Aprotinin Use in Cardiac Surgery Patients at Low Risk for Requiring Blood Transfusion

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Study Objectives. To determine if aprotinin is safe and effective in patients at low risk for requiring blood transfusion after cardiac surgery by evaluating whether there is any significant difference in blood product use or other significant clinical outcomes between patients who received aprotinin versus those who did not.

Design. Retrospective review.

Setting. Inpatient community nonteaching hospital.

Patients. Three hundred thirty-five patients who underwent primary cardiac surgery involving cardiopulmonary bypass between November 1, 2003, and December 31, 2005, and were considered at low risk for requiring postoperative blood transfusion; 162 patients received aprotinin and 173 patients received aminocaproic acid (control).

Measurements and Main Results. Comparison of patients in the aprotinin group versus those in the aminocaproic acid group revealed no difference in total donor exposures to blood products (1.86 vs 1.16 units/patient, p=0.07), total packed red blood cells (PRBCs) received (1.25 vs 0.86 units/patient, p=0.09), postoperative donor exposures to blood products (0.91 vs 0.48 unit/patient, p=0.13), or postoperative PRBCs received (0.61 vs 0.40 unit/patient, p=0.23). No difference was noted in any other clinical outcome in the aprotinin group versus the aminocaproic acid group, including postoperative azotemia (13.0% vs 10.4%, p=0.46), new onset of atrial fibrillation (14.8% vs 15.0%, p=0.95), myocardial infarction, stroke, or death. Mean ± SD total hospital length of stay was similar in the aprotinin group versus the aminocaproic acid group (8.1 ± 3.8 vs 7.4 ± 2.8 days, p=0.08), but length of stay from surgery to discharge was longer in the aprotinin group than in the aminocaproic acid group (5.9 ± 0.17 vs 5.4 ± 0.12 days, p=0.032).

Conclusion. Although aprotinin appeared to be safe in this low-risk patient population, it was not more effective than aminocaproic acid in reducing blood product use after cardiac surgery. More robust evidence is needed from a controlled randomized trial to demonstrate the safety, efficacy, and pharmacoeconomic benefit of aprotinin.

Key Words: Aprotinin, blood transfusion, cardiac surgery, cardiopulmonary bypass, open-heart surgery.

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Postoperative bleeding is a common complication of cardiac surgery and can require transfusion of homologous blood products, including packed red blood cells (PRBCs), plasma, and platelets. An estimated 10% of blood use in the United States is attributable to cardiac surgery.[1–3] Aprotinin is a serine protease inhibitor with antifibrinolytic and antiinflammatory effects. It

is most often used to prevent postoperative blood transfusions in patients undergoing complex cardiac operations or repeat cardiac surgeries. Although a recent controversy regarding its safety has emerged, aprotinin has generally been considered safe and effective in minimizing postoperative blood loss.[4–7] It has also been postulated that the antiinflammatory properties of aprotinin may contribute to beneficial effects, including cerebral protection and reduction in postoperative stroke.[4, 5, 8–10] It remains unclear, however, if routine use of aprotinin in all cardiac surgery patients is justified when considering the efficacy, safety, and cost-effectiveness of this drug.

Aminocaproic acid, another agent with antifibrinolytic and possibly antiinflammatory effects, is a relatively inexpensive alternative to aprotinin. This synthetic derivative of lysine inhibits fibrinolysis by blocking the lysine binding site on plasminogen, thus preventing formation of plasmin. In a small number of trials, aminocaproic acid has been shown to reduce postoperative blood loss and transfusion requirements.[11] The superiority of aprotinin over aminocaproic acid has not been established; however, more clinical evidence supports the safety and efficacy of aprotinin versus aminocaproic acid as an agent for blood conservation in patients undergoing cardiac surgery.

Nearly all heart centers engage in efforts at blood conservation. Patient characteristics that predict a heightened likelihood of receiving a blood transfusion include preoperative anemia, low body mass index, low red blood cell volume, recent use (within 5 days) of clopidogrel, and requirement for complex procedures, such as combined valve and coronary bypass operations and urgent or emergent surgery.[1, 12–14] Although these characteristics are useful in identifying high-risk patients, the risk of coagulopathy and bleeding cannot be predicted with precision. Some have advocated the use of aprotinin for all patients whose cardiac surgery involves cardiopulmonary bypass, given its potential neuroprotective and hemostatic effects.

In this study, we evaluated a group of patients at low risk for postoperative blood transfusion who received either aprotinin or aminocaproic acid. Our objective was to determine if aprotinin is safe and effective by evaluating whether there is any significant difference in blood product use or other significant clinical outcomes between patients who received aprotinin versus those who did not.

Methods

Approximately 300 cardiac surgeries are performed yearly at Community Medical Center (Scranton, PA) by two cardiothoracic surgeons. For all patients undergoing cardiac surgery, information regarding their preoperative characteristics, surgery techniques, processes of care, and postoperative outcomes are recorded in a computerized database using MIDAS software (ACS Healthcare Solutions, Tucson, AZ). We retrospectively analyzed 742 patients undergoing cardiac surgery involving cardiopulmonary bypass between November 1, 2003, and December 31, 2005, and identified 335 patients considered at low risk for requiring postoperative blood transfusion based on preoperative characteristics. Patients were considered to be at low risk if they were undergoing isolated first-time coronary artery bypass grafting (CABG) or CABG plus another surgical procedure that did not add significantly to the duration or complexity of surgery. These other surgical procedures were ligation of the left atrial appendage, transmyocardial laser revascularization, and atrial fibrillation ablation.

Patients were excluded from the analysis if they had undergone valve or aortic surgeries, urgent or emergent operations, or repeat cardiac surgeries. Other exclusion criteria were preoperative hemoglobin concentration below 12 g/dl, use of clopidogrel within 5 days before surgery, elevated international normalized ratios in patients receiving warfarin, and end-stage renal disease requiring dialysis.

The 335 patients identified as low risk for requiring postoperative blood transfusions were divided into two groups: those who received aprotinin and those who did not. All patients not receiving aprotinin were administered aminocaproic acid. This retrospective review covered a time period when our institution made the transition from using aprotinin exclusively in patients considered to be at high risk for bleeding

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Table 1. Baseline Characteristics

Characteristic	Aprotinin Group (n=162)	Control Group (n=173)	p Value
	No. (%) of Patients		
Female	29 (17.9)	44 (25.4)	0.08
Underlying chronic kidney disease	11 (6.8)	3 (1.7)	0.02
Diabetes mellitus	57 (35.2)	59 (34.1)	0.83
	Mean		
Age (yrs)	65.95	63.7	0.05
Preoperative hemoglobin level (g/dl)	13.82	13.98	0.19
Preoperative creatinine level (mg/dl)	1.12	0.99	0.05
Body mass index (kg/m^2)	29	30	0.07
Red blood cell volume (ml)[a]	2657	2745	0.20

[a]Red blood cell volume was estimated as follows: 75 ml x weight (kg) x hematocrit for men, and 65 ml x weight (kg) x hematocrit for women.

to providing full-strength aprotinin to all patients undergoing cardiac surgery involving cardiopulmonary bypass. Aprotinin was administered as a loading dose of 280 mg (2 million Kallikrein Inhibitor Units [KIU]) before the start of cardiopulmonary bypass, followed by 280 mg (2 million KIU) added to the cardiopulmonary bypass circuit, followed by continuous intravenous infusion of 70 mg/hour (500,000 KIU/hr) during bypass. This form of aprotinin dosing is known as the full Hammersmith regimen. All patients undergoing elective cardiac surgery at our institution receive aspirin preoperatively. With the exception of our institution's change in aprotinin use, the two groups were treated by the same personnel using a transfusion protocol and similar processes of care during the time period under evaluation.

Outcomes recorded included total donor exposures to blood products/patient and number of postoperative donor exposures to blood products/patient. A donor exposure was defined as either 1 unit of PRBCs, 1 unit of fresh frozen plasma (FFP), or 1 unit of pheresed platelets (no pooled platelet transfusions were used at our institution during this study). Other clinical outcomes recorded were postoperative azotemia, myocardial infarction, stroke, new-onset atrial fibrillation, length of hospital stay, discharge disposition of the patient, and mortality. Azotemia was defined as a serum creatinine level greater than or equal to 1.7 mg/dl at any time postoperatively, regardless of preoperative creatinine level. Myocardial infarction was defined as the presence of new Q waves or loss of R waves, together with an elevation of the creatine kinase–myocardial band (CK-MB) isoenzyme fraction to greater than 30 times normal and a new wall motion abnormality on echocardiography. Stroke was defined as a clinically apparent new neurologic deficit as determined by a neurologist, together with new radiologic evidence of ischemia or an infarct on computed tomography of the head. New-onset atrial fibrillation was defined as the detection of atrial fibrillation by continuous telemetry monitoring for more than 60 seconds at any time during postoperative hospitalization in a patient who did not have atrial fibrillation before surgery. Length of hospital stay was represented two ways. Total length of stay was defined as number of days from admission to discharge. Surgical length of stay was the number of days from surgery until hospital discharge. The discharge disposition was defined as home with or without a home health referral, or transfer to a rehabilitation or skilled nursing unit.

All patients gave informed consent for the surgical procedure itself, as well as for recording of clinical data. This study was approved by the institution's investigational review board.

Statistical Analysis

Nonparametric baseline characteristics and clinical outcomes were assessed using the χ^2 test, and parametric data were assessed using a 1-way analysis of variance. A p value of less than 0.05 was considered to indicate a statistically significant difference for all tests. All statistical analyses were conducted using SPSS software, version 14.0 (SPSS Inc., Chicago, IL).

Results

During the 2-year time period of this study, 45% (335/742) of all patients undergoing

Table 2. Use of Blood Products

Variable	Aprotinin Group (n=162)	Control Group (n=173)	p Value
Total donor exposure	1.86 ± 4.65	1.16 ± 1.96	0.07
Total PRBC	1.25 ± 2.86	0.86 ± 1.24	0.09
Total platelets	0.25 ± 0.83	0.10 ± 0.52	0.05
Total FFP	0.36 ± 1.25	0.21 ± 0.77	0.18
Postoperative donor exposure	0.91 ± 3.48	0.48 ± 1.10	0.13
Postoperative PRBC	0.61 ± 2.17	0.40 ± 0.81	0.23

Data are mean ± SD units/patient.
PRBC = packed red blood cells; FFP = fresh frozen plasma.

cardiopulmonary bypass were classified as low risk for requiring blood transfusions based on the inclusion criteria. There were 162 patients in the aprotinin group and 173 patients in the aminocaproic acid (control) group. Baseline characteristics for the two groups are provided in Table 1. The groups were similar with respect to sex, age, preoperative hemoglobin level, diabetes mellitus, body mass index, and estimated red blood cell volume. In addition to age and body mass index, the estimated red blood cell volume is a reliable predictor of transfusion requirements.[13] The only significant difference between the groups was underlying renal insufficiency, present in 6.8% of patients in the aprotinin group compared with 1.7% of patients in the control group (p=0.02). This characteristic is assessed preoperatively in all patients and is based on documentation of renal insufficiency in the physician's history and physical or consultation notes, or a baseline serum creatinine level of greater than 1.7 mg/dl. The mean preoperative creatinine level was 1.12 mg/dl in the aprotinin group compared with 0.99 mg/dl in the control group (p=0.05).

The use of blood products for the two groups is summarized in Table 2. There were no statistically significant differences between the groups with regard to total donor exposure (intra- and postoperative exposures) or use of individual blood components. Mean donor exposure in the aprotinin group was 1.86 units/patient, compared with 1.16 units/patient in the control group (p=0.07). Mean postoperative donor exposure was 0.91 unit/patient in the aprotinin group and 0.48 unit/patient in the control group (p=0.13). Patients in the aprotinin group received an average of 0.61 unit/patient of PRBCs in the postoperative period compared with 0.40 unit/patient in the control group (p=0.23).

Intraoperative factors were similar for the two groups. Mean aortic cross-clamp times were 63.2 minutes/patient in the aprotinin group and 61.8 minutes/patient in the control group (p=0.50), mean cardiopulmonary bypass times were 95.2 minutes/patient in the aprotinin group and 92.4 minutes/patient in the control group (p=0.33), and internal mammary arteries were used in 91.3% of patients in the aprotinin group and 97.1% of patients in the control group (p=0.07). A significant difference between groups was that patients who received aprotinin had more grafts versus those in the control group (1.5 vs 1.3, p=0.015).

Clinical outcomes for the two groups are summarized in Table 3. The groups were similar with regard to postoperative azotemia, new-onset atrial fibrillation, myocardial infarction, stroke, and death. The mean ± SD total hospital length of stay was similar in the aprotinin versus control groups (8.1 ± 3.8 vs 7.4 ± 2.8 days, p=0.08); however, patients receiving aprotinin had a longer mean length of stay from surgery until hospital discharge than those in the control group (5.9 ± 0.17 days vs 5.4 ± 0.12 days, p=0.032). Similar percentages of patients were discharged home in the two groups.

Discussion

This study compared two groups of patients who were considered at relatively low risk for requiring perioperative blood transfusion and who underwent coronary artery bypass surgery at a single institution. One group received aprotinin at the full Hammersmith dosage whereas the control group received aminocaproic acid. Although this was not a randomized prospective study, the two groups were remarkably similar with regard to baseline and intraoperative characteristics. We found no demonstrable clinical benefit from the use of

Table 3. Clinical Outcomes

Outcome	Aprotinin Group (n=162)	Control Group (n=173)	p Value
	No. (%) of Patients		
Postoperative azotemia	21 (13.0)	18 (10.4)	0.46
New-onset atrial fibrillation	24 (14.8)	26 (15.0)	0.95
Myocardial Infarction	1 (0.6)	0	NS
Stroke	1 (0.6)	1 (0.6)	NS
Death	1 (0.6)	1 (0.6)	NS
Discharged home	131 (80.9)	139 (80.3)	0.67
	Mean ± SD		
Total hospital length of stay (days)	8.1 ± 3.8	7.4 ± 2.8	0.08
Length of stay from surgery until hospital discharge (days)	5.9 ± 0.17	5.4 ± 0.12	0.032

aprotinin in these patients. Of interest, a trend of reduced total donor exposures occurred in patients who received aminocaproic acid. No increased risk of azotemia, new atrial fibrillation, myocardial infarction, stroke, or death was observed in the patients treated with aprotinin. Length of stay between surgery and discharge was shorter in patients who did not receive aprotinin; however, there was no significant difference between the two groups in total hospital length of stay (admission through discharge). No significant difference was noted in the number of patients discharged home. This represents an important outcome related to the use of health care resources because patients who are discharged home consume significantly fewer health care resources than those who are transferred to rehabilitation or transitional care facilities.

Risk factors for postoperative blood loss should be considered when evaluating the clinical efficacy of aprotinin. A considerable amount of evidence suggests that aprotinin is effective in decreasing blood loss and transfusions in patients at high risk for postoperative blood loss.[5, 15] A modest benefit with regard to postoperative blood loss in a relatively low-risk population, defined as patients undergoing primary elective cardiopulmonary bypass surgery, has also been described.[16–18] Other investigators have determined that aprotinin is efficacious in men undergoing primary cardiopulmonary bypass, a subgroup also considered to be at low risk for postoperative bleeding.[19, 20] Other characteristics associated with reduced risk for postoperative blood loss include baseline hemoglobin level greater than 12 g/dl and lack of exposure to clopidogrel before surgery.[1, 12] For our study, we defined low risk as nonanemic patients undergoing elective surgery (all elective surgery is scheduled at least 5 days after the last clopidogrel dose).

To our knowledge, our study differs from earlier studies because of its focus on a subset of patients considered to be at low risk for bleeding. Given modern efforts at risk stratification, quality management, and cost reduction, an algorithm to optimize aprotinin use in patients most likely to benefit from the hemostatic effects could optimize resource utilization.

Findings from two recent observational studies have raised concern over the safety of aprotinin, prompting a U.S. Food and Drug Administration advisory committee meeting. A large, observational, phase IV study reported the risks associated with aprotinin in 4374 patients who underwent cardiac surgery.[21] Comparing aprotinin with a control using propensity adjustment, the odds ratio for a cerebrovascular event, defined as stroke, encephalopathy, or coma, was 1.42 (95% confidence interval 1.09–1.86, p=0.01). Other risks attributed to aprotinin were renal failure and myocardial infarction or heart failure. The results of this retrospective analysis have been criticized on the basis of its nonrandomized nature and potentially inadequate risk matching.[22] Another study used propensity score matching in a retrospective evaluation of 898 high-risk cardiac surgery patients.[23] Aprotinin was compared with tranexamic acid, another antifibrinolytic agent used to reduce postoperative blood loss. Postoperative renal dysfunction occurred in 24% of patients given aprotinin compared with 17% of matched patients who received tranexamic acid (p=0.01). Our study

does not concur with these results. Despite a higher frequency of baseline renal insufficiency in patients receiving aprotinin versus those receiving aminocaproic acid, we found no significant difference in the development of postoperative azotemia between the two groups.

Our study was limited by its retrospective nature and relatively small sample size. Its nonrandomized nature may have predisposed the heart surgery team to treatment bias. However, the only significant change in treatment policy during this time period was the extension of aprotinin treatment to all patients undergoing cardiac surgery. This shift in policy allowed us to retrospectively review groups of low-risk patients who either did or did not receive aprotinin. The small sample size is a limitation, especially considering the low-risk patient population. More than 500 patients are required to demonstrate a reduction in transfusions in low-risk patients (elective surgery, nonanemic). A smaller population is sufficient to show a reduction in transfusions in high-risk patients (emergent surgery, concomitant clopidogrel), who are more likely to receive transfusions.

Other limitations of the study were our method of assessing chronic renal insufficiency, which may have introduced errors of omission, and our lack of a standardized definition for postoperative azotemia. Renal insufficiency can predispose a patient to increased postoperative bleeding; thus, differences in renal function could have had significant effects on bleeding risk within the two groups.

Conclusion

Aprotinin did not reduce either total donor exposures or postoperative blood transfusions in patients at low risk for bleeding who underwent cardiac surgery involving cardiopulmonary bypass. Aprotinin appeared to be safe, however, in that it did not lead to stroke, myocardial infarction, or renal insufficiency in this patient population. More robust evidence is needed from a controlled randomized trial to demonstrate aprotinin's safety, efficacy, and pharmacoeconomic benefit.

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