be increased with RBC transfusion and, in particular, allogeneic RBC transfusion.[14,15] Thus, the independent effect of PLT transfusion on postoperative infection rates is not clear. However, a cohort analysis of aspirin use and mortality after CABG surgery indicated that PLT transfusion was associated with a sixfold increase in mortality and reduced in patients who received aspirin.[16] A second cohort study of surgical ICU patients with and without thrombocytopenia, reported that although PLT transfusion failed to restore a normal PLT count, thrombocytopenia, and presumably PLT transfusion, were associated with increased mortality.[17]

A relationship between residual donor WBCs and a purported transfusion-associated immunosuppression has been previously proposed. The studies we analyzed were conducted before the widespread use of leukoreduction technology. Whether our findings would still be observed among patients receiving leukoreduced blood would require additional study.

The use of aprotinin is an important potential confounder in our study. PLT transfusions were used approximately one-third less often in patients receiving full-dose

aprotinin compared to placebo. When analyzed in a model adjusting for aspirin use (yes/no), stratification (primary/reoperative CABG), and study period (early/late), aprotinin appeared to have an independent effect upon stroke.[18] These data, recently supported by an analysis in high-risk patients, suggest that aprotinin has anti-inflammatory effects, which may contribute independently to its effect upon stroke.[19]

This analysis was not the prospective, randomized, and controlled study required to prove that PLT transfusion results in increased adverse events, and, as such, these data may simply indicate that PLT transfusions are a surrogate marker for sicker patients. However, because a full description of the potential adverse effects of transfusion remain uncertain, the current data are sobering and should be taken into account when determining the risk-benefit ratio of PLT transfusion therapy. Our findings support the conservative and targeted use of PLT transfusions.

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