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Original Article

Effectiveness and Safety of Aprotinin Use in Thoracic Aortic Surgery

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Objective: To determine the effectiveness and safety of aprotinin use in adult patients undergoing thoracic aortic surgery.
Design: Single-center, retrospective study.
Setting: All cases performed at a single university hospital.
Participants: Between January 2004 and December 2014, 846 adult patients underwent thoracic aortic surgery. Due to missing or duplicated data on primary outcomes, 314 patients were excluded. The final sample of 532 patients underwent surgery on the thoracic aorta.
Interventions: The patients were divided in the following 2 groups: 107 patients (20.1%) received aprotinin during the surgery, which represented the study group, whereas the remaining 425 patients (79.9%) underwent surgery without the use of aprotinin.
Measurements and Main Results: To adjust for patient selection and preoperative characteristics, a propensity score–matched analysis was conducted. Mean total blood loss at 12 hours after surgery was similar between the 2 groups. The blood product transfusion rates did not differ in the 2 groups, except for the rate of fresh frozen plasma transfusion being significantly higher in the aprotinin group. Re-exploration for bleeding and the incidence of a major postoperative bleeding event were similar between the groups. Rates of in-hospital mortality, renal failure, and cerebrovascular accidents did not show any statistically significant difference. Aprotinin did not represent a risk factor for mortality over the long term (hazard ratio 1.14, 95% confidence interval 0.62-2.08, p = 0.66).
Conclusions: The use of aprotinin demonstrated a limited effect in reducing postoperative bleeding and prevention of major bleeding events. Aprotinin did not adversely affect early outcomes and long-term survival.

Key Words: aprotinin; antifibrinolytic agents; thoracic aortic surgery; outcomes; survival rate; bleeding

PATIENTS UNDERGOING cardiac surgery are at increased risk for excessive perioperative blood loss requiring transfusion of blood products, mainly due to the effects of preoperative medications, cardiopulmonary bypass (CPB), and hypothermia, which can cause thrombocytopenia and platelet dysfunction, dilution and consumption of coagulation factors, hyperfibrinolysis, and residual heparin effect. Intraoperative and postoperative bleeding remains a major complication of aortic surgery, having a significant effect on the clinical outcomes.[1] A strong relationship between bleeding after cardiac surgery and subsequent mortality has been described already, although it is not completely clear whether this is attributable to blood loss or transfusion-related side effects. Recently, a large, single-center, retrospective analysis of all types of cardiac surgery found that a major bleeding event was an independent predictor of surgical mortality.[2]

Three antifibrinolytic agents (aprotinin, tranexamic acid, and aminocaproic acid) commonly are used to minimize bleeding and reduce the need for blood products after cardiac surgery.[3]

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Aprotinin is a nonspecific serine protease inhibitor associated with reduced inflammatory response and organ-protective effects.[4] The mechanisms for these beneficial effects include inhibition of kallikrein, preservation of platelet (PLT) membranes, inhibition of neutrophil activation, and a reduction in fibrinolysis.[5–7] Several randomized controlled trials have shown that aprotinin decreases perioperative bleeding and the need for allogeneic blood transfusions.[8,9] However, concerns about the safety of aprotinin have been raised on the basis of findings from observational studies suggesting that aprotinin is associated with increased renal dysfunction, cerebrovascular accidents (CVAs), and mortality.[10–12]

Limited data are available about the effect of aprotinin in thoracic aortic surgery. Here, the authors report on a single-center, retrospective analysis comparing the early and mid-term clinical outcomes in patients undergoing adult thoracic aortic surgery with or without the use of aprotinin.

Materials and Methods

Study population

This was a single-center, retrospective, observational study on prospectively collected data obtained from the authors' institutional cardiac surgery dataset with some customized variables (ie, postoperative bleeding, use of blood products). The study was conducted in accordance with the principles of the Declaration of Helsinki. The local audit committee approved the study, and the requirement for individual patient consent was waived. Between January 2004 and December 2014, 846 adult patients underwent thoracic aortic surgery at Bristol Heart Institute. Data on the primary outcomes were not available for the entire population; for this reason and/or duplicated records, 314 patients were excluded from analysis (Fig 1). The final sample of 532 patients underwent surgeries on the thoracic aorta and included patients requiring circulatory arrest and surgery for acute aortic syndrome. The patients were divided in the following 2 groups: 107 patients (20.1%) received aprotinin during the surgery and represented the study group (Group A), whereas the remaining 425 patients (79.9%) underwent surgery without the use of aprotinin (Group B).

Endpoint and definitions

The primary endpoints were postoperative bleeding, redo surgery for bleeding and/or tamponade, and transfusion of blood products (packed red blood cells [RBCs], PLTs, fresh frozen plasma [FFP], and cryoprecipitate). A composite outcome of major bleeding was defined as 12 hours postoperative bleeding exceeding the 90th percentile of the entire distribution and/or the need for reoperaion for postoperative bleeding. This parameter was found to be an independent risk factor for postoperative mortality in cardiac surgery.[2]

In-hospital mortality was defined as death due to all causes within 30 days of surgery.

Secondary outcomes included acute kidney injury (AKI), defined per RIFLE (Risk, Injury, Failure, Loss of function, and End-stage renal disease) criteria using maximal change in serum creatinine[13]; evidence of postoperative stroke (defined as clinical and radiologic evidence of a new postoperative CVA); and long-term survival.

Surgical and intensive care management

Aprotinin was administered as a 280 mg (2 × 106 kIU) loading dose, followed by a maintenance infusion of 70 mg/h and priming of the CPB pump with 280 mg.

Anticoagulation during CPB was achieved with unfractionated heparin according to standard protocols: the initial dose was 300 IU/kg adjusted with further administration to achieve and maintain an activated clotting time >480 seconds. Heparin reversal was achieved with protamine sulfate (100 mg per 300 U of heparin) to normalize the activated clotting time after CPB. The decision for re-sternotomy for excessive bleeding was made on the basis of individual patient clinical status, mainly depending on the amount of blood drainage

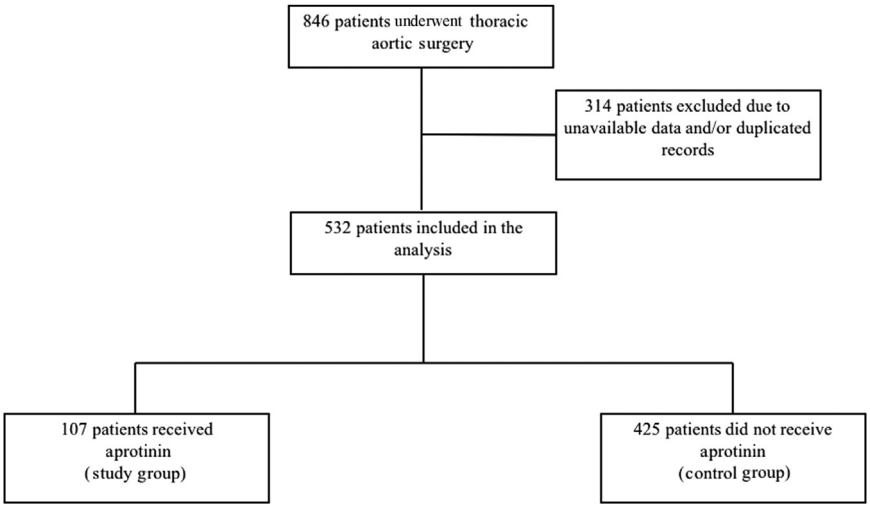

Fig 1. Patient selection flowchart.

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