# Safety and Efficacy of Aprotinin and Tranexamic Acid in Pulmonary Endarterectomy Surgery With Hypothermia: Review of 200 Patients

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*Background.* **The effectiveness and safety of aprotinin in cardiac surgery has been questioned. The study aim was to compare both the blood-sparing effect and side effects of aprotinin and tranexamic acid in patients undergoing pulmonary endarterectomy.**

*Methods.* **Data were analyzed retrospectively for 200 consecutive patients who underwent pulmonary endarterectomy between October 2006 and September 2009. Pulmonary endarterectomy was performed with deep hypothermia (20°C) in all patients. Antifibrinolytic therapy changed from aprotinin to tranexamic acid in June 2008 after the withdrawal of aprotinin in the United Kingdom.**

*Results.* **Mean age was 55.9 years, and 58% of subjects were male. One hundred patients were studied in each group. Postoperatively, a higher incidence of seizures in the first 48 hours was seen with tranexamic acid compared with aprotinin (11% versus 4%, $p = 0.06$). This difference became statistically significant when excluding patients with structural brain lesions from both groups (7 versus 0, $p = 0.02$). Tranexamic acid patients had significantly higher median blood loss (700 mL versus 525 mL, $p = 0.01$). There was no significant difference between the groups in reexploration for bleeding, renal failure requiring hemofiltration, intensive care unit stay, median total stay in hospital, or in-hospital mortality.**

*Conclusions.* **In our experience of patients undergoing pulmonary endarterectomy, the tranexamic acid group had a higher median blood loss and more seizures. The trend to increased seizure frequency in the tranexamic acid group may be a direct consequence of this treatment, consistent with other recently published reports.**

**(Ann Thorac Surg 2010;90:1432–6)**



Pulmonary endarterectomy (PEA) surgery is associated with prolonged cardiopulmonary bypass using hypothermia for organ protection, placing the patients at a high risk for bleeding during the postoperative period. Antifibrinolytic drugs, such as the bovine-derived polypeptide aprotinin, are used to reduce blood loss during cardiac surgery. Meta-analyses of randomized controlled studies have consistently showed that the use of aprotinin reduces the need for blood transfusion and reoperation due to excessive bleeding [1–4]. The synthetic lysine derivative tranexamic acid has become more popular in recent years after reports of decreased blood loss compared with placebo and an excellent safety profile; in addition, it is considerably less costly than aprotinin [2].

In the past, aprotinin was used for the majority of high-risk cardiac surgical patients in the UK as the antifibrinolytic agent of choice because of its superior efficacy compared with tranexamic acid [5]. Some studies showed no difference between aprotinin and tranexamic acid in adverse outcomes of mortality, stroke, myocardial infarction, or renal failure [6–9], whereas others reported an increased risk of postoperative dialysis [3, 10] in the aprotinin group.

Recently published prospective studies suggested that aprotinin was associated with increased mortality [11, 12], and it was subsequently withdrawn from the market after publication of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study [13]. After the publication of this study, we stopped using aprotinin, replacing it with tranexamic acid for all high-risk cardiac surgery patients. Shortly after this change, we observed an increased incidence of seizures, which has subsequently been documented in two published reports from another center [6, 11].

This study was conducted to evaluate the safety and efficacy of the current practice of using tranexamic acid compared with aprotinin in patients undergoing PEA.

## Material and Methods

Data were prospectively entered into a pulmonary hypertension and blood transfusion database and retrospectively analyzed for all patients who underwent pulmonary endarterectomy between October 2006 and

Accepted for publication June 14, 2010.

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0003-4975/$36.00
doi:10.1016/j.athoracsur.2010.06.083

September 2009 at the end of the 3-year period. Survival status and date of death after discharge was obtained using the UK's National Health Service tracing service. Administrative censoring time was taken to be January 29, 2010. This allowed 3 to 4 months from the last procedure, so there should be minimum bias due to reporting delays in the context of differential follow-up times. The local Research Ethics Committee approved the study; the requirement for written informed consent was waived as the study was retrospective and individual patients were not identified. Aprotinin was replaced by tranexamic acid in May 2008. We compared consecutive patients immediately before and after this change in antifibrinolytic strategy.

The aprotinin group received a $2 \times 10$ KIU loading dose, followed by a continuous infusion of $5 \times 10$ KIU/h until the end of the procedure, then for 1 more hour in the intensive care unit (ICU). In addition, $2 \times 10$ KIU was added to the cardiopulmonary bypass (CPB) circuit. The tranexamic acid group received a 30 mg/kg loading dose, followed by a continuous infusion of 15 $mg \cdot kg^{-1} \cdot h^{-1}$ until the end of the surgery. No tranexamic acid was added to the CPB circuit, and no other drugs were administered after induction of anesthesia and before surgical incision. Anticoagulation therapy for CPB was provided with heparin, 400 U/kg, to achieve an activated clotting time greater than 400 s.

All patients underwent surgery through median sternotomy with hypothermic CPB—core temperature of 20°C—using techniques similar to those established by the University of California at San Diego group [14], modified by our own experience. We have previously reported that complete circulatory arrest is not necessary in all patients [15], so some patients in this cohort had endarterectomies completed with partial circulation arrest and maintained antegrade cerebral perfusion (ACP), whereas others required complete deep hypothermic circulatory arrest (DHCA). Gradual rewarming to a bladder temperature of 36°C before the termination of CPB was identical with a standard protocol for all patients. Anticoagulation was reversed with protamine sulphate, 1 mg/100 U heparin. Further boluses of 50 mg protamine were administered if activated clotting time was elevated by more than 10% from baseline. Blood from the operative field was salvaged, processed, and reinfused using continuous cell salvage (CATS [Fresenius Kabi, Warrington, United Kingdom]). Triggers for transfusion were hemoglobin less than 6 g/dL during CPB or hemoglobin less than 10 g/dL after CPB. Cell salvage blood was administered before allogeneic blood.

Data collected included demographics, hourly postoperative blood loss (chest tube drainage), transfusion requirements, renal dysfunction requiring dialysis, seizures, ICU and hospital stay, and 30-day mortality. All PEA patients who suffered seizures in ICU underwent computed tomography of the brain within 24 hours of the seizure, and any structural defects were recorded. Intraoperative data consisted of CPB, cross-clamp, and DHCA times.

Continuous variables were summarized as the mean and standard deviation or, if the distribution of the variable was skewed, median and interquartile range (IQR). Categorical variables were summarized using frequencies. Differences between the two antifibrinolytic therapy groups were assessed using Fisher's exact test, the independent groups Student $t$ test, or the Mann-Whitney $U$ test as appropriate. The odds ratio and 95% confidence interval for acute events incidence, for tranexamic acid relative to aprotinin, were estimated using logistic regression, and inference was based on the likelihood ratio test. Estimation of cumulative survival was performed using the Kaplan-Meier method and compared using the log rank test.

## Results

Two hundred patients underwent PEA between October 2006 and September 2009. The drugs were used in consecutive periods, with tranexamic acid (n = 100) replacing aprotinin (n = 100) in June 2008. Demographic and operative summaries are presented in Tables 1 and 2. Although all patients were cooled to 20°C, complete circulatory arrest was utilized significantly more frequently in the tranexamic acid group compared with the aprotinin group (76 versus 51 patients, $p < 0.001$).

Postoperative variables are shown in Table 3. Patients in group tranexamic acid suffered significantly greater total blood loss (median 700 versus 525 mL, p = 0.014). This was true for both the patients who had complete DHCA (aprotinin median 525 [IQR 675]) versus tranexamic acid median 700 [IQR 800]) and patients who had partial arrest and ACP (aprotinin median 500 [IQR 500] versus tranexamic acid median 650 [IQR 750]). The subgroup differences were not significant at traditional thresholds owing to the smaller size of each subgroup ($p = 0.114$ and 0.144, respectively). Although more tranexamic acid patients required transfusion (any packed red blood cells, fresh frozen plasma, platelets, or cryoprecipitate), the difference was not statistically significant (77 versus 70, $p = 0.336$).

The incidence of the main outcome events for the two groups, along with an estimate of odds ratios and confidence intervals where appropriate, is shown in Table 4. There were no significant differences between the groups

*Table 1. Demographic and Operative Characteristics*

| Characteristic | Aprotinin (n = 100) | Tranexamic Acid (n = 100) | $p$ Value[a] |
|---|---|---|---|
| Sex, male:female | 58:42 | 57:43 | 1.000 |
| Age, years | 55.8 (16.6) | 56.1 (16.6) | 0.922 |
| First single PEA | 81 | 88 | 0.241 |
| Combined/redo | 19 | 12 | |
| Body mass index, $kg/m^2$ | 29.7 (5.9) | 28.4 (5.8) | 0.100 |

Data shown as mean (SD) or frequency. [a] The $p$ values refer to the Student $t$ test for continuous variables and Fisher's exact test for categorical variables.

PEA = pulmonary endarterectomy.