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The Effect of Antifibrinolytic Prophylaxis on Postoperative Outcomes in Patients Undergoing Cardiac Operations

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Antifibrinolytic agents such as aprotinin and epsilon aminocaproic acid limit postoperative bleeding and blood transfusion in patients undergoing cardiac operations using cardiopulmonary bypass (CPB). Recent evidence suggests that these agents have adverse side effects that influence operative mortality and morbidity. We studied postoperative bleeding, transfusion rates, and operative outcomes in our patients in order to assess the efficacy of these agents during cardiac operations requiring CPB. We reviewed records of 520 patients undergoing a variety of cardiac operations between January 2005 and May 2009. We measured multiple variables including pre-operative risk factors, antifibrinolytic agent used, and outcomes of operation, such as measures of bleeding and blood transfusion, as well as serious operative morbidity and mortality. Postoperative bleeding rates varied significantly between patients receiving aprotinin and those receiving aminocaproic acid ($P < 0.05$). There was an associated 12% decrease in operative site bleeding in aprotinin-treated patients compared with aminocaproic acid. There was no significant difference in the transfusion rates of packed red blood cells between patients receiving aminocaproic acid or aprotinin ($P > 0.05$), though individuals in the aprotinin group did receive FFP more frequently than patients in the aminocaproic acid group ($P < 0.05$). There was no significant difference in morbidity and mortality rates between patients in either drug group ($P > 0.05$). Our study shows that aprotinin is

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more effective at controlling operative site bleeding than aminocaproic acid. Reduced operative site bleeding did not portend better outcome or differences in transfusion requirements. Aminocaproic acid remains a safe and cost-effective option for antifibrinolytic prophylaxis because of unavailability of aprotinin.

Key words: Aprotinin – Aminocaproic acid – Cardiac surgery – Postoperative bleeding – Chest tube output – Transfusion – Morbidity – Mortality

Postoperative hemorrhage is a common complication of cardiac operations, with over 50% of patients receiving blood product transfusions.[1] For several years aprotinin was an antifibrinolytic drug used to decrease postoperative bleeding in patients undergoing cardiac surgery. This drug was removed from the United States market in November 2007 as studies suggested that its use is associated with increased end-organ damage and increased operative mortality rates.[2,3] Since that time, aminocaproic acid has been the most commonly used prophylactic agent for control of postoperative hemorrhage during cardiac operations.

Several previous studies have suggested that aprotinin controls bleeding more effectively than other antifibrinolytic agents such as aminocaproic acid,[1,3–5] while others have suggested an equivalent hemostatic effectiveness among these agents.[6] Several studies demonstrate reduced transfusion requirements in patients receiving aprotinin either compared with placebo or with other antifibrinolytic agents.[7–11] Since a preponderance of evidence points towards aprotinin being a more powerful antifibrinolytic drug, one might expect an increase in postoperative bleeding and postoperative blood product transfusions in patients undergoing cardiac surgery after aprotinin was taken off the market. Therefore, we wanted to compare postoperative hemorrhage and transfusion rates, as well as morbidity and mortality rates in patients undergoing on-pump cardiac operations receiving either aprotinin or aminocaproic acid.

Methods

Institutional Review Board approval was obtained prior to data collection for this retrospective chart review. Data from paper charts and from electronic medical records were entered into a custom Microsoft Excel database. Categories in this database included patient demographics, procedure data, pre-operative risk factors, antifibrinolytic agent given, blood products transfused, 24-hour chest-tube output, cardiopulmonary bypass time, ischemic time, and development of postoperative complications including renal failure, peri-operative myocardial infarction (MI), stroke, and bleeding requiring re-operation. All patients included in this study were over 18 years of age and received standardized doses of either aprotinin or aminocaproic acid prior to their cardiac procedures. Patients receiving aprotinin were administered a ''Hammersmith dose,'' consisting of 2 million Kallikrein inhibiting units (KIU), prior to incision; 2 million KIU in the cardiopulmonary bypass pump (CPBP); and 500,000 KIU continuously infused until chest closure. Patients receiving aminocaproic acid were administered a 10-g bolus prior to incision, 10 g into the heart–lung machine circuit, and an additional 10 g after chest closure. Data were collected from patients who underwent on-pump cardiac operations performed by two surgeons (CR and VF). All procedures were performed at the University of Kentucky Medical Center between January 2005 and May 2009.

Patients were categorized based on the antifibrinolytic agent they were given and their estimated preoperative risk. Subjects' risk category was determined by their mortality risk as estimated by the online Society of Thoracic Surgeons (STS) risk calculator.[12] This calculator took into account factors such as patient age, body mass index (BMI), race, procedure performed, and several other pre-operative risk factors. A pre-operative mortality risk of less than 3% was considered to be low risk, while a preoperative mortality risk of greater than 3% was considered to be high risk. It should be noted that an STS mortality risk could not be calculated for 81 (15.5%) subjects because the procedures performed on these patients were unsupported by the STS calculator. These patients were automatically put into a high-risk category as they all underwent very complex procedures, such as a coronary artery bypass graft (CABG) along with aortic and mitral valve replacements.

Chest-tube output was calculated using the total volume collected from chest tubes draining the surgical site during the immediate 24-hour postoperative period. Blood product usage was assessed by measuring the volume of Cell Saver (Harmonetics

Table 1 A summary of the baseline characteristics of the patients included in this retrospective study as well as their variance by drug group

Characteristic	No. (%)	Aminocaproic acid (%)	Aprotinin (%)	*P* value
Aprotinin	185 (35.6)	—	—	—
Aminocaproic acid	335 (64.4)	—	—	—
Male	411 (79.0)	77.9	81.1	0.395
Female	109 (21.0)	22.1	18.9	
Low-risk procedures	318 (61.2)	64.2	55.7	0.057
High-risk procedures	202 (38.8)	35.8	44.3	
Surgeon A	440 (84.6)	68.3	31.7	<0.001
Surgeon B	80 (15.4)	42.5	57.5	
BMI group				
Normal (≤25.0)	141 (27.1)	28.7	24.3	0.506
Overweight (25.1–30.0)	197 (37.9)	36.4	40.5	
Obese (≥30.1)	182 (35.0)	34.9	35.1	
Age (mean ± SD)	60.4 ± 12.9	60.1 ± 13.5	61.0 ± 11.6	0.440
Cell Saver (mean ± SD)[a]	890 ± 440	870 ± 410	940 ± 500	0.080

[a]The *P* value for Cell Saver was calculated using the log-transformed Cell Saver values, although the untransformed means and standard deviations are reported here for clarity.

Corporation, Braintree, MA 02184) given to patients intra-operatively as well as the number of units of blood products transfused during the intra-operative and postoperative periods.

A comparison of 24-hour chest-tube output between these patient groups was performed using a univariate analysis with a Student *t* test for continuous variables and χ^2 test for discrete variables. A multivariable linear regression using 24-hour chest-tube output as the dependent outcome variable identified independent predictor variables from patient age, gender, BMI, volume of Cell Saver transfused, preoperative risk, cardiopulmonary bypass (CPB) time, and ischemic time. The intra-operative and postoperative transfusion rates of packed red blood cells (PRBCs) and fresh frozen plasma (FFP) between patients receiving aminocaproic acid and those receiving aprotinin were also compared using χ^2 tests. These transfusion rates were measured using the number of units of PRBCs and FFP transfused from the initiation of surgery until the patient's discharge from the hospital. A comparison of in-hospital mortality and morbidity rates between patients receiving aprotinin and those receiving aminocaproic acid was also performed using Fisher exact test. The morbidities examined include the postoperative development of renal failure, peri-operative myocardial infarction, stroke, and bleeding requiring re-operation.

Results

There were 520 patients included in the analysis; of these, 335 (64.4%) were given aminocaproic acid and 185 (35.6%) were given aprotinin. A summary of the baseline characteristics of the patients included in the study is shown in Table 1. A total of 16 (3.1%) patients died intra-operatively or postoperatively from their procedures; the majority were high-risk patients.

Surgical site bleeding

Multivariate predictors of 24-hour chest-tube output included patients' BMI group, antifibrinolytic agent used, gender, amount of Cell Saver transfused, and CPB time (Table 2). This analysis also showed that subjects' risk category, surgeon, and ischemic time were not significant modifiers of 24-hour chest-tube output ($P > 0.05$). Patients with a BMI > 30 were shown to have significantly less chest-tube drainage than patients with a BMI < 25 ($P < 0.001$). However, subjects with a BMI between 24.1 and 30.0 were not shown to have significantly lower chest-tube output than those with a BMI < 25 ($P > 0.05$).

Figure 1 compares the mean surgical site bleeding as measured by 24-hour chest-tube output in patients undergoing low-risk and high-risk procedures, as well as the overall 24-hour chest tube drainage adjusted by multivariable regression analysis. Low-risk patients who received aprotinin had significantly less surgical site bleeding compared with aminocaproic acid–treated patients (760 ± 330 mL versus 850 ± 350 mL, $P = 0.021$). In the high-risk group, there was no significant difference in surgical site bleeding between patients treated with aminocaproic acid and those treated with aprotinin ($P = 0.506$). The overall mean 24-hour chest-tube drainage also varied significantly between aprotinin-treated and aminocaproic acid–treated patients (680 ± 45 mL versus 770 ± 40 mL, $P = 0.002$).

Table 2 A summary of the multivariate analysis demonstrating variables that predict 24-hour chest-tube output (N = 518 owing to 2 patients missing predictor variables)

		95% Wald confidence interval		
Parameter	β	Lower limit of β	Upper limit of β	*P* value
BMI ≤25.0	0			
BMI 25.1–30.0	−0.082	−0.177	0.013	0.090
BMI >30	−0.216	−0.313	−0.118	<0.001
High-risk category	0			
Low-risk category	−0.018	−0.103	0.066	0.668
Aminocaproic acid received	0			
Aprotinin received	−0.129	−0.210	−0.049	0.002
Male gender	0			
Female gender	−0.181	−0.274	−0.087	<0.001
Surgeon (A versus B)	−0.084	−0.190	0.022	0.122
CPB time	0.001	0.000	0.002	0.020
Cell Saver[a]	0.024	−0.008	0.057	0.146
Age	0.007	0.004	0.010	<0.001

[a]Natural log transformation of Cell Saver plus 1. The β values for BMI category, risk category, antifibrinolytic agent given, and gender are presented relative to the parameter with a β value of zero. For example, patients with a BMI > 30 had less chest-tube drainage than patients with a BMI ≤ 25, as indicated by a negative β value. It should also be noted that the surgeon performing the procedure was not a significant modifier of chest-tube drainage.

Blood product transfusion

Blood product transfusion varied among the two groups. Aprotinin-treated patients received FFP transfusions more frequently than those treated with aminocaproic acid (Fig. 2). However, there was no significant difference in the transfusion rates of PRBCs between patients receiving aminocaproic acid and those receiving aprotinin (Fig. 3).

Outcomes of operation

In the entire study group, in-hospital mortality rates were not significantly different between patients

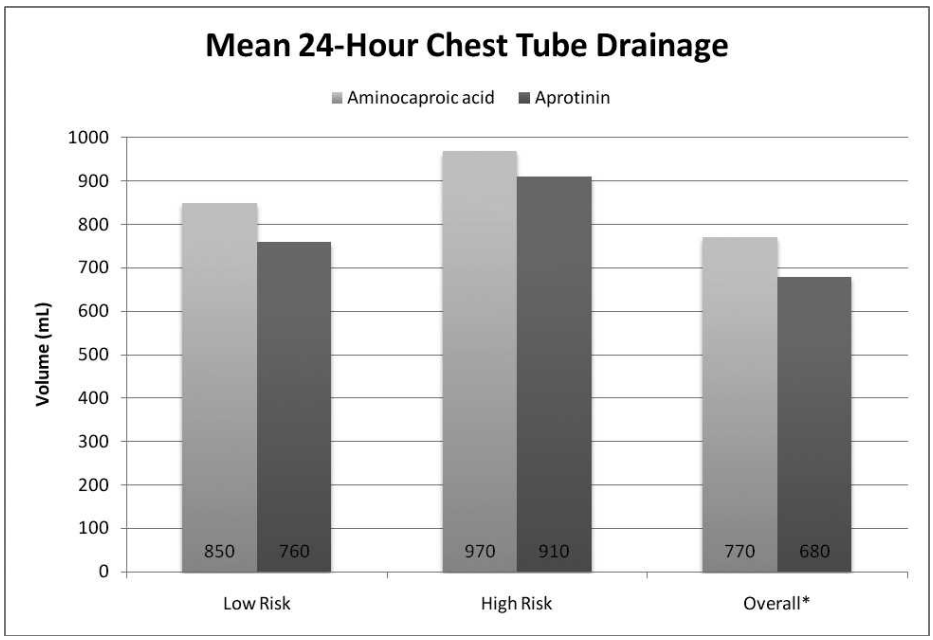

Fig. 1 The mean 24-hour chest-tube drainage in patients receiving aminocaproic acid and aprotinin in both low-risk and high-risk groups and overall. A significant difference existed between low-risk patients receiving aprotinin versus aminocaproic acid (*t* test, $P = 0.021$). No significant difference existed between high-risk patients receiving aprotinin and patients receiving aminocaproic acid (*t* test, $P = 0.506$). *The overall 24-hour chest-tube output is an adjusted value calculated with a multivariable regression analysis. A significant difference existed between these two patient groups ($P = 0.002$). Refer to Table 2 for details on the covariates in the multivariable regression analysis.

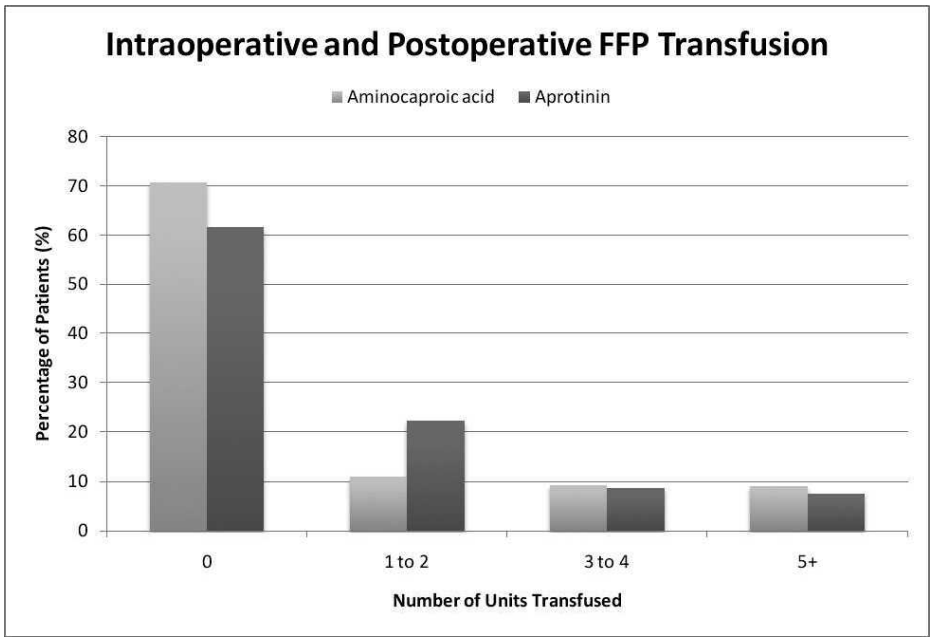

Fig. 2 A comparison of the percentage of patients requiring intra-operative and postoperative transfusions of FFP within the aminocaproic acid and aprotinin drug groups. There was a significant difference in transfusion rates of FFP between these two groups (Pearson χ^2, $P = 0.009$).

receiving aminocaproic acid and those receiving aprotinin. Operative mortality was 3.3% in patients receiving aminocaproic acid and 2.7% in patients receiving aprotinin (Fig. 4). However, when examining low-risk and high-risk patients separately, there was a nonsignificant trend toward increased operative mortality in high-risk patients receiving aminocaproic acid.

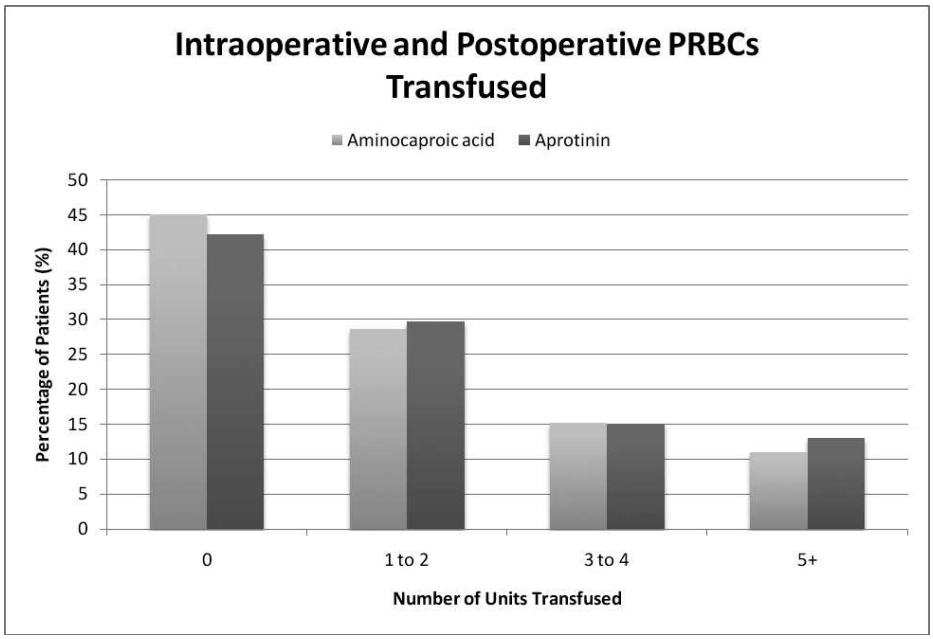

Fig. 3 A comparison of the percentage of patients requiring intra-operative and postoperative transfusions of PRBCs within the aminocaproic acid and aprotinin drug groups. There was no significant difference in transfusion rates of PRBCs between these two groups (Pearson χ^2, $P = 0.884$).

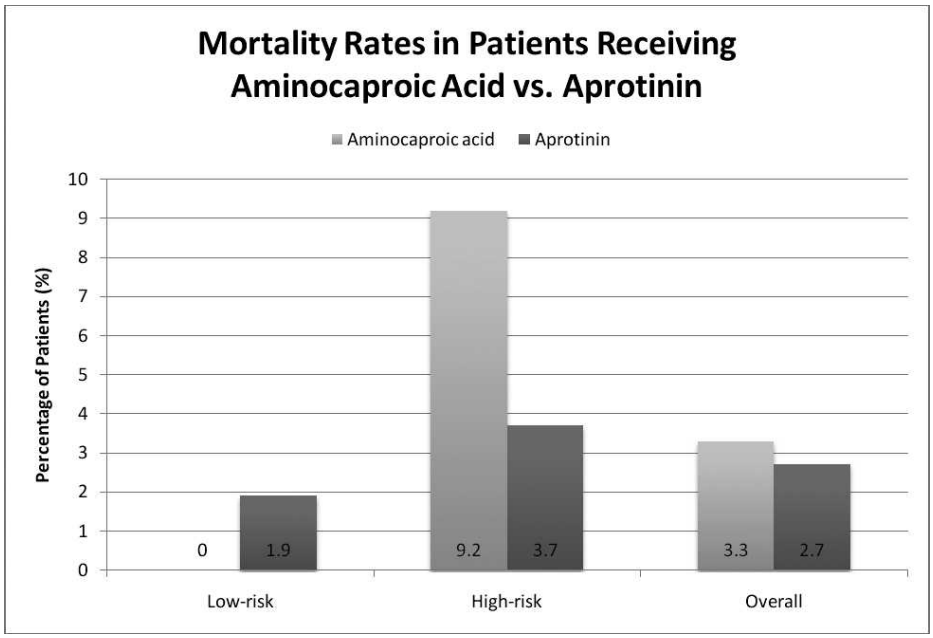

Fig. 4 Mortality rates in patients receiving aprotinin versus patients receiving aminocaproic acid. No significant difference in mortality rates existed between these two groups overall (Fisher exact test, $P = 0.797$). There was also no significant difference between individuals receiving aminocaproic acid and those receiving aprotinin when comparing mortality rates separately among low-risk patients (Fisher exact test, $P = 0.104$) and high-risk patients (Fisher exact test, $P = 0.164$).

A comparison of the development of postoperative morbidities between patients receiving aminocaproic acid and those receiving aprotinin did not demonstrate significant differences. Again, there were some nonsignificant trends toward increased morbidity in aminocaproic acid–treated patients (Fig. 5).

When examining the development of postoperative renal failure specifically, 0.5% of low-risk aminocaproic acid patients acquired this morbidity, while 1.0% of low-risk aprotinin patients developed renal failure (Fisher exact test, $P = 0.598$). In the high-risk group, 1.7% of patients receiving aminocaproic acid developed renal failure postoperatively, while 3.7% of individuals receiving aprotinin acquired this morbidity (Fisher exact test, $P = 0.371$). Overall, 0.9% of patients receiving aminocaproic acid and 2.2% of patients receiving aprotinin developed postoperative renal failure (Fisher exact test, $P = 0.255$). For other non-renal morbidities, there was a nonsignificant trend towards excess non-renal morbidities in aminocaproic acid–treated patients.

Low-risk aprotinin-treated patients had significantly less postoperative bleeding requiring re-operation compared with aminocaproic acid–treated patients (0% versus 3.7%, $P = 0.041$). In the high-risk group, 5.8% of patients receiving aminocaproic acid required re-operation, and 3.7% of patients receiving aprotinin underwent a re-operation for bleeding (Fisher exact test, $P = 0.484$). Overall, 4.5% of patients receiving aminocaproic acid and 1.6% of patients receiving aprotinin underwent re-operation for bleeding (Fisher exact test, $P = 0.131$).

Intensive care unit (ICU) length of stay was not significantly different between the aminocaproic acid and aprotinin groups (median of 2 days with interquartile range [IQR] of 2–4 days for both groups; Mann-Whitney U test, $P = 0.776$), nor was postoperative length of stay (median of 6 days with IQR of 4–9 days for aminocaproic acid group; median of 6 days with IQR of 5–10 days for aprotinin group; Mann-Whitney U test, $P = 0.290$). Approximately 11.1% of aminocaproic acid patients and 11.4% of aprotinin patients spent greater than 48 hours on the ventilator during their hospital stays ($P = 0.925$).

Discussion

Surgical site bleeding, measured using 24-hour chest-tube drainage, during on-pump cardiac procedures, varied significantly between patients receiving aminocaproic acid and those receiving aprotinin. Patients receiving aprotinin intra-operatively had close to 12% less surgical site bleeding on average in the 24-hour postoperative period than those who received

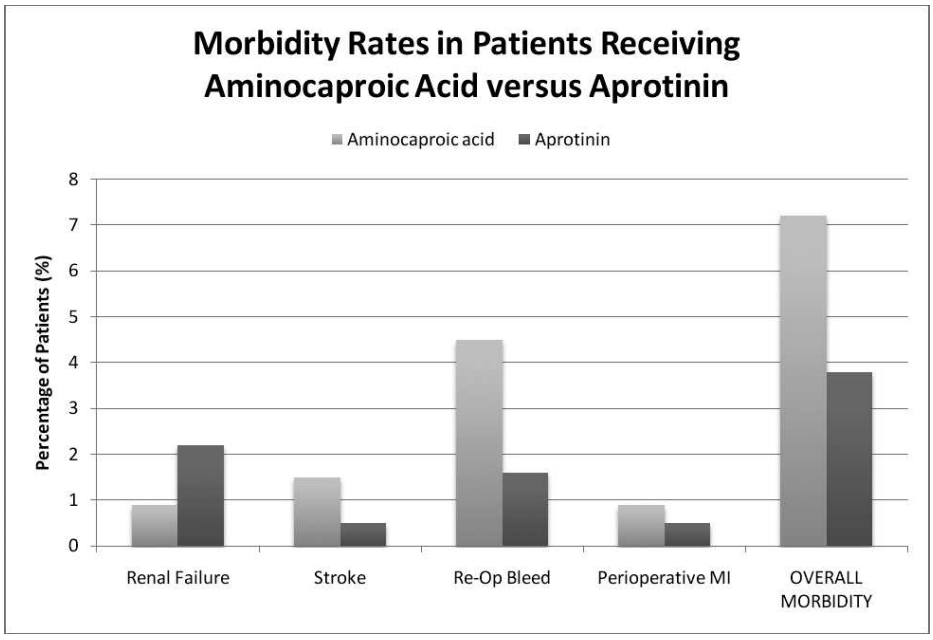

Fig. 5 Morbidity rates in patients receiving aminocaproic acid versus patients receiving aprotinin. There was no significant difference in overall morbidity between patients in either drug group (Fisher exact test, $P = 0.126$). There was no significant difference between patients in either drug group when examining the development of postoperative renal failure (Fisher exact test, $P = 0.255$), stroke (Fisher exact test, $P = 0.429$), bleeding requiring re-operation (Fisher exact test, $P = 0.131$), and perioperative MI (Fisher exact test, $P = 1.00$).

aminocaproic acid. This finding correlates with previous studies demonstrating aprotinin to be a more powerful antifibrinolytic agent than other drugs in this class.[1,3–5] There was no significant difference in transfusion requirements of PRBCs between the two patient groups, which does not support findings from previous studies suggesting that aprotinin reduces transfusion requirements in patients undergoing cardiac surgery.[7–11] However, patients in the aprotinin group appeared to receive FFP more frequently than patients in the aminocaproic acid group. However, several patients in the aprotinin group were still taking clopidogrel prior to surgery and were therefore prophylactically given FFP at the end of the operation likely causing this variance. These results suggest that aprotinin remains superior to aminocaproic acid in controlling postoperative hemorrhage during on-pump cardiac surgeries, though aprotinin use does not reduce the risk of intra-operative or postoperative blood product transfusions.

While our results show that aprotinin controls postoperative hemorrhage more effectively than aminocaproic acid, there was no significant difference in overall in-hospital mortality rates between these two patient groups. These findings suggest that the type of antifibrinolytic prophylaxis given during on-pump cardiac operations is not a factor in patients' risk of mortality. Though previous studies indicate increased postoperative mortality rates in patients receiving aprotinin,[2,3] our results do not support this relationship. This lack of variance in mortality rates between our two patient groups also indicates that the decreased postoperative bleeding in patients receiving aprotinin was not clinically significant.

The development of postoperative morbidities also did not vary significantly between patients receiving aprotinin and those receiving aminocaproic acid, which is again not consistent with findings from previous studies.[2,3] However, when examining the low-risk patient group, individuals who received aminocaproic acid had significantly increased morbidity rates compared with those who received aprotinin. The majority of the increased morbidity in the aminocaproic-acid patient group stemmed from increased bleeding requiring re-operation (Fig. 5). However, it is difficult to assess the increased morbidity due to bleeding requiring re-operation, since there is likely to be a component of discrete surgical bleeding from an un-sutured vessel or other technical problems unrelated to fibrinolysis.

When examining the development of postoperative renal failure specifically, no significant difference

was noted between the aminocaproic-acid and aprotinin patient groups (Fig. 5). This finding does not substantiate results from previous studies that have suggested aprotinin causes ischemic injury to the kidney, heart, and brain.[2,3] Other reports have also proposed that patients with diabetes mellitus have an increased risk of developing postoperative renal failure after undergoing aprotinin therapy.[13,14] These findings would be expected since diabetes mellitus causes ischemic end-organ damage, which would be compounded by the theorized ischemic injury caused by aprotinin. Though we did not analyze the renal failure rates in patients with diabetes mellitus, because of the small sample size, our results did not show a significant difference in postoperative renal failure rates between patients receiving aprotinin and those receiving aminocaproic acid.

Previous studies also suggest that aprotinin decreases the rates of stroke and atrial fibrillation in patients, postoperatively.[7] While the development of atrial fibrillation was not one of the postoperative morbidities examined in this study, there was a decreased rate of postoperative stroke in patients receiving aprotinin versus those receiving aminocaproic acid (Fig. 5). However, this difference was not statistically significant, and it also contradicts the idea that aprotinin may instigate microvascular and macrovascular thrombosis.[3] Though a possible connection between aprotinin and intravascular thrombosis has been observed in many *in vivo* animal models as well as in sponsor-supported clinical trials,[15–17] this correlation was not supported by the results of this study.

Limitations of this study are that it was not a prospective randomized study and that it occurred at a single institution only. This study also did not look specifically at one cardiothoracic procedure, which may have introduced an additional variance when comparing outcomes between patient groups. In addition, the multivariable regression analysis of 24-hour chest-tube output performed in this study took into account the amount of Cell Saver that patients received intra-operatively. However, the transfusion of other blood products intra-operatively and in the 24-hour postoperative period, such as packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate, was not considered in the multivariable analysis of 24-hour chest-tube drainage.

Further, certain areas of analysis in our study did not duplicate findings reported by other authors. For example, many literature reports and meta-analyses suggest that aprotinin is superior to aminocaproic acid in limiting blood transfusion after operations requiring CPB.[2] Given the small sample size of our study population, it is likely that our study did not contain sufficient statistical power to adequately address the comparative efficacy of aprotinin versus aminocaproic acid in limiting perioperative blood transfusion. It is not possible to make meaningful conclusions regarding perioperative blood transfusion from our study population because of these sample-size limitations.

Conclusion

This study's comparison of the effect of aminocaproic acid versus aprotinin on postoperative bleeding shows that aprotinin given intra-operatively controls surgical site bleeding more effectively than aminocaproic acid. However, reduced bleeding after surgery did not translate into significant decrease in transfusion of blood products. Also, neither drug was associated with an increased risk of mortality or the development of postoperative morbidities. Aprotinin in our institution costs around $900/case (US) compared with aminocaproic acid cost of less than $100/case (US). These results support the use of aminocaproic acid as a cost-effective agent for antifibrinolytic prophylaxis during cardiac operations.

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