

## Topical use of tranexamic acid in open heart surgery

Farid Ahmad Chaudhary,<sup>1</sup> Zahid Pervaz,<sup>2</sup> Sana Ilyas,<sup>3</sup> Muhammad Nabeel Niaz<sup>4</sup>

### Abstract

**Objective:** To determine the efficacy of topical pouring of tranexamic acid in reducing post-operative mediastinal bleeding, requirement for blood products and the rate of re-exploration for re-securing haemostasis or relief of pericardial tamponade after open heart surgery.

**Method:** The prospective, randomised, placebo-controlled, double-blind comparative study was conducted from March 2013 to September 2015 at Rehmatul-lil-Alameen Institute of Cardiology, Punjab Employees Social Security Institution, Lahore, and comprised patients scheduled for primary isolated elective or urgent open heart surgery. The subjects were divided into two equal groups. The tranexamic acid group received cardiac bath with 2gm of tranexamic acid diluted in 50ml of normal saline, while the placebo group received cardiac bath without tranexamic acid. Before the closure of sternum, the solution was poured into pericardial cavity as cardiac bath while the chest tubes were temporarily clamped. Data was entered into a pre-designed proforma.

**Results:** Of the 100 subjects, there were 50(50%) in each of the two groups. There was no difference in surgical characteristics and perioperative complications in the groups ( $p>0.05$ ). After 48 post-operative hours, total blood loss was significantly less in the tranexamic acid group compared to the placebo group ( $p<0.05$ ). Significantly less number of blood pints were transfused in the acid group than the placebo group ( $p<0.05$ ). No patient in the acid group was re-explored for excessive bleeding compared to 4(8%) in the placebo group.

**Conclusion:** There was significant reduction in post-operative blood drainage, need of blood products and rate of re-exploration after topical use of tranexamic acid in open heart surgery.

**Keywords:** Topical, Tranexamic acid, Surgery, Cardiac, Bleeding, (JPMA 68: 538; 2018)

### Introduction

Post-operative bleeding is one of the exigent issues in cardiac surgery. This entity may lead to an increase in need for transfusion of blood products that lengthens the period of stay in intensive care unit (ICU) and in hospital.<sup>1</sup>

Pericardial blood activates the extrinsic coagulation pathway whereas the non-endothelialised materials in the extracorporeal circuit during cardiopulmonary bypass (CPB) is activated by intrinsic pathway. Despite systemic doses of heparin, thrombin generation is observed during CPB. Thrombin not only converts fibrinogen to fibrin but also acts as the most powerful platelet activator. It activates the endothelium and fibrinolysis via release of tissue plasminogen activator from the endothelium. Consequently, generalised fibrinolysis occurs during and immediately after CPB.<sup>2</sup> In Lemer's observation, cardiopulmonary bypass circuit leads to significant fibrinolysis causing increased concentrations of plasmin and fibrin degradation products both of which are deleterious to platelet function.<sup>3</sup>

Exposing the blood to heart-lung machine and the use of systemic heparinisation change the character of blood and its coagulability. Dilution with priming solution is another major factor that affects the blood coagulation. Accurate reversal of the heparin effect will not be attained by protamine and it is one of the causes of excessive post-operative bleeding. Platelet dysfunction might be the result of dilution effect of perfusion circuit and also churning of platelets during circulation in the heart-lung machine. Critical thrombocytopenia may occur in platelet count to drop below 50,000 per cumm. Interaction of blood with the air and material of the pump circuit will cause consumption coagulopathy as it is an extracorporeal system and platelets will stick to the walls of tubing circuit. All the above mentioned factors lead to an excessive physiological, non-surgical blood loss.

Incidence of re-exploration due to bleeding in cardiac surgery with CPB was reported 2-7%, and among these 50-80% of bleeding was from medical reasons rather than surgical. Fibrinolysis was found to be one of the key factors leading to 25-45% of significant post-operative blood loss. Many anti-fibrinolytic drugs have long been used to decrease this issue of post-operative cardiac surgical bleeding. These include tranexamic acid (TXA), aminocaproic acid and aprotinin, but it carries a high risk of thromboembolic events and early graft closure due to

<sup>1</sup>Cardiothoracic Surgery, <sup>4</sup>Rehmatul-lil-Alameen Institute of Cardiology, PESSI, University of Lahore, <sup>2</sup>Cardiac Surgery, Sheikh Zayed Hospital, Lahore, <sup>3</sup>University of Lahore.

**Correspondence:** Farid Ahmad Chaudhary. Email: farid.chaudhary@yahoo.com

their non-selective systemic drug effects.<sup>4</sup>

TXA acts by forming a reversible complex with plasminogen and plasmin through the lysine binding site, thus blocking interaction with the specific lysine residue of fibrin. This process retards the fibrinolysis even though plasmin is still formed but unable to bind to fibrin.<sup>5</sup> TXA also preserves platelet function by reducing the effect of plasmin platelet glycoprotein 1b receptors.<sup>6</sup>

Furthermore, in cardiac surgery, especially in coronary artery bypass surgery (CABG) patients, surgeons have always been concerned about the venous and arterial graft patency. Graft patency is directly related to post-operative outcome along with mortality and morbidity.

Since long TXA is used not only systemically but also topically. Systemic TXA increased the risk of thromboembolic complications and resulted in an early graft closure in CABG.<sup>7</sup> This turned out to be the prime reason why surgeons hesitate to use anti-fibrinolytic agents intravenously or systemically. Topical TXA is not a novel method but it has not been widely accepted as a routine part of cardiac procedure.<sup>8</sup> When used topically, it was found to have low systemic absorption, no risk of graft closure, more rapid action in pericardial cavity, reasonably effective in controlling bleeding in haemorrhagic diathesis and in patients who were pre-operatively on anticoagulants. Other specialties also share positive experience with topical use of TXA, like bladder, gynaecological, oral and otolaryngeal surgeries.<sup>9-11</sup>

The current study was planned to find an alternative and effective drug which can be used with minimum systemic side effects in cases of open heart surgery.

## Patients and Methods

The prospective, randomised, placebo-controlled, double-blind comparative study was conducted from March 2013 to September 2015 at Rehmatul-lil-Alameen Institute of Cardiology, Punjab Employees Social Security Institution (PESSI), Lahore, and comprised patients scheduled for primary isolated elective or urgent open heart surgery. After approval was obtained from the institutional ethics committee, all potential subjects were scrutinised for eligibility. Patients who had coagulation profile not within the normal range were excluded. Informed consent was obtained from the subjects enrolled. The patients were randomly divided by computer software into two groups. Patients in Group 1 received cardiac bath with 2gm of TXA diluted in 50ml of normal saline. Group 2 patients received cardiac bath without TXA. Before the closure of sternum, the solution was poured into the pericardial cavity as a cardiac bath

while the chest tubes were clamped. After the completion of sternotomy closure by wires and skin suturing, the chest drain clamps were released. Doing this, approximately 15±5 minutes were given to the topically poured TXA to act and get absorbed in the pericardial cavity.

The anaesthetic management and conduction of CPB, closure technique and operating surgeons were standardised. Patients were pre-medicated using Inj. cefuroxime 1.5gm, Inj. vancomycin 500mg along with oral preparations of clobazam 10mg tablet, allopurinol 300mg tablet twice a day and omeprazole 20mg capsule.

Induction was done by using nalbuphine 0.3-3 mg/kg over 10-15 minutes while maintenance doses of 0.25-0.5 mg/kg were given as required. Other induction medications included propofol 100-150 mcg/kg/min or ketamine 1-4.5 mg/kg, midazolam 0.3-0.35 mg/kg and atracurium bromide 0.4-0.5 mg/kg. Isoflurane/sevoflurane 0.5-2.0%, pancuronium 0.06mg/kg were used to maintain anaesthesia during CPB. Besides, 400 units/kg of heparin was infused 4 minutes before CPB commencement. Target activated clotting time (ACT) of  $\geq 480$  seconds was achieved. Heparin boosters were given during CPB to maintain the ACT when needed. At CPB weaning off, protamine sulphate was administered (1mg/100 units heparin) to reverse the heparin, targeted to bring the ACT back to 80-120 seconds. Once the patient was shifted to surgical ICU, continuous low-grade suction at 5-10 cm of water (H<sub>2</sub>O) was initiated along with periodic milking of the drains. Pre and post-operative haemoglobin (Hb) level, platelet count, haematocrit (Hct%), activated partial thromboplastin time (APTT) and international normalized ratio (INR) were measured. Hourly drainage of the chest tubes was noted. Chest drains were removed once the drainage became nil and drainage fluid became serous. The subsequent total drainage volume was calculated.

A pre-designed study proforma was added to the routine post-operative documentary log of patient, recording blood drainage (hr./total), number of blood transfusions, event of re-exploration and other related incidences remarked with time and date.

Two-tailed unpaired student t-test was applied on parametric and non-parametric data and represented as mean  $\pm$  standard deviation.  $P < 0.05$  was considered statistically significant.

## Results

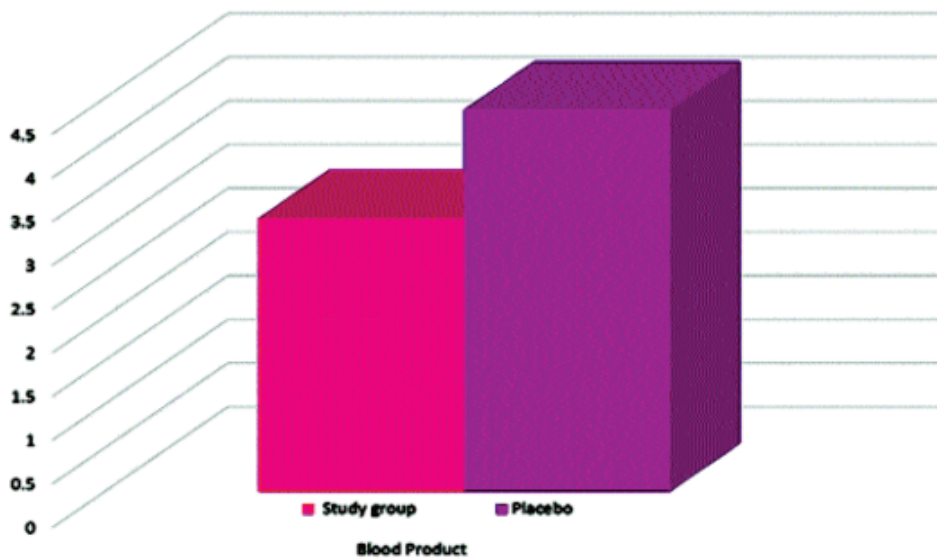
Of the 100 patients, there were 50(50%) in each of the two groups. There were 35(70%) males and 15(30%) females in Group 1 compared to 29(58%) males and 21(42%)

**Table-1:** Amount of blood drainage (ml).

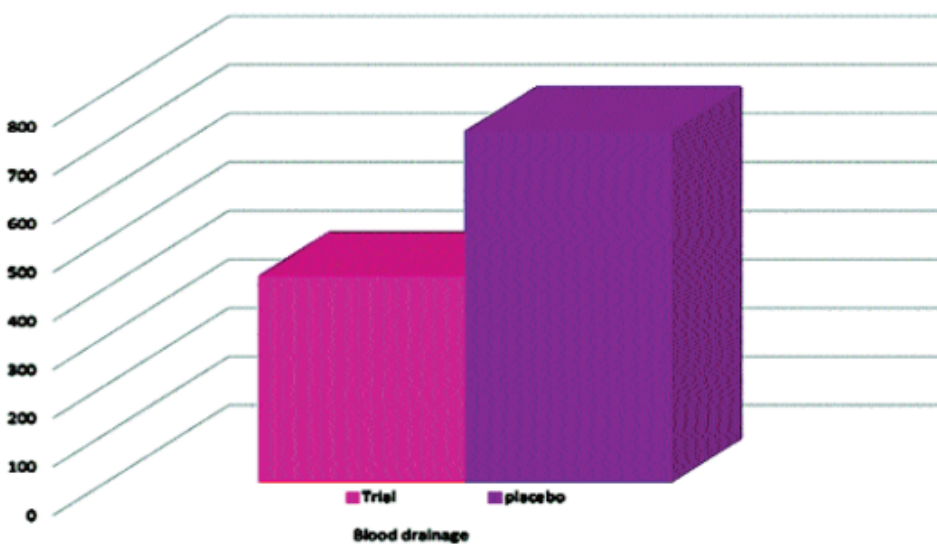
	Trial Drug	Placebo
Number of participant Analysed[unit: participants]	50	50
Total blood drainage from Mediastinal chest tubes at Time of removal(Assuming total blood loss)[units: ml]Mean ± Standard deviation	424.50±232.101	721.46±445.941

**Table-2:** Number of blood products required and used.

	Trial Drug	Placebo
Number of participant Analysed[unit: participants]	50	50
Number of Units of Blood Product Mean ± Standard deviation	3.12 ± 0.918	4.36 ± 1.225



**Figure-1:** Comparison of Total number of Blood products required and used in post operative period.



**Figure-2:** Comparison of Total amount of post operative Blood drainage in millilitres.

females in Group 2. There was no significant difference at baseline in terms of demographic and surgical data between the groups ( $p > 0.05$ ). Also, there was no difference in pre and post-operative Hb concentrations, platelet counts, Hc, APTT and INR between the groups ( $p > 0.05$  each). Chest drain output was significantly less in the first 48 hours in Group 1 compared to Group 2 ( $p < 0.05$ ) (Table-1).

There was a significant disparity in the number of post-operated blood transfusions in the two groups ( $p < 0.05$ ), with Group 2 requiring more blood products than Group 1 (Table-2).

There was no difference noted in intubation times between the groups ( $p > 0.05$ ). Apart from excessive bleeding, chest drain output led 4(8%) patients in Group 2 to surgical re-exploration in the immediate post-operative period. In contrast, Group 1 had no such case. There were no deaths reported in either of the two groups.

### Discussion

Mediastinal haemorrhage secondary to open heart surgery is one of the most known and fairly common complications of heart surgery.

In addition, the exposure of blood to CPB circuit and its dilutional effect results in altered coagulability which cannot be accurately reversed by protamine. Although technical errors in haemostasis account for the majority of cases, but fibrinolysis, coagulopathy originating from heart-lung machine, churning of platelets in perfusion circuit and its dilution effect may cause platelet dysfunction and critical thrombocytopenia leading to a drop in platelet count and an excessive non-surgical blood loss<sup>1</sup>.

Several antifibrinolytic agents have been introduced to decrease post-operative bleeding due to heart-lung machine and minimise transfusion requirements in cardiac surgery. Aprotinin was one of the most effective drugs of this class, but its use was discouraged by the Food and Drug Administration (FDA) after studies like international multicenter aprotinin graft patency experience (IMAGE) and blood conservation using antifibrinolytics randomized trial (BART) in high-risk cardiac surgery.<sup>4,12</sup>

In the IMAGE trial, use of aprotinin led to a statistically significant difference in graft occlusion rate against their controls when the results were adjusted contrary to the risks known to be associated with graft failure.<sup>4</sup> According to BART investigators, the risks of aprotinin far exceeded its benefits. It further mentioned that despite the possibility of a modest reduction in the risk of massive bleeding, the strong and consistent negative mortality trend associated with aprotinin compared with lysine analogues precludes its use in patients undergoing high-risk cardiac surgery.<sup>12</sup> Therefore, the benefit of systemic use of anti-fibrinolytic agents must always be reviewed against a possible risk of thromboembolic complications which might lead to an early graft closure. Moreover, these patients are at increased risk of mesenteric, cerebral, retinal and pulmonary thrombosis.<sup>4</sup> Following some admonishing reports of sudden deaths by aprotinin, TXA is another drug of this class with multiple studies suggestive of its usefulness in the reduction of post-operative blood loss in cardiac surgical cases.

TXA is an antiplasminic agent which acts by inhibiting the plasmin activation and this very plasmin is responsible for fibrinolysis by converting fibrin into fibrin degradation products (FDPs). TXA binds strongly with the lysine binding site (LBS), the site of fibrin affinity of plasmin, and plasminogen, thus, strongly inhibits the binding of plasmin and plasminogen to fibrin. In the presence of antiplasmins, such as alpha-2 macro globuli, in the plasma, the anti-fibrinolytic action of TXA is potentiated. Abnormal exacerbated plasmin causes inhibition of platelet aggregation and decomposition of coagulation

factors. Even mild exacerbation causes characteristic fibrin degeneration to occur first. Hence, in cases of ordinary haemorrhages, TXA appears to cause haemostasis by suppressing this fibrin degradation.<sup>13</sup>

First study of topical application of anti-fibrinolytic agents was reported back in 1993 which demonstrated evident reduction of both post-operative bleeding and need of transfusion after topical use of aprotinin in 25 coronary patients.<sup>14</sup> The results were further verified by double-blind, randomised trial on 100 patients undergoing cardiac operations with CPB in 1995.<sup>15</sup> Similar results were described by a study in 2004.<sup>16</sup>

TXA. In 2000, a study used TXA as topical application in a double-blind, controlled trial with 40 patients undergoing primary CABG with 36% reduction of bleeding during the first 3 post-operative hours. Though it failed to sustain itself in next 24 hours compared to the placebo group, there was no reduction in allogenic transfusions.<sup>17</sup> This encouraged another study in 2006 on the effect of the topical use of TXA in the pericardial cavity on post-operative bleeding following various open heart procedures in 100 patients. That study reported that topical application of TXA in patients led to a significant reduction of both post-operative mediastinal bleeding, and rate of re-exploration for haemostasis.<sup>18</sup> Another study in 2009 reported significant reduction with only 37% in post-operative blood loss occurrences in the first 24 hours after open heart surgery.<sup>4</sup>

Our study demonstrated that topical pouring of solution containing 2gm of TXA into the pericardial cavity after open heart surgery significantly reduced post-operative blood loss in the first 48 hours (43%). Contrary to these findings, a study did not find a statistically significant reduction in post-operative blood loss neither with topical application of aprotinin nor with TXA.<sup>19</sup>

In our study, the TXA group revealed lesser need of blood transfusions (Figure-1), decreased amount of bleeding (Figure-2) and decreased incidence of re-exploration for tamponade due to excessive bleeding in early post-operative period, without adding extra risk of early graft occlusion or early post-operative thromboembolic events due to the widespread systemic action of TXA compared to the placebo group.

Regarding the need of blood products, one study<sup>4</sup> achieved significant reduction only in platelet transfusions,<sup>4</sup> while another one<sup>18</sup> reported statistically significant reduction only in packed cells use with TXA topical pouring. Our study showed statistically significant decrease of blood products transfusion requirements

(Figure-1) in contrast to studies of either topical or systemic application of anti-fibrinolytic agents which failed to show significant differences in blood products transfusions.<sup>17,20-22</sup>

No patient in TXA group was re-explored for excessive bleeding compared to 4 in the placebo group in the current study.

The advantages of topical use of anti- fibrinolytic drugs in open heart surgery for reducing post-operative bleeding and transfusion requirement needs further clinical trials enrolling even larger number of patients.

In terms of limitations, the study could not measure TXA levels in serum, so it cannot comment on the magnitude of exact amount of drug absorption in systemic circulation through pericardial contact. The sample size was also relatively small. Multi-centre prospective control trials using a larger sample size combined with measuring of TXA serum levels and post-operative computed tomography (CT) angiogram graft studies are needed to further establish and authenticate its topical use in cardiac surgical procedures with higher risk of bleeding.

## Conclusion

There was significant reduction in post-operative blood drainage, need of blood product and rate of re-exploration after topical use of TXA in open heart surgery cases without adding extra risk of early graft thrombosis and other thromboembolic complications to the patients.

**Disclaimer:** The study was first presented at the 2015 annual meeting of Pakistan Society of Cardiothoracic Surgeons.

**Conflict of Interest:** None.

**Source of Funding:** None.

## References

- Ghavidel AA, Jalilifar N, Sharifi M, Ghasemzadeh B, Alinejad Z, Ghafarinejad MH, Khamushi A et al. Role of epsilon aminocaproic acid & tranexamic acid, vs placebo in reduction of mediastinal bleeding following open heart surgery. *Iranian J Card Surg* 2009; 2: 13-7.
- Santos AT, Kalil RA, Bauemann C, Pereira JB, Nesralla IA. A randomized, double-blind, and placebo-controlled study with tranexamic acid of bleeding and fibrinolytic activity after primary coronary artery bypass grafting. *Braz J Med Biol Res.* 2006; 39: 63-9.
- Lemmer JH Jr, Stanford W, Bonney SL, Breen JF, Chomka EV, Elderger WJ et al. Aprotinin for coronary bypass operations: efficacy, safety, and influence on early saphenous vein graft patency: A multicenter, randomized, double blind, placebo-controlled study. *J Thorac Cardiovasc Surg.* 1994; 107: 543-53.
- Fawzy H, Elmistekawy E, Bonneau D, Latter D, Errett L. Can local application of Tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trail. *J Cardiothorac Surg.* 2009; 4: 25.
- Dunn CJ, Goa KL. Tranexamic acid: A review of its use in surgery and other indications. *Drugs* 1999; 57: 1005-32.
- Hardy JF, Desroches J. Natural and synthetic antifibrinolytics in cardiac surgery. *Can J Anesth.* 1992; 39: 353-65.
- Ovrum E, Am Holen E, Abdelnoor M, Oystese R, Ringdal ML. Tranexamic acid (Cyklokapron) is not necessary to reduce blood loss after coronary artery bypass operations. *J Thorac Cardiovasc Surg.* 1993; 105: 78-83.
- Baric D, Biocina B, Unic D, Sutlic Z, Rudez I, Bacic VV et al. M. Topical use of antifibrinolytic agents reduce postoperative bleeding: A double-blind, prospective, randomized study. *Eur J Cardiothorac Surg.* 2007; 31: 366-71.
- Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs.* 1985; 29: 236-61.
- Valsecchi A. Further notes on the topical use of tranexamic acid in the treatment of gynaecological hemorrhage. *Minerva Ginecol.* 1980; 32: 825-30.
- Sindet-Pedersen S, Ramstrom G, Bernvil S, Blomback M. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. *N Engl J Med.* 1989; 320: 840-3.
- Fergusson DA, Hébert PC, Mazer CD, Frenes S, MacAdams C, Markin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med.* 2008; 358: 2319-31.
- Haemic (Tranexamic acid) antiplasmin action [image on internet] [Online]. 2015 [Cited 2016 August 7]. Available from URL: [http://genixpharma.com/wp-content/uploads/2015/08/Haemic\\_Insert1.pdf](http://genixpharma.com/wp-content/uploads/2015/08/Haemic_Insert1.pdf).
- Tatar H, Çiçek S, Demirkiliç U, Ozal E, Süer H, Öztürk O et al. Topical use of aprotinin in open heart operations. *Ann Thorac Surg.* 1993; 55: 659-61.
- O'Regan DJ, Giannopoulos N, Mediratta N, Kendall SW, Furni A, Pillai R et al. Topical aprotinin in cardiac operations. *Ann Thorac Surg.* 1994; 58: 778-81.
- Khalil PN, Ismail M, Kalmar P, von Knobelsdorff G, Marx G. Activation of fibrinolysis in the pericardial cavity after cardiopulmonary bypass. *Thromb Haemost.* 2004; 92: 568-74.
- De Bonis M, Cavaliere F, Alessandrini F, Lapenna E, Santarelli F, Moscato U et al. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. *J Thorac Cardiovasc Surg.* 2000; 119: 575-80.
- Abul-Azm A, Abdullah KM. Effect of topical tranexamic acid in open heart surgery. *Eur J Anaesthesiol.* 2006; 23: 380-4.
- Yasim A, Asik R, Atahan E. Effects of topical applications of aprotinin and tranexamic acid on blood loss after open heart surgery. *Anadolu Kardiyol Derg.* 2005; 5: 36-40.
- Vanek T, Jares M, Fajt R, Straka Z, Jirasek K, Kolesar M, et al. Fibrinolytics inhibitors in off-pump coronary surgery: a prospective, randomized, double-blind TAP study (tranexamic acid, aprotinin, placebo). *Eur J Cardiothorac Surg* 2005; 28: 563-8.
- Mongan PD, Brown RS, Thwaites BK. Tranexamic acid and aprotinin reduce postoperative bleeding and transfusions during primary coronary revascularization. *Anesth Analg.* 1998; 87: 258-65.
- Casati V, Guzzon D, Oppizzi M, Cossolini M, Torri G, Calori G et al. Tranexamic acid compared with high-dose aprotinin in primary elective heart operations: effects on perioperative bleeding and allogeneic transfusions. *J Thorac Cardiovasc Surg.* 2000; 120: 520-7.