Coronary artery bypass grafting after aprotinin: Are we doing better?

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Objective: Cardiac surgery patients are treated with antifibrinolytic agents to reduce intra- and postoperative bleeding. Until 2007, lysine analogues (aminocaproic acid and tranexamic acid) and serine protease inhibitors (aprotinin) were recommended. In 2008, the U.S. Food and Drug Administration prohibited aprotinin use because of associated postoperative complications, including cerebrovascular accidents and renal failure. This work aimed at reevaluating the efficacy and safety of aprotinin versus tranexamic acid in patients undergoing elective coronary artery bypass surgery.

Methods: Two groups were enrolled in this study. Group A ($n = 256$), operated from January 2005 to August 2007, was treated with the half-Hammersmith aprotinin regime whereas group B ($n = 104$), operated after 2008, was treated with the full-dose tranexamic acid regime. All patients were of low-risk profile, and underwent an elective, on-pump coronary artery bypass surgery. The main outcome measures were safety, assessed in relation to thrombosis-related cardiac, cerebral, and renal events; and efficacy, investigated in terms of postoperative bleeding and infusions of blood products.

Results: Postoperatively, group B demonstrated greater bleeding during the operative and first postoperative days, and total bleeding (P values $\leq .001$); a greater requirement of blood and/or blood products infusions ($P = .024$); higher postoperative acute renal failure rates ($P = .028$); lower platelet count ($P = .002$); and a higher postoperative increase in troponin levels ($P < .0001$).

Conclusions: Among low-risk patients undergoing coronary artery bypass surgery, the half-Hammersmith aprotinin-based antifibrinolytic management proved to be more efficacious in terms of bleeding and consumption of blood products, with no evidence of associated increased rates of postoperative complications. Accordingly, the usage of aprotinin should be reconsidered for treatment among cohorts of low-risk cardiac patients. (*J Thorac Cardiovasc Surg* 2013;145:243-8)

Cardiac surgery patients are treated routinely with antifibrinolytic agents to reduce intra- and postoperative bleeding as well as infusions of blood products. Until 2007, widespread use of 2 classes of agents was recommended, both proven to mitigate bleeding: lysine analogues (aminocaproic acid and tranexamic acid) and serine protease inhibitors (aprotinin). Compared with lysine analogues, aprotinin treatment was associated with an increased risk of mortality and morbidity,¹ a finding corroborated by ensuing studies.² The main postoperative complications associated with aprotinin use were reported to include cerebrovascular accidents (CVAs), renal failure, and reduced graft patency. These findings led the U.S. Food and Drug Administration (FDA) to prohibit the use of aprotinin as an antifibrinolytic agent in 2008.²

The complications associated with aprotinin in comparison with lysine analogues presumably stemmed from the postulated propensity of aprotinin to favor thrombosis.³ Aprotinin distinguishes itself from lysine analogues by its (1) inhibition of soluble proteases (eg, kallikreins, plasmin, and trypsin), (2) inhibition of activated protein C, (3) preservation of platelet adhesive and aggregatory properties, (4) impairment of vascular endothelial cell function in the coronary and cerebral arteries and aorta, and (5) selective impairment of endothelium-derived relaxation by dose-dependent inhibition of nitric oxide synthesis and release.²

Notably, the aforementioned studies on which the FDA's recommendation was based enrolled either high-risk patients with multiple comorbidities^{1,2} or an assorted cohort of patients of both low- and high-risk status undergoing complex cardiac procedures.⁴ Such heterogeneous recruitment of patients of diverse preoperative risk levels may have veiled the differential clinical effects of aprotinin in the management of low- versus high-risk cardiac patients. The current literature necessitates an assessment of the effectiveness of aprotinin treatment in a homogenous cohort of low-risk patients. Such an investigation may indicate an advantageous treatment regime in a significant fraction of open-heart cardiac surgery patients.

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Abbreviations and Acronyms

ACT	= activated clotting time
APTT	= activated partial thromboplastin time
ARF	= acute renal failure
BPT	= bypass time
BW	= body weight
CABG	= coronary artery bypass graft
CCT	= crossclamp time
CHF	= congestive heart failure
CVA	= cerebrovascular accident
FDA	= Food and Drug Administration
MI	= myocardial infarction
PT	= prothrombin time

The aim of this work was to revisit the relevance of the aforementioned aprotinin-related studies and FDA recommendations to low-risk cardiac patients. Accordingly, the current study focused on elective coronary artery bypass graft (CABG) patients by comparing the consequences of the half-Hammersmith aprotinin regime and a full-dose tranexamic acid regime in terms of safety and efficacy. Safety was assessed in relation to thrombosis-related cardiac, cerebral, and renal events. Efficacy was investigated in terms of postoperative bleeding and infusions of blood products.

Because the use of antifibrinolytic agents presents an embedded clinical routine dictated by guidelines,¹ conducting independent, placebo-controlled clinical studies investigating the safety and efficacy of antifibrinolytic agents becomes unfeasible. In addition, regulatory approval for using these agents differs among countries, thus making a large-scale, multicountry, comparative study challenging. Therefore, the current work investigated retrospectively the study population in 2 different time periods, distinguished by the governing antifibrinolytic treatment regime.

METHODS**Patients**

In our institute, all patients routinely received intraoperative aprotinin; this policy ceased in our institute in January 2008. The current study compared 2 patient groups. The first, designated group A (n = 256), was operated between January 2005 and August 2007 and received aprotinin. The second, designated group B (n = 104), was operated between September 2009 and April 2010 and received tranexamic acid. A total of 1134 patients were operated during both periods, of whom 360 (groups A and B, collectively) were elective patients who underwent on-pump CABG.

The study question focused on a cohort of low-risk patients. Accordingly, inclusion criteria were patients (1) undergoing elective CABG surgery, (2) demonstrating a normative preoperative coagulation profile (namely, values within the normal range of platelet counts, activated partial thromboplastin time [APTT], prothrombin time [PT], and international normalized ratio), (3) with a left ventricular ejection fraction $\geq 50\%$, (4) with a preoperative creatinine level ≤ 2 mg/dL; and (5) not on preoperative clopidogrel or anticoagulation treatment. Aspirin administration was not discontinued at any point before or after the surgery.

Declaration of Helsinki

This study complies with the Declaration of Helsinki and was approved by a locally appointed ethics committee (0335-10-RMB).

Antifibrinolytic Treatment Protocol

Aprotinin was administered routinely to all patients in group A according to the half-Hammersmith regime. Initially, a test dose (10,000 kIU) was given intravenously. Ten minutes later, the loading dose (1 million kIU) was administered intravenously over a time period of 20 to 30 minutes. Finally, the pump prime was given in 2 parts: First, it was added during the recirculation of the priming fluid (1 million kIU) and, second, it was given intravenously as a continuous infusion during operation (250,000 kIU/hour).

The tranexamic acid treatment regime in group B was based on the patient's body weight. Accordingly, a loading dose was given immediately before skin cut (calculated as $12.5 \times \text{Body weight [BW]}$, measured in milligrams), and afterward a maintenance dose was started and continued until 4 hours postoperatively (calculated as $6.5 \times \text{BW}$, measured in milligrams per hour).⁵

Blood and Blood Products Transfusion Protocol

Packed cells transfusion was indicated for patients in whom hemoglobin levels were <7 g/dL and for patients in whom the hemoglobin level was between 7 g/dL and 8 g/dL and were symptomatic (demonstrated clinical signs of hypovolemia and anemia). Fresh-frozen plasma and platelet infusions were given only in cases of excessive postoperative bleeding (ie, > 200 mL/hour or > 100 mL/hour after the first hour with normal activated clotting time [ACT] or APTT). Fresh-frozen plasma was administered in case of abnormal PT, only after correction of APTT by protamine infusions. Platelets were administered after correcting both APTT and PT if excessive bleeding continued, regardless of the platelet count.

Statistical Analysis

All analyses were conducted using SPSS version 19 (SAS Institute, Inc, Cary, NC). The study outcome measures were stratified into 3 levels: pre-, intra-, and postoperative parameters. Preoperatively, relevant operative risk factors, demographic variables, and baseline illnesses were documented. Intraoperatively, factors that are known to influence postoperative bleeding were collected and compared—namely, cross-clamp time (CCT), bypass time (BPT), minimal operative temperature, and last operative ACT. In addition, the intraoperative usage of blood product infusion was compared. Postoperatively, total bleeding amount and infusion of blood products were compared. The main outcome measures of the current study were postoperative platelet count, acute renal failure (ARF), CVA, acute myocardial infarction (MI), and 30-day mortality. Acute renal failure was defined as an elevation of the preoperative creatinine level to >1.5 times the baseline or the need for dialysis. Acute MI was diagnosed as troponin elevation >4 times the upper limit of the normal range. The TROPONIN-I test was performed in all cases (normal range: 0-0.028 ng/mL). Total bleeding was calculated as the sum of the average bleeding on the operative day between the patients operated during the morning and afternoon hours, postoperative day 1, and postoperative day 2. Because of data availability, comparison of troponin values was performed among 144 patients in the aprotinin-treated group and 121 patients in the tranexamic acid-treated group. Continuous variables are presented as mean $\pm$ standard deviation. Unpaired *t* tests were used to compare the means of continuous variables between group A and group B. Mann-Whitney *U* tests were used to compare data of nonnormal distribution, which are described by their median and interquartile range (25%-75%). Statistical significance was set at $P < .05$.

RESULTS

The groups were comparable demographically and had the same mean age of 64 ± 10 years. The male-to-female

TABLE 1. Demographics and past diagnoses

Parameter	Group A (aprotinin; n = 256)	Group B (tranexamic acid; n = 104)	P value
Demographics			
Male-to-female ratio (%)	199:57 (78:22)	80:24 (77:23)	NS
Age, n ± SD	64 ± 10	64 ± 10	NS
Past diagnoses, n (%)			
Ischemic heart disease	193 (75)	72 (69)	NS
Smokers	106 (41)	39 (38)	NS
Hyperlipidemia	200 (78)	85 (82)	NS
Hypertension	186 (73)	75 (72)	NS
Diabetes mellitus	99 (39)	49 (47)	NS
Renal failure	12 (5)	10 (10)	NS
Peripheral vascular disease	22 (9)	11 (11)	NS
Congestive heart failure	9 (4)	14 (14)	.001
Cerebrovascular accident	10 (4)	11 (11)	.023
Chronic obstructive pulmonary disease	12 (5)	6 (6)	NS
Obesity	26 (10)	12 (12)	NS
Atrial fibrillation	14 (6)	7 (7)	NS

NS, Not significant; SD, standard deviation.

ratio was also comparable between the 2 groups, with 78% men and 22% women in group A, and 77% men and 23% women in group B.

The 2 groups differed in relation to their baseline mean hemoglobin levels: 14 ± 2.5 g/dL in the aprotinin group and 13.4 ± 1.8 g/dL in the tranexamic acid group (*P* = .03).

Table 1 presents preoperative variables and diagnoses prior to the CABG surgery. The groups were comparable with regard to prior diagnoses of ischemic heart disease, smoking, hyperlipidemia, hypertension, diabetes mellitus type 2, renal failure, chronic obstructive pulmonary disease, obesity, and previous history of atrial fibrillation, either paroxysmal or chronic. However, the groups differed with regard to previous history of congestive heart failure and previous CVAs, which were more prevalent in group B.

Table 2 delineates the operative parameters that have an influence on the homeostatic system and postoperative bleeding—namely, CCT, BPT, minimal operative temperature, and last ACT. No differences were found in these parameters between the 2 groups examined. No significant differences were observed between groups A and B in terms of the end operative fluid balance, packed cells infusions, and platelets transfusion. Packed cells were infused to 71 patients (28%) in group A versus 42 patients (40%) in group B (*P* = .024). Fresh-frozen plasma was infused to 3 patients (1%) in group A versus 7 patients (7%) in group B (*P* = .008).

The postoperative parameters and primary end points of the current study are compared in Table 3. Greater postoperative bleeding was observed in the tranexamic acid-treated group during the operative and first postoperative days (*P* values ≤ .001). In keeping, the total postoperative

TABLE 2. Operative parameters

Parameter	Group A (aprotinin)	Group B (tranexamic acid)	P value
Cross clamp time, min; mean ± SD	69 ± 21	73 ± 28	NS
Bypass time, min; mean ± SD	116 ± 31	107 ± 39	NS
Minimal temperature, °C; mean ± SD	33 ± 2	33 ± 1	NS
Activated clotting time, min; mean ± SD	130 ± 44	130 ± 13	NS
Balance, mL; mean (range)	2414 (1036-3097)	2631 (1633-3427)	NS
Packed cells, mL; mean (range)	371 (96-591)	421 (113-612)	NS
Packed cells, n (%)	71 (28)	42 (40)	0.024
Platelet infusion, n (%)	4 (1.6)	3 (2.9)	NS
Fresh-frozen plasma, n (%)	3 (1)	7 (7)	0.008

SD, Standard deviation; NS, not significant.

bleeding was greater in the tranexamic acid-treated group (*P* < .0001). A greater proportion of tranexamic acid-treated patients required blood and/or blood product infusions (*P* = .024).

In the tranexamic acid-treated group, more events of postoperative ARF were observed (*P* = .028), as well as a lower platelet count (*P* = .002) and a higher postoperative increase in troponin levels (*P* < .0001).

DISCUSSION

The main finding of the current study is that, among low-risk patients undergoing CABG, the half-Hammersmith aprotinin-based antifibrinolytic management resulted in lower bleeding rates during the operative and the first postoperative day, and decreased blood product infusions compared with the full-dose tranexamic acid treatment management. Regarding postoperative complications, the aprotinin-treated group demonstrated lower rates of ARF, decreased troponin levels, and higher platelet counts. The aprotinin- and tranexamic acid-based treatment regimes yielded comparable postoperative CVAs and 30-day mortality rates (Table 3).

Bleeding and Infusion of Blood Products

In relation to the baseline characteristics of the patients, as discussed previously, none received antiplatelet treatment (except for aspirin, which was used routinely). Nevertheless, the baseline hemoglobin level differed between the groups. Although statistically significant, this result has limited clinical relevance because of the minor difference in mean hemoglobin values and comparable confidence intervals.

In terms of efficacy—namely, reduction of blood loss and the proportion of transfused patients—current findings

TABLE 3. Postoperative bleeding, transfusion, and postoperative complications

Parameter	Group A (aprotinin)	Group B (tranexamic acid)	P value
Postoperative bleeding, median (interquartile 25% and 75% range)			
Morning operations, mL	300 (210-440)	465 (331-790)	.001
Afternoon operations, mL	250 (150-380)	415 (250-580)	.0001
Bleeding, mL, POD1	270 (190-390)	440 (300-690)	.0001
Bleeding, mL, POD2	90 (50-248.75)	160 (65-285)	NS
Total bleeding	869	1347	<.0001
Blood products			
Packed cells, n transfused patients (%)	71 (28)	42 (40)	.024
Packed cells, mean transfused volume $\pm$ SD	380 $\pm$ 206	440 $\pm$ 264	NS
Platelets, n (%)	4 (1.6)	3 (2.9)	NS
Fresh-frozen plasma, n (%)	3 (1.2)	7 (6.7)	.008
Morbidity and mortality			
Reoperation, n (%; range)	4 (1.6; 0.006-0.04)	2 (1.9; 0.006-0.07)	NS
Cerebrovascular accident, n (%; range)	1 (0.4; 0.0009-0.02)	1 (1; 0.002-0.05)	NS
Cardiogenic shock, n (%; range)	4 (1.6; 0.006-0.04)	3 (2.9; 0.01-0.08)	NS
Acute pulmonary edema, n (%; range)	12 (4.7; 0.03-0.08)	2 (1.9; 0.006-0.07)	NS
Septic shock, n (%; range)	4 (1.6; 0.06-0.04)	2 (1.90.006-0.07)	NS
Acute renal failure, n (%; range)	14 (5.5; 0.03-0.09)	13 (12.5; 0.07-0.2)	.028
Platelet count, minimum (range)	143 (113.7-176)	123 (100-149)	.002
Troponin, POD1; mean (range)	2.3 (0.9-5.1)	6.6 (5.9-11.4)	<.0001
Troponin, maximum postoperative; mean (range)	2.9 (0.7-5.5)	8.4 (6.9-12.9)	<.0001
30-Day mortality, n (%; range)	5 (1.9; 0.009-0.04)	4 (3.8; 0.02-0.09)	NS

POD, Postoperative day; NS, not significant; SD, standard deviation.

demonstrate that aprotinin is more effective than tranexamic acid. These findings are in line with previous reports, encompassing 17 randomized controlled trials of approximately 5000 patients that compared treatment with the full-Hammersmith dose of aprotinin with tranexamic acid.^{1,6-21} Of these studies, 5 indicated aprotinin as the most effective in terms of reduction of blood loss and transfusion requirements,^{6,10,14,18,22} whereas none identified tranexamic acid as such. Wang and colleagues²² investigated patients who underwent isolated CABG and concluded that, compared with the 981 control patients who received no aprotinin, the 4122 patients treated with the full-Hammersmith aprotinin regimen demonstrated significantly reduced blood loss. The current study contributes to this line of findings by documenting a similar efficacy using the half-Hammersmith regime of aprotinin. This follows the lines of previous studies^{23,24} that reported that, compared with control patients who received no aprotinin, patients treated perioperatively with low-dose aprotinin demonstrated a reduced risk of peri- and postoperative use of packed red blood cells and decreased postoperative blood loss. Stressing the potential efficacy of aprotinin in blood loss reduction, Maddali and associates²⁵ reported that, compared with the half-Hammersmith regimen, a microdose was more effective in reducing postoperative blood loss and blood transfusion. An additional efficacy-related attribute of the aprotinin-treated group in the current study was their comparable requirement of reexploration compared with the tranexamic acid-treated group.

Mortality

In terms of mortality, no significant difference was found in 30-day mortality rates between the groups treated with the half-Hammersmith aprotinin dose and tranexamic acid. The documented increased risk of death associated with aprotinin in recent trials, including the BART trial by Fergusson and colleagues,¹ which compared the effect of aprotinin with that of tranexamic acid, was shown either in patients undergoing high-risk cardiac surgery or in mixed groups undergoing both high- and low-risk cardiac surgery. Fergusson and colleagues¹ reported a relative 30-day mortality risk of 1.55 (95% confidence interval, 1.06-2.22) in the aprotinin group compared with tranexamic acid-treated patients. The investigators concluded that aprotinin should no longer be used in high-risk cardiac surgery. These recommendations address a cohort of distinctive characteristics, including older age, higher incidence of poor or moderate left ventricular function, and a need for urgent surgery. Furthermore, the BART trial included patients with higher incidence of body mass and diabetes mellitus, history of thromboembolism, and preoperative chronic renal dysfunction. In the same vein, a portion of these patients underwent surgery of the ascending aorta or aortic arch. Importantly, no study, including the current one, has reported a higher mortality risk associated with aprotinin among low-risk patients.

Morbidity

With regard to morbidity, the most widely reported postoperative aprotinin-related complications include

ARF, graft occlusion (ie postoperative MI), and CVA.^{1,2} Compared with the tranexamic acid, the half-Hammersmith aprotinin-treated group of the current study demonstrated lower ARF incidence, lower troponin levels, and comparable CVA rates. In addition, the aprotinin-treated group demonstrated a lower incidence of thrombocytopenia. Because the previously mentioned complications are suspected to be related to a state of increased or unopposed thrombosis, and are increased with the full-Hammersmith aprotinin regime, it may be postulated that the lower rate of major complications observed in the current study is associated with the implementation of the half-Hammersmith aprotinin regime. The current complication event rates and the matching 95% confidence intervals are smaller than in corresponding studies that focused on high-risk patients, and are comparable with investigations of patients with similar preoperative risks.^{1,6} Notably, the higher troponin levels in the tranexamic acid group of the current study were not associated with relevant clinical findings.

Sander and associates²⁶ demonstrated that the routine use of tranexamic acid did not result in a decreased relative risk for the development of postoperative neurologic dysfunction and/or renal injury compared with aprotinin among a cohort of low-risk patients. In the aforementioned study by Wang and colleagues,²² aprotinin use was associated with neither major complications nor with long-term major adverse cardiac or cerebrovascular events. Examining a group of low-risk patients, Dietrich and associates²⁷ also demonstrated no association between aprotinin, administered according to the full-Hammersmith protocol, and an increased risk for postoperative complications (ie, renal failure and MI, as well as mortality).

It is noteworthy that the investigated thrombosis-related complications were increased in the tranexamic acid-treated group. A possible explanation for this finding may be delineated by Terrell and colleagues,²⁸ who studied the effect of aprotinin and tranexamic acid on thrombosis and fibrinolysis in a model of cardiopulmonary bypass in dogs. In the aprotinin-treated group, the presence of heparin was associated with reduction in blood loss, but also with diminished filter deposits.²⁸ This counterbalancing effect of thrombosis and fibrinolysis seen with aprotinin could not be observed with tranexamic acid. Tranexamic acid diminishes bleeding, but the thrombus formation during contact activation is augmented. It is postulated that the sole inhibition of the fibrinolytic system by tranexamic acid, with no anticoagulant/antithrombotic activity, may advance unsuitable thrombus development.²⁹

Comparing the adverse event rates of the current study with those reported by Fergusson and colleagues¹ indicates that CVA, cardiogenic shock, and ARF were less prevalent in our sample (CVA: 0.4% vs 2.9% and 1% vs 3.7% in the aprotinin and tranexamic acid groups, respectively;

cardiogenic shock: 1.6% vs 14.5% and 2.9% vs 14.6% in the aprotinin and tranexamic acid groups, respectively; ARF: 5.5% vs 13.2% and 12.5 vs 12.7% in the aprotinin and tranexamic acid groups, respectively). It should be noted that the patients of the current study were low-risk patients treated with the half-Hammersmith aprotinin dose compared with the high-risk patients treated with the full-Hammersmith regime in the BART study.

Study Limitations

Several limitations in the current study are to be addressed. First, the present report is of a retrospective design; however, such a design is the only feasible one, considering the FDA constraints associated with the current study question. Second, the aprotinin-treated group demonstrated preoperatively lower CVA and congestive heart failure (CHF) rates, which may resemble a lower risk patient population. Regarding the former complication, it developed postoperatively in only 1 patient in either group. Therefore, it would be safe to assume that preoperative and postoperative CVA rates are independent. Furthermore, neither group demonstrated neurologic dysfunction preoperatively, which may have pertained to a minor, resolved CVA. The difference in CHF may have been derived from the various approaches of the clinicians regarding its determination and the retrospective design of the current study. The difference in CHF rates probably had no impact on the study outcomes, because patients with a reduced left ventricular ejection fraction, based on either echocardiography or ventriculography, were excluded; thus, preoperative CHF was probably a result of diastolic dysfunction. Third, a comparison of the half- and full-Hammersmith regimes could have yielded more informative results. Last, although the major operative variables known to influence postoperative bleeding were comparable in both groups (BPT, CCT, and minimal operative temperature), additional operative factors may have been left unaddressed.

CONCLUSIONS

Among low-risk patients undergoing CABG, half-Hammersmith aprotinin-based antifibrinolytic management proved to be more efficacious in terms of bleeding and infusion of blood products, with no evidence of associated increased rates of postoperative complications. Accordingly, the usage of aprotinin should be reconsidered for treatment in cohorts of low-risk cardiac patients.

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