Prospective, Randomized, comparative study between aprotinin and tranexamic acid in cardiac surgery

Rabie Soliman3*, Hassan Yousef 4, Faisal Alghadam1, Adel Ragheb1, Mohamed Hussein6, Howaida Al Qethamy1, Makhlouf Belghith1 and Tarek Abdel Mageed2,3
*Correspondence: rabiesoliman@hotmail.com
1Prince Sultan cardiac center, Riyadh, Saudi Arabia.
2Madinah cardiac center, Madinah, Saudi Arabia.
3Cairo University, Egypt.
4 Ein Shams University, Egypt.
5Alazhar University, Egypt.

Abstract

Background: Cardiac surgery is associated with perioperative bleeding and a significant consumption of allogenic blood products. Minimizing blood loss and transfusion requirements is of vital importance to avoid complication related to blood products transfusion. This study was done to compare the hemostatic effects of aprotinin and tranexamic acid (TA) on reducing bleeding and blood products transfusion in adult cardiac surgery.

Methods: A prospective study involved 100 patients, classified randomly into two groups (N=50 each). Group A patients received intravenous infusion of 2 000 000 kallikrein inhibitory units (KIU) of aprotinin over 30 minutes, then infusion of 500 000 KIU/hr throughout the operation and 2 000 000 aprotinin KIU) were added to the CPB circuit. Group B patients received TA as 20 mg/kg over 10 minutes, then infusion 5 mg/kg/hr throughout the operation. The effects of aprotinin and TA were monitored by ACT, PT, INR, aPTT, platelets, fibrinogen, D-dimer, troponin I, blood losses, blood products transfusion, duration of thorax closure and serum creatinine level.

Results: Both groups were comparable in their baseline demographic and surgical characteristics. The differences of ACT, PT, INR, aPTT, platelets, fibrinogen, D-dimer, troponin I, blood losses, blood products transfusion, duration of thorax closure and serum creatinine level.

Conclusion: Aprotinin decreases fibrinolysis, blood losses, and need for blood products transfusion in comparison to TA during adult cardiac surgery. It is however associated with a trend for an increased incidence of acute renal failure. Use of aprotinin should be useful for cases at high risk for bleeding such as redo surgery. It should be used cautiously in patients with preoperative renal impairment.

Keywords: Adult cardiac surgery, aprotinin, tranexamic acid, cardiopulmonary bypass, blood loss, blood products transfusion

Introduction

Cardiopulmonary bypass (CPB) alters the hemostatic balance and predisposes cardiac surgery patients to an increased risk of coagulopathy and excessive perioperative bleeding [1]. This is one of the main causes of postoperative morbidity in cardiac surgical patients who require transfusion of blood components after cardiopulmonary CPB [2]. The pathophysiology of bleeding after CPB is multifactorial and complex, involving hypothermia, hemodilution, activation of coagulation, endothelial cell and tissue injury, foreign-surface contact, consumption of clotting factors, platelet activation, platelets dysfunction and hyperfibrinolysis [3,4,5]. Thrombin level increases during CPB despite systemic heparinization. This leads to generalized fibrinolysis during and immediately after CPB, with deleterious effects on platelets function. Increased fibrinolytic activity and platelets dysfunction are important causes of postoperative bleeding [4]. Procedures such as autologous blood predonation, isovolumic hemodilution, and equipment for blood cell saving [6], in addition to antifibrinolytic drugs such as aprotinin, tranexamic acid and ε-aminocaproic acid, were introduced in cardiac surgery to reduce the need for allogenic blood transfusions. Anti-fibrinolytic drugs are used to prevent platelets dysfunction and decrease perioperative bleeding. Varying results in terms of perioperative blood loss and blood transfusion requirements in different clinical settings have been described with the use of tranexamic acid and aprotinin [7].

The mechanism of action of aprotinin is complex. This agent has anti-inflammatory and anticoagulant properties that preserve hemostasis by inhibiting the contact pathway and possibly the tissue-factor pathway [8]. Aprotinin reversibly complexes with the active serine site in various proteases, including trypsin, plasmin, and kallikrein. It inhibits factor XIIa,
activation of complement, and kallikrein-mediated conversion of plasminogen to plasmin, thereby diminishing fibrinolysis, the increase in D-dimer levels and decreases thrombin generation during CPB [9,10,11].

Tranexamic acid is a synthetic lysine analogue antifibrinolytic drug. It acts by forming a reversible complex with plasminogen and plasmin through the lysine-binding sites, thereby blocking interaction with the specific lysine residues of fibrin. Although plasmin is still formed, it is unable to bind to fibrinogen. This minimizes the increase in primary fibrinolysis that occurs during CPB. Tranexamic acid preserves platelets function by reducing the effect of plasmin on platelets glycoprotein 1b receptors [12,13].

Our study was performed to compare the hemostatic effects of aprotinin and tranexamic acid on reducing bleeding and blood products transfusion in adult cardiac surgery patients.

Methods
The study was carried out as a prospective randomized investigation. After local ethics committee approval, all patients scheduled for coronary artery bypass graft (CABG) or valve surgery at Prince Sultan Cardiac Center, Riyadh, Saudi Arabia, during the period from December 2007 to November 2010, were screened for eligibility enrolment. The exclusion criteria included patients who had preoperative coagulopathy, recent administration of antiplatelets or anticoagulants (aspirin <5 days, heparin <4 hours, low molecular weight heparin <12 hours, clopidogrel <7 days, warfarin <3 days, or thrombolytic therapy <24 hours preoperatively), preexisting renal dysfunction (serum creatinine>115mmol/l), elevated liver enzymes more than 2 folds (aspartate transaminase, alanine transaminase and alkaline phosphatase), or aortic aneurysm surgery. One hundred patients met the requirements for inclusion, and informed consent was obtained from all of them. The patients were randomly allocated into one of the two groups (50 patients in each group). Group A (aprotinin, Trasylol, Bayer AG Germany): The patients received intravenous infusion of 2 000 000 kallikrein inhibitory units (KIU) of aprotinin over 30 minutes, then 5000 KIU/hr of aprotinin were administered continuously throughout the operation, until skin closure. In addition, 2 000 000 KIU were added to the priming solution of the CPB circuit.

Group B (Tranexamic acid, Cyklokapron, Pfizer, Belgium): The patients received tranexamic acid as 20 mg/kg as a bolus dose over 10 minutes, then infusion 5 mg/kg/hr after induction and continuously throughout the operation until skin closure.

Anaesthetic techniques included a variety of drugs, including etomidate, rocuronium, fentanyl, propofol, and sevoflurane, often in combination. All patients received 4mg/kg of heparin before bypass, aiming to provide an activated clotting time (ACT) > 480 seconds. After bypass, heparin was reversed with protamine which was titrated to achieve an ACT <140 seconds. CPB used centrifugal pumps with 1 to 1.5 L prime of ringer lactate, in addition to antibiotics, solutedrol and mannitol. Both antegrade and retrograde blood cardioplegia were used. Cooling was passive to around 34°C or active to 22°C. Packed red cells were administered to keep hemoglobin above 9 g/dl. Platelets, fresh frozen plasma, and cryoprecipitate were administered either intraoperatively if there was excessive generalized oozing with inability to close the chest, or postoperatively, if the chest drains loss was more than 3 ml/kg/hr. Acute renal failure was diagnosed according to RIFLE criteria [14].

Patients monitoring
For all patients, the following variables were closely monitored; the mean arterial pressure (MAP), heart rate, central venous pressure (CVP), laboratory investigations including hemoglobin, activated clotting time (ACT), prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), platelets, fibrinogen, D-dimer, troponin I, and creatinine. Also the thorax closure time, amount of blood losses, blood products transfusion through the postoperative 24 hours were monitored. Chest X-ray (CXR) was done preoperatively and on admission to CSICU, and as indicated to rule out widened mediastinum.

Statistical methods
Data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi square ($\chi^2$) test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results
Preoperative clinical data of Patients
Group A included 23 male and 27 female patient and group B included 26 male patient and 24 female patient. The mean age of group A patients was 49.10±16.65 year and group B was 48.12±16.09 year (P=0.786). The mean weight of group A patients was 81.57±19.74 kg and group B was 83.30±19.05 kg (P=0.692). Regarding the preoperative medical diseases when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi square ($\chi^2$) test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Surgical Data of patients
The elective cases included 40 patients in group A and 44 patients in group B(P=0.556), and the emergency cases were 10 patients in group A and 6 patients in group B(P=0.709). There were 15 CABG patients in group A and 19 CABG patient in group B (P=0.464), 23 patient had CABG with valvular surgery and 26 patients in group B(P=0.502), and 12 patients had
Table 1. Preoperative data of patients.

| Item                        | Group A (n=50) | Group B (n=50) | P-value |
|-----------------------------|----------------|----------------|---------|
| Sex                         | male           | female         |         |
| Age (year)                  | 49.10±16.65    | 48.12±16.09    | 0.786   |
| Weight (Kg)                 | 81.57±19.74    | 83.30±19.05    | 0.692   |
| Hypertension                | 11(22%)        | 10 (20%)       | 0.691   |
| DM                          | 12(24%)        | 9 (18%)        | 0.446   |
| Serum creatinine (mmol/l)   | 74±22          | 79±25          | 0.633   |
| Elevated liver enzymes<2folds | 6 (12%)    | 4 (8%)         | 0.105   |
| Carotid stenosis<50%        | 2 (4%)         | 4 (8%)         | 0.105   |
| Hemoglobin, EF: ejection fraction | 43.12±11.24 | 39.25±10.89    | 0.122   |
| DM                          | 3 (6%)         | 4 (8%)         | 0.385   |
| Troponin I (ng/ml)          | 0.046±0.128    | 0.041±0.149    | 0.736   |
| Aspirin                     | 17 (34%)       | 13 (26%)       | 0.648   |
| Clopidogrel                 | 12 (24%)       | 15 (30%)       | 0.457   |
| Warfarin                    | 14 (28%)       | 10 (20%)       | 0.251   |
| Heparin                     | 8 (16%)        | 5 (10%)        | 0.827   |
| LMWH                        | 3 (6%)         | 2 (4%)         | 0.208   |
| Heparin                     | 8 (16%)        | 5 (10%)        | 0.827   |
| Warfarin                    | 14 (28%)       | 15 (30%)       | 0.457   |
| Heparin                     | 8 (16%)        | 5 (10%)        | 0.827   |
| LMWH                        | 3 (6%)         | 2 (4%)         | 0.208   |
| EF%                         | 43.12±11.24    | 39.25±10.89    | 0.122   |
| MI                          | 3 (6%)         | 4 (8%)         | 0.385   |
| Fibrinogen                  | 3.57±0.51      | 3.51±0.55      | 0.001   |
| D-dimer                     | 1.12±0.429     | 2.56±0.48      | 0.001   |

Cardiopulmonary bypass data of patients

The mean heparin dose was 314.13±62.34 mg in group A and 304.00±74.85 mg in group B (P=0.511) and the mean ACT was 572.43±110.20 seconds in group A and 618.73±131.91 seconds in group B (P=0.092). After weaning from CPB, and stabilization of the patients, protamine was given. The mean dose of protamine was 326.25±60.10 mg in group A and 310.75±74.25 mg in group B (P=0.355). The mean ACT after protamine was 133.30±13.88 seconds in group A and 136.38±5.61 seconds in group B (P=0.308). The mean duration of CPB time was 123.65±23.84 minute in group A and 119.90±23.01 minute in group B (P=0.467). The aortic cross clamping time was 95.30±22.55 minute in group A and 98.60±20.96 minute in group B (P=0.316) and the mean temperature during CPB was 29.83±2.91°C in group A and 28.33±3.39 °C in group B (P=0.117) (Table 2).

Coagulation profiles

The mean preoperative PT in group A was 10.61±0.92 seconds and 11.12±1.28 seconds in group B (P=0.051). The mean INR was 1.02±0.12 in group A and 1.05±0.10 in group B (P=0.140). The mean aPTT was 40.02±7.92 seconds in group A and 41.60±9.02 seconds in group B (P=0.431). The mean ACT was 135.70±12.28 seconds in group A and 138.67±16.21 seconds in group B (P=0.358). The mean preoperative platelets number was 288.35±76.21(x10³/µl) in group A and 303.35±101.96(x10³/µl) in group B (P=0.458) (Tables 3,4). The mean postoperative PT was 10.05±1.04 seconds in group A and 10.13±1.13 seconds in group B (P=0.744). The mean INR was 1.20±0.22 in group A and 1.18±0.20 in group B (P=0.942). The mean aPTT was 41.60±7.56 seconds in group A and 41.38±7.71 seconds in group B (P=0.086). The mean ACT was 130.2±11.7 seconds in group A and 127.2±15.4 seconds in group B (P=0.245). The mean postoperative platelets number was 254.63±61.40(x10³/µl) in group A and 255.90±59.10(x10³/µl) in group B (P=0.060) (Tables 3,4).

Fibrinogen and D-dimer

The mean preoperative level of fibrinogen was 3.57±0.51 g/l in group A and 3.51±0.55 g/l in group B (P=0.625). The postoperative level mildly decreased in group A patients (3.25±0.51 g/l) and decreased greatly in patients of group B (2.56±0.48 g/l) (P=0.001) (Tables 3,4). The preoperative D-dimer level was within normal range in patients of both groups. The mean level was 0.27±0.116 µg/ml in group A and 0.27±0.117 µg/ml in group B (P=0.848). Postoperatively, the D-dimer mildly increased in group A patients (1.12±0.429 µg/ml) and greatly increased in group B patients (2.33±0.709 µg/ml) (P=0.001) (Tables 3,4).
Table 3. Preoperative coagulation profiles of patients.

| Item                  | Group A (n=50) | Group B (n=50) | P-value |
|-----------------------|----------------|----------------|---------|
| PT (second)           | 10.61 ± 0.92   | 11.12 ± 1.28   | 0.051   |
| INR                   | 1.02 ± 0.12    | 1.03 ± 0.10    | 0.140   |
| aPTT (second)         | 40.02 ± 7.92   | 41.60 ± 9.02   | 0.431   |
| ACT (second)          | 135.70 ± 12.28 | 138.67 ± 16.21 | 0.358   |
| Platelets (x10^3/µl) | 288.35 ± 76.21 | 303.35 ± 101.96 | 0.458   |
| Fibrinogen (g/l)      | 3.57 ± 0.51    | 3.51 ± 0.55    | 0.625   |
| D-dimer (µg/ml)       | 0.27 ± 0.116   | 0.27 ± 0.117   | 0.848   |

PT: prothrombin time, INR: international normalized ratio, aPTT: activated thromboplastin time, ACT: activated clotting time. Values are expressed as mean(SD).

Table 4. Postoperative coagulation profiles of patients.

| Item                  | Group A (n=50) | Group B (n=50) | P-value |
|-----------------------|----------------|----------------|---------|
| PT (second)           | 10.05 ± 1.04   | 10.13 ± 1.13   | 0.744   |
| INR                   | 1.20 ± 0.22    | 1.18 ± 0.20    | 0.942   |
| aPTT (second)         | 41.60 ± 7.56   | 41.38 ± 7.71   | 0.896   |
| ACT (second)          | 130.2 ± 11.7   | 127.2 ± 15.4   | 0.245   |
| Platelets (x10^3/µl) | 254.63 ± 61.40 | 255.90 ± 59.10 | 0.060   |
| Fibrinogen (g/l)      | 3.25 ± 0.51    | 2.56 ± 0.48    | 0.001   |
| D-dimer (µg/ml)       | 1.12 ± 0.42*   | 2.33 ± 0.70*   | 0.001   |

PT: prothrombin time, INR: international normalized ratio, aPTT: activated prothrombin time, ACT: Activated clotting time. Values are expressed as mean(SD). *P-value<0.05 in comparison to preoperative level.

Table 5. Blood losses and blood products transfusion.

| Item                  | Group A (n=50) | Group B (n=50) | P-value |
|-----------------------|----------------|----------------|---------|
| Blood loss (ml/24hour) | 775.38 ± 116.69 | 1125.00 ± 151.95 | 0.001   |
| P-RBC (unit)           | 2.95 ± 0.71    | 5.43 ± 1.31    | 0.001   |
| Platelets (unit)       | 2.98 ± 2.37    | 6.65 ± 4.08    | 0.001   |
| FFP (unit)             | 2.95 ± 2.06    | 7.33 ± 4.01    | 0.001   |
| Cryoprecipitate (unit) | 2.45 ± 2.05    | 5.75 ± 3.84    | 0.001   |
| HR (g/dl)              | 11.14 ± 1.18   | 10.89 ± 0.92   | 0.513   |

P-RBC: packed- red blood cells, FFP: fresh frozen plasma, HB: hemoglobin. Values are expressed as mean(SD).

Blood losses and blood products transfusion
The mean blood loss during the first 24 postoperative hours was 775.38±116.69 ml in group A and 1125.00±151.95 ml in group B (P=0.001). The number of transfused packed RBC units, was 2.95±0.71 unit in group A and 5.43±1.31 unit in group B (P=0.001). Group A patients received 2.98±2.37 unit compared to 6.65±4.08 unit in group B patients (P=0.001). Also the number of fresh frozen plasma units was 2.95±2.06 in group A compared to 7.33±4.01 unit in group B (P=0.001). Similarly, the number of cryoprecipitate units received in group A was 2.45±2.05 compared to 5.75±3.84 in group B (P=0.001). (Table 5).

Troponin I
The mean preoperative troponin I level was 0.046±0.128 ng/ml in group A and 0.041±0.149 ng/ml in group B (P=0.736). Postoperatively, there was mild elevation of troponin I in patients of both groups, but there was no ECG changes or hemodynamic instability. The mean postoperative troponin I level in group A was 1.02±0.56 ng/ml and in group B was 0.90±0.66 ng/ml (P=0.362). In both groups, the postoperative Troponin I level increased in comparison to the preoperative level (P<0.05) (Tables 1,6).

Creatinine level
There was no significant difference between the mean preoperative creatinine level in groups A and B (74±22 vs 79±25 mmol/l, respectively, P=0.633). The postoperative creatinine level increased in both groups, but still there was no significant difference between groups A and B (102±56 ng/ml vs 93±24 mmol/l, P=0.362). Four patients in group A suffered from acute renal failure and 2 patients in group B (P=0.05). and renal dialysis was needed for all those patients (Table 1,6).

Postoperative outcomes
There were 2 patients with acute myocardial infarction (AMI) in group A and one patient in group B (P=1.000), one patient with stroke (diagnosed by brain CT-scan) in group A and 2 patients in group B (P=1.000). One case in group A suffered from multisystem organ failure involving the lung (acute respiratory distress syndrome), the kidneys, the liver, and the heart (low cardiac output) as well as one case in group B (P=1.000). One case in group A and 2 cases in group B died due to intractable cardiogenic shock (within one week), as well as one case in each group due to multisystem organ failure (after one week) (P>0.05) (Table 6). No cases in either group had evidence of deep venous thrombosis or disseminated intravascular coagulopathy, DIC: disseminated intravascular coagulopathy, MOF: multisystem organ failure. Values are expressed as mean(SD), numbers (%). *P-value<0.05 in comparison to preoperative level.

Table 6. Postoperative outcomes.

| Item                      | Group A (n=50) | Group B (n=50) | P-value |
|---------------------------|----------------|----------------|---------|
| Creatinine (mmol/l)       | 100±28*        | 93±24*         | 0.065   |
| Renal impairment          | 6 (12%)        | 4 (8%)         | 0.460   |
| Postoperative ARF and HD  | 4 (8%)         | 2 (4%)         | 0.325   |
| AMI                       | 2 (4%)         | 1 (2%)         | 1.000   |
| Troponin I (ng/ml)        | 1.02±0.56*     | 0.90±0.56*     | 0.66*   |
| Neurological complication (stroke) | 1 (2%) | 2 (4%) | 1.000   |
| DVT                       | -              | -              |         |
| DIC                       | -              | -              |         |
| Mortality                 |                |                |         |
| Early (within one week)   | 1(2%)          | 2(4%)          | 1.000   |
| Late (after one week)     | 1(2%)          | 1(2%)          | 1.000   |
| MOF                       | 1(2%)          | 1(2%)          | 1.000   |

ARF: acute renal failure, HD: hemodialysis, AMI: acute myocardial infarction, DVT: deep venous thrombosis, DIC: disseminated intravascular coagulopathy, MOF: multisystem organ failure. Values are expressed as mean(SD), numbers (%). *P-value<0.05 in comparison to preoperative level.
group suffered from seizures, disseminated intravascular coagulopathy (DIC) or deep venous thrombosis.

**Discussion**

Cardiovascular surgery is associated with a remarkable use of allogenic blood products. Minimizing blood losses and transfusion requirements is of vital importance in cardiac surgery to avoid complication related to blood products transfusion. These complications may include increased risk for transfusion related reactions or infections, hypothermia, DIC, excessive fibrinolysis, dilutional coagulopathy, and metabolic acidosis, which may further exacerbate bleeding. Renal failure, arrhythmias, prolonged requirement for mechanical ventilation, longer hospital stay and increased mortality may also occur [15,16,17].

Our study showed that patients who received aprotinin during cardiac surgery had significantly lower blood losses and blood products transfusion compared to patients who received tranexamic acid (P<0.05). Later et al., indicated that aprotinin was about twice as effective as tranexamic acid in reducing total postoperative blood losses (P<0.001) and aprotinin reduced packed red blood cell transfusions more than tranexamic acid, although the difference did not reach statistical significance [18]. A prospective, randomized, double-blind study was done by Dietrich et al., enrolled 220 patients undergoing CABG or aortic valve replacement (AVR). The study demonstrated that, in the aprotinin group 47% of patients received allogenic blood during the hospital stay as compared to 61% in the tranexamic acid group (P=0.036) [19]. Other studies had the same results [20,21,22].

In our study, there were no significant differences regarding the coagulation profiles (PT, INR, aPTT, ACT, platelets) between the two groups (P>0.05). The heparin dosage between the two groups during CPB were also insignificant(P>0.05). Despotis GI et al., and Valter C. et al., reported that aPTT was significantly longer in the aprotinin group. This difference is due to the inhibition of the bean phosphatide activator used in the whole blood aPTT assay induced by aprotinin [23,24]. One study showed that heparin requirements were significantly reduced with aprotinin more than with tranexamic acid (P<0.001) [19].

The difference in the incidence of AMI between the two groups was insignificant (P>0.05). In spite of the elevated postoperative troponin I level in both groups, in comparison to the preoperative level, there was no ECG changes and the elevated troponin may be due to myocardial injury after cardiotoomy in cases associated with valvular surgery. Another study showed that troponin T levels postoperatively and on postoperative day 1 were significantly higher in the TA group (P=0.017), but finally, no difference in cardiac outcomes was observed [19]. Others have demonstrated an increased risk of AMI with aprotinin [25] and that administration of aprotinin should be avoided in coronary artery bypass graft and high-risk patients [26].

In our study, there were significant elevated levels of postoperative D-dimer and decreased fibrinogen with TA more than with aprotinin and this means that aprotinin decreases the fibrinolysis during CPB more than tranexamic acid and also this may explain the decreased blood losses and the decreased need for blood products. However, Barbara et al., reported that the concentrations of D-dimer remained at baseline in the recipients of aprotinin and TA acid but tripled in the controls (P<0.05) [27]. One study showed that, at all times intraoperatively and postoperatively, levels of D-dimer were greatly decreased with aprotinin and TA versus control (P<0.001), indicating that fibrinolysis persists after surgery [28]. Contrary to our findings, Valter et al., showed no difference in the levels of fibrinogen and D-dimer with time between tranexamic acid and aprotinin (P>0.05) [24].

There was no increase in mortality between the two study groups (P>0.05), and early mortality in both groups was due to severe preoperative AMI and refractory cardiogenic shock. Postoperatively, the patients were on inotropic supports and intra-aortic balloon pump. Late mortality was due to multi-system organ failure (acute respiratory distress syndrome, kidney, liver, heart (low cardiac output)) and severe sepsis. One study demonstrated that aprotinin decreases mortality in cardiac surgery [29]. In contrast another study showed that neither antifibrinolytic agents increased the incidence of mortality (P=0.62 compared with placebo) [18], while others have demonstrated an increased incidence of mortality with aprotinin [25].

In our study, there was a trend for a higher incidence of postoperative renal failure and hemodialysis in the aprotinin group compared to the TA group (8% vs 4% respectively). However, this did not reach statistical significance (P=0.325), most probably due to the small sample size. Several previous retrospective studies have shown aprotinin to be associated with an increased risk of postoperative renal failure [25,30,31,32]. In contrast, a prospective, randomized, placebo-controlled trial showed no significant difference between aprotinin and control groups on kidney function postoperatively [33]. Also several retrospective studies have shown no increased incidence of dialysis in aprotinin-treated patients compared with control [22,34,35,36]. So, there is a certain degree of controversy over the effect of aprotinin on kidney function postoperatively.

In our study, cerebral stroke affected one case in group A and 2 cases in group B (P>0.05). Those patients had bilateral carotid artery stenosis preoperatively, and it is possible that the cerebral insult was due to hypoperfusion or embolization from aortic cannulation during CPB. There was no postoperative seizures. However, other studies reported an increase in the number of seizures in patients treated with tranexamic acid [34,37]. This can be explained by the antagonistic effect of tranexamic acid on gamma-aminobutyric acid (GABA) receptors [38]. Some investigators have demonstrated that aprotinin decreases the incidences of stroke or encephalopa-
thy [36,39] and other have demonstrated an increased risk of stroke or encephalopathy [25].

Conclusion
Aprotinin decreases fibrinolysis, blood losses, and the need for blood products transfusion in comparison to TA during adult cardiac surgery. However, it was associated with a trend for an increased incidence of acute renal failure. Use of aprotinin should be useful for cases at high risk for bleeding such as redo surgery. It should be used cautiously in patients with preoperative renal impairment.

Limitations
Our study recognizes some limitations such as being single center study as well the small number of patients. Another shortcoming of this study, is the absence of a control group.

Competing interests
The authors declare that they have no competing interests.

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