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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Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication June 4, 2012; revisions received July 30, 2012; accepted for publication Sept 13, 2012; available ahead of print Oct 15, 2012.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2012.09.032

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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 $\leq$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 $\times$ Body weight [BW], measured in milligrams), and afterward a maintenance dose was started and continued until 4 hours postoperatively (calculated as 6.5 $\times$ 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 $\pm$ 10 years. The male-to-female

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