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ORIGINAL ARTICLE

Tranexamic acid after cardiopulmonary bypass does not increase risk of postoperative seizures: a retrospective study

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Abstract

Objective To evaluate the effects of administering tranexamic acid (TXA) after cardiopulmonary bypass, instead of after anesthesia induction, on postoperative seizures and blood transfusion requirements.

Methods Adult patients who underwent valve surgery and/or coronary artery bypass grafting at West China Hospital between July 1, 2011 and December 31, 2016 were retrospectively analyzed. Patients either received TXA after bypass ($n=2062$) or not ($n=4236$). Logistic regression and propensity score matching analysis were performed to assess effects of TXA on postoperative seizures and blood product requirements in hospital.

Results Among 6298 patients, seizures occurred in 2.4% (102/4236) in the no-TXA group and 2.7% (56/2062) in the TXA group ($P=0.46$). The number of patients receiving any blood products was greater in the no-TXA group (57.3%, 2428/4236) than in the TXA group (53.1%, 1095/2062) ($P<0.01$), and the volume of blood products was also greater in the no-TXA group (1.5 vs. 1.0 units, $P<0.01$). TXA was not associated with increased incidence of postoperative seizures (adjusted OR 1.16, 95% CI 0.83–1.62) but was associated with lower incidence of a requirement for blood products (adjusted OR 0.82, 95% CI 0.73–0.92). Similar results were obtained after patients from the two groups were matched based on propensity scoring. TXA was associated with reduced requirements for fresh frozen plasma, platelets and cryoprecipitate, but not red blood cells.

Conclusions Administering TXA after bypass may reduce requirements for blood products without increasing risk of seizures following cardiac surgery.

Keywords Tranexamic acid · Cardiopulmonary bypass · Seizures · Blood product requirements

Introduction

Cardiac surgery under cardiopulmonary bypass (CPB) is often associated with a greater requirement for blood products than procedures without CPB [1], which may be due to excessive bleeding induced by the consumption of coagulation factors and activation of fibrinolysis during CPB [2, 3]. Tranexamic acid (TXA), a lysine analogue that inhibits fibrinolysis, has been increasingly used to reduce bleeding and requirements for allogeneic blood products in cardiac surgery [4–6]. However, some authors report a dose-dependent association between TXA and seizures [7, 8], which may lead to neurological deficits and perioperative mortality [9, 10].

TXA is recommended to be given as a bolus after induction of anesthesia, and then to be continuously administered intravenously to maintain an effective concentration in the plasma [11–13]. Since TXA inhibits fibrinolysis during CPB, microthrombi inevitably form, even when high-dose heparin is used [14]. This may explain why administering TXA after anesthesia induction increases risk of cerebral infarction [15]. To avoid the risk of thrombus formation, it may be safer to administer TXA after CPB instead of after anesthesia induction, because the vascular endothelium transitions from a procoagulation state during CPB to an anticoagulation state after CPB [16].

These considerations led us to administer TXA after CPB rather than after anesthesia induction at West China Hospital from July 1, 2011 onwards. The present study retrospectively examined patients' records from this date until the end of 2016 to assess whether this alteration mitigated risk

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of postoperative seizures without compromising the drug's ability to reduce blood product requirements.

Methods

Patients

This retrospective study considered patients at least ≥ 18 years old who underwent elective valve surgery and/or coronary artery bypass grafting (CABG) involving CPB in the Heart Center of West China Hospital between July 1, 2011 and December 31, 2016. Those who died within 24 h after surgery or for whom medical records were incomplete were excluded.

This study was approved by the Ethics Committee of West China Hospital (no. 256, 2017), which waived the requirement for informed consent since it was retrospective.

Data collection

Demographic characteristics, medical and medication history, duration of stay in the intensive care unit (ICU) and postoperative hospitalization stay were collected from the Hospital Information System. Previous medication included beta blockers, anticoagulant and antiplatelets. Laboratory results, blood cell counts, conventional coagulation examinations and blood biochemistry tests were collected from the Laboratory Information System. Intra-operative data, including type of surgery, duration of CPB, aortic clamp duration and use of TXA were collected from operating records. Data on blood product use were collected from the laboratory information system of the Department of Blood Transfusion.

Cardiac surgical procedure

Based on recommendations [4], aspirin was used until the day of surgery, and clopidogrel use was suspended for 5 days before surgery.

Anesthesia induction and CPB were performed according to standard protocols at our hospital [17]. Briefly, anesthesia was induced with midazolam, sufentanil, and muscle relaxant; then maintained with continuous infusion of remifentanil and propofol, intermittent muscle relaxant, and/or inhalation of sevoflurane. Pump equipment included a roller pump, membrane oxygenator (Medtronic, Minneapolis, MN, USA), and tubing system. Heparin was used to maintain an activated clotting time > 480 s. During CPB, body temperature was maintained at 32–33 °C. Patients in both groups were primed with 1600–1800 mL solution (colloid and crystalloid in a 2:1 ratio with 3750 units of heparin) [18], and cardiac arrest was achieved by 4:1 cold blood cardioplegia. After bypass, heparin was neutralized by administering protamine in a 1:1 ratio with the initial heparin dose. After CPB, anesthesiologists administered TXA (15–50 mg kg^{-1}) for 30 min when coagulation disorders and hemorrhaging in the surgical field and based on personal experience.

Outcomes

Outcomes were compared between patients who received TXA after bypass and those who did not receive TXA. The primary outcome was postoperative seizures, defined as new-onset transient dysfunction of the nerve system manifesting as abnormal involuntary movement of the limbs [19]. The diagnosis of postoperative seizures was examined by a neurologist who was blinded to whether a given patient received TXA or not.

The secondary outcome was perioperative requirements for blood products including packed red blood cells, fresh frozen plasma, platelets and cryoprecipitate. As per standard protocols at our hospital, red blood cells were given when hemoglobin concentration was lower than 8 g dL^{-1} during surgery and 9.5 g dL^{-1} in the intensive care unit (ICU). One unit (200 mL) of fresh frozen plasma was given when prothrombin time was longer than 15 s and mediastinal drainage was also in excess of 150 mL h^{-1} [20]. Platelets were transfused without strict adherence to predefined rules but rather at the attending physician's discretion, typically when platelet count was below 50×10^9 L^{-1} during routine blood analysis performed as a result of obvious bleeding.

Other outcomes included length of ICU stay, length of postoperative hospitalization and surgical re-exploration for hemostasis.

Statistical analysis

Data were analyzed using the "MatchIt", "sqldf" and "epiDisplay" packages in R 3.5.1 (https://www.r-project.org). Skewed data were reported as median and interquartile range. Differences in categorical variables between TXA and no-TXA patients were assessed for significance using chi-squared or Fisher's exact tests; differences in continuous variables were assessed using Kruskal–Wallis tests. Multivariate logistic regression was used to determine factors associated with the risk of seizures and with consumption of blood products.

To balance patient characteristics between the TXA and no-TXA groups, patients from the two groups were matched based on propensity scores calculated for the following parameters: age, gender, history of smoking, history of hypertension, infective endocarditis, atrial fibrillation, cardiac catheterization, repeat surgery, respiratory dysfunction, stroke, diabetes mellitus, liver dysfunction and gastrointestinal bleeding, preoperative medication (beta blockers, anticoagulants, antiplatelet drugs), preoperative laboratory

results (hemoglobin, white blood cell count, platelet count, international normalized ratio, fibrinogen), type of surgery, and CPB time. The matching ratio was 1:1. Patients were considered well matched if the two groups showed a mean difference of no more than 0.1 for the abovementioned variables.

Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant, and all reported P values were two-tailed.

Results

Patient characteristics

A total of 6333 adult patients were screened from the database, of whom 3 were excluded because they underwent aortic replacement surgery, 10 because CPB time was not recorded and 9 because outcomes data were incomplete. And 13 patients who died within 24 h after operation were also excluded, 4 received 15–20 mg kg^{-1} TXA after CPB. All of these four patients, together with other seven patients who did not receive TXA, died from severe circulatory failure. The other two patients died of cardiac rupture. The resulting 6298 were included in the final analysis (Fig. 1). These patients were divided into a TXA group ($n = 2062$) who received the drug after bypass at a median dose of 31 mg kg^{-1} (interquartile range 18–36), and a control group ($n = 4236$) who did not receive TXA at any time.

Patients in the TXA group were more likely to have a higher preoperative level of fibrinogen, and their CPB lasted longer. Patients in the control group showed higher platelet counts and were more likely to undergo CABG or combined surgery and to have a history of infective endocarditis and use of β-blockers and anticoagulants.

Propensity score matching generated 2062 control-TXA pairs, which were well matched at baseline (Table 1).

Postoperative seizures

Among all patients, postoperative seizures occurred in 158 (2.5%); seizure incidence was similar in the TXA group (2.7%) and no-TXA group (2.4%; $P = 0.463$) (Table 2). Logistic regression identified the following independent risk factors of seizures: male, older age, use of beta blockers, and longer CPB duration (Table 3). After adjustment for these factors, logistic regression suggested that TXA after CPB was unrelated to seizures (OR 1.16, 95% CI 0.83–1.62; $P = 0.385$; Table 4).

In the matched subset of 4124 patients, 102 (2.5%) developed seizures, for which incidence was similar in the TXA group (2.7%) as in the no-TXA group (2.2%, $P = 0.316$; Table 2). TXA after CPB was not associated with increased risk of postoperative seizures (OR 1.22, 95% CI 0.82–1.82; Table 4).

Restricted cubic spline (RCS) graph was performed to clarify if TXA dose-dependently affect the risk of convulsive seizures. The horizontal axis was referred to the dose of

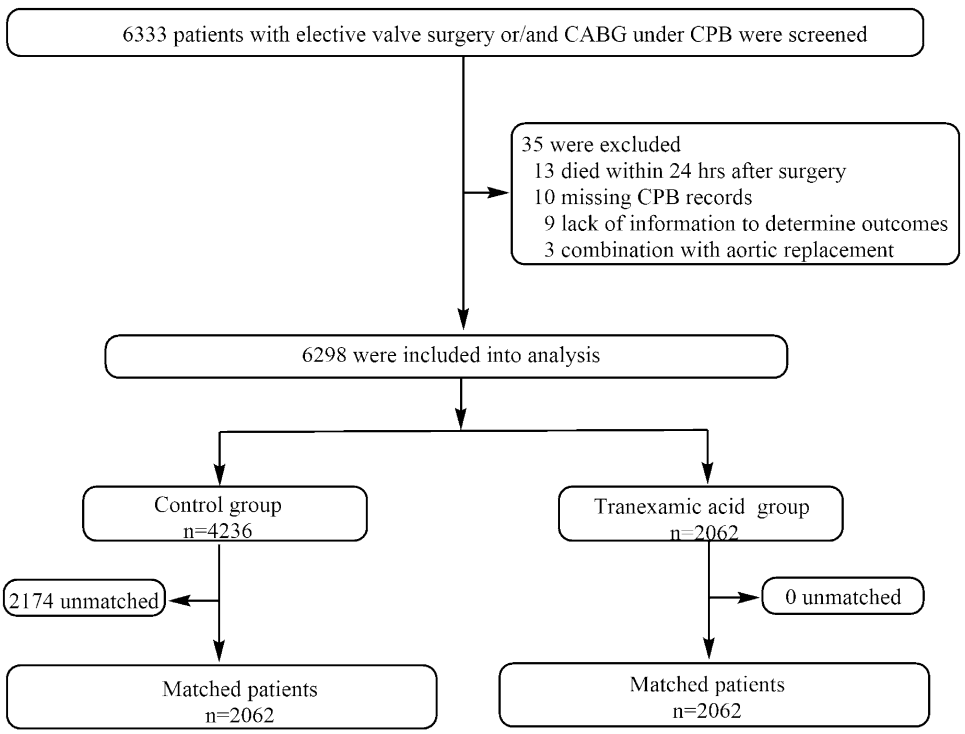

Fig. 1 Patients screening. A total of 6333 adult patients were screened from the database. After 35 were excluded, 6298 were included in the final analysis, which were divided into a TXA group ($n = 2062$) and the no-TXA group ($n = 4236$) according to whether they received TXA. Propensity score matching was used to generate 2062 control-TXA pairs

Table 1 Characteristics of the patients who received or did not receive tranexamic acid, before and after propensity score matching

Variables	Before matching			After matching		
	TXA ($n=2062$)	No TXA ($n=4236$)	Mean diff.	TXA ($n=2062$)	No TXA ($n=2062$)	Mean diff.
Demographics						
Male, *n* (%)	817 (39.6)	1695 (40.0)	− 0.004	817 (39.6)	821 (39.8)	− 0.008
Age, years	50 (44, 59)	51 (44, 60)	− 0.229	50 (44, 59)	51 (44, 59)	− 0.060
Smoking, *n* (%)	557 (27.0)	1147 (27.1)	− 0.001	557 (27.0)	571 (27.7)	− 0.009
Medical history						
Circulation						
Hypertension, *n* (%)	255 (12.4)	556 (13.1)	− 0.008	255 (12.4)	265 (12.9)	− 0.019
Infective endocarditis, *n* (%)	32 (1.6)	99 (2.3)	− 0.008	32 (1.6)	40 (1.9)	0.002
Atrial fibrillation, *n* (%)	1018 (49.4)	1999 (47.2)	0.022	1018 (49.4)	1017 (49.3)	0.015
History of cardiac catheterization, *n* (%)	309 (15.0)	812 (19.2)	− 0.042	309 (15.0)	298 (14.4)	− 0.007
History of repeat cardiac surgery, *n* (%)	18 (0.9)	34 (0.8)	0.001	18 (0.9)	17 (0.8)	0.001
Lung						
Respiratory dysfunction, *n* (%)	50 (2.4)	88 (2.1)	0.004	50 (2.4)	52 (2.5)	0.004
Stroke						
Transient ischemic attack, *n* (%)	9 (0.4)	21 (0.5)	− 0.001	9 (0.4)	12 (0.6)	− 0.001
Stroke-ischemia, *n* (%)	75 (3.6)	143 (3.4)	0.003	75 (3.6)	74 (3.6)	− 0.001
Stroke-bleeding, *n* (%)	5 (0.2)	11 (0.3)	− 0.000	5 (0.2)	7 (0.3)	0.001
Endocrine system						
Diabetes mellitus, *n* (%)	104 (5.0)	264 (6.2)	− 0.012	104 (5.0)	103 (5.0)	− 0.001
Digestive system						
Liver dysfunction, *n* (%)	108 (5.2)	261 (6.2)	− 0.009	108 (5.2)	113 (5.5)	0.000
Gastrointestinal bleeding, *n* (%)	10 (0.5)	17 (0.4)	0.001	10 (0.5)	11 (0.5)	0.001
Renal dysfunction, n (%)	3 (0.1)	11 (0.3)	0.001	3 (0.1)	4 (0.2)	0.000
Medicines						
Beta blockers, *n* (%)	170 (8.2)	570 (13.5)	− 0.052	170 (8.2)	173 (8.3)	0.001
Anticoagulant, *n* (%)	248 (12.0)	652 (31.6)	− 0.034	248 (12.0)	253 (12.3)	− 0.002
Antiplatelet drugs, *n* (%)	15 (0.7)	34 (0.8)	− 0.001	15 (0.7)	19 (0.9)	0.002
Preoperative laboratory examination						
Hemoglobin, g dL^{-1}	13.6 (12.4, 14.6)	13.5 (12.4, 14.6)	0.025	13.6 (12.4, 14.6)	13.5 (12.5, 14.7)	0.021
WBC, $\times 10^9$ L^{-1}	5.7 (4.8, 6.9)	5.8 (4.9, 7.0)	− 0.138	5.7 (4.8, 6.9)	5.8 (4.9, 6.9)	− 0.003
Platelets, $\times 10^9$ L^{-1}	146 (111, 186)	150 (115, 191)	− 4.916	146 (111, 186)	146 (112, 183)	0.029
INR	1.0 (1.0, 1.1)	1.1 (1.0, 1.1)	0.001	1.0 (1.0, 1.1)	1.1 (1.0, 1.1)	0.005
Fibrinogen, g L^{-1}	2.8 (2.4, 3.3)	2.7 (2.4, 3.2)	0.011	2.8 (2.4, 3.3)	2.8 (2.4, 3.2)	− 0.000
In the operating room						
Surgery type, *n* (%)			− 0.032			− 0.013
Valve surgery	1911 (92.7)	3804 (89.8)		1911 (92.7)	1914 (92.8)	
CABG	134 (6.5)	384 (9.1)		134 (6.5)	128 (6.2)	
Valve + CABG	17 (0.8)	48 (1.1)		17 (0.8)	20 (1.0)	
CPB duration, min	115 (92, 142)	113 (88, 139)	2.771	115 (92, 142)	117 (90, 143)	0.022

Values are *n* (%) or median (interquartile range)

TXA, tranexamic acid; CABG, coronary artery bypass grafting; WBC, white blood cell; INR, international normalized ratio; CPB, cardiopulmonary bypass

TXA (mg kg^{-1}), while vertical axis represented risk index of seizures (log [$risk_{TXA}/risk_{no\text{-}TXA}$]). When the risk index was equal to zero, the corresponding dose of TXA was 31 mg kg^{-1} (Fig. 2), which indicated higher dose of TXA (more than 31 mg kg^{-1}) may increase the risk of convulsive seizures. So, patients were divided into three groups

Table 2 Outcomes in the two patient groups, before and after propensity score matching

Outcome	Before matching			After matching		
	TXA ($n=2062$)	No TXA ($n=4236$)	*P* value	TXA ($n=2062$)	No TXA ($n=2062$)	*P* value
Seizures, *n* (%)	56 (2.7)	102 (2.4)	0.463	56 (2.7)	46 (2.2)	0.316
Blood product requirements						
Any blood products						
Median (P_{25}, P_{75}) (units)	1.0 (0, 3.5)	1.5 (0, 4.0)	0.002	1.0 (0, 3.5)	1.5 (0, 4.0)	0.014
n (%)	1095 (53.1)	2428 (57.3)	0.002	1095 (53.1)	1161 (56.3)	0.039
Packed red blood cells						
Median (P_{25}, P_{75}) (units)	0 (0, 2.0)	0 (0, 2.0)	0.150	0 (0, 2.0)	0 (0, 2.0)	0.190
n (%)	860 (41.7)	1684 (39.8)	0.138	860 (41.7)	811 (39.3)	0.120
Fresh frozen plasma						
Median (P_{25}, P_{75}) (units)	0 (0, 1.4)	0 (0, 1.8)	< 0.001	0 (0, 1.4)	0 (0, 1.9)	< 0.001
n (%)	547 (26.5)	1353 (31.9)	< 0.001	547 (26.5)	667 (32.3)	< 0.001
Platelets						
Median (P_{25}, P_{75}) (units)	0 (0, 0)	0 (0, 0)	< 0.001	0 (0, 0)	0 (0, 0)	< 0.001
n (%)	205 (9.9)	718 (16.9)	< 0.001	205 (9.9)	311 (15.1)	< 0.001
Cryoprecipitate						
Median (P_{25}, P_{75}) (units)	0 (0, 0)	0 (0, 0)	0.008	0 (0, 0)	0 (0, 0)	0.009
n (%)	109 (5.3)	297 (7.0)	0.009	109 (5.3)	149 (7.2)	0.010
Length of ICU stay, day	2 (2, 3)	2 (2, 3)	0.387	2 (2, 3)	2 (2, 3)	0.625
Length of postoperative hospitalization, day	8 (7, 10)	8 (7, 10)	< 0.001	8 (7, 10)	8 (7, 10)	< 0.001
Surgical re-exploration for hemostasis, *n* (%)	18 (0.9)	48 (1.1)	0.341	18 (0.9)	27 (1.3)	0.177

ICU intensive care unit

Table 3 Assessment of potential risk factors of postoperative seizures

Variable	Unadjusted		Adjusted[a]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male vs. female	1.93 (1.40, 2.65)	< 0.001	1.74 (1.25, 2.41)	0.001
Age	1.04 (1.02, 1.06)	< 0.001	1.04 (1.03, 1.06)	< 0.001
Atrial fibrillation	1.34 (0.98, 1.84)	0.069	1.29 (0.92, 1.81)	0.137
History of cardiac catheterization	1.32 (0.91, 1.94)	0.149	0.66 (0.42, 1.03)	0.066
Respiratory dysfunction	0.57 (0.14, 2.31)	0.427	0.32 (0.07, 1.36)	0.121
Beta blockers	1.87 (1.25, 2.79)	0.002	1.61 (1.05, 2.46)	0.028
CPB duration (min)	1.01 (1.01, 1.01)	< 0.001	1.01 (1.01, 1.01)	< 0.001
CABG vs. valve surgery	1.79 (1.12, 2.86)	0.015	1.84 (0.78, 4.33)	0.163
Combined surgery vs. only valve surgery	3.53 (1.39, 8.92)	0.008	3.01 (0.96, 9.51)	0.060

[a]Adjusted by gender, age, atrial fibrillation, history of cardiac catheterization, respiratory dysfunction, beta blockers, surgery type and CPB duration

Table 4 Relationship between tranexamic acid after cardiopulmonary bypass and postoperative seizures

Outcome	Before matching[a]		After matching	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Seizures	1.16 (0.83, 1.62)	0.385	1.22 (0.82, 1.82)	0.317

[a]Risk of seizures was adjusted by gender, age, use of beta blockers and CPB duration

including low-dose TXA (L-TXA for short, < 31 mg kg^{-1}), high-dose TXA (H-TXA for short, ≥ 31 mg kg^{-1}), and no-TXA group. Based on the chi-squared test, the incidence of seizures both in L-TXA group and H-TXA group had no significant difference compared with that of no-TXA group ($P=0.153$ before matching; $P=0.119$ after matching) (Table 5). These results suggested that the dose of TXA raging from 15 to 50 mg kg^{-1} had no significant influence

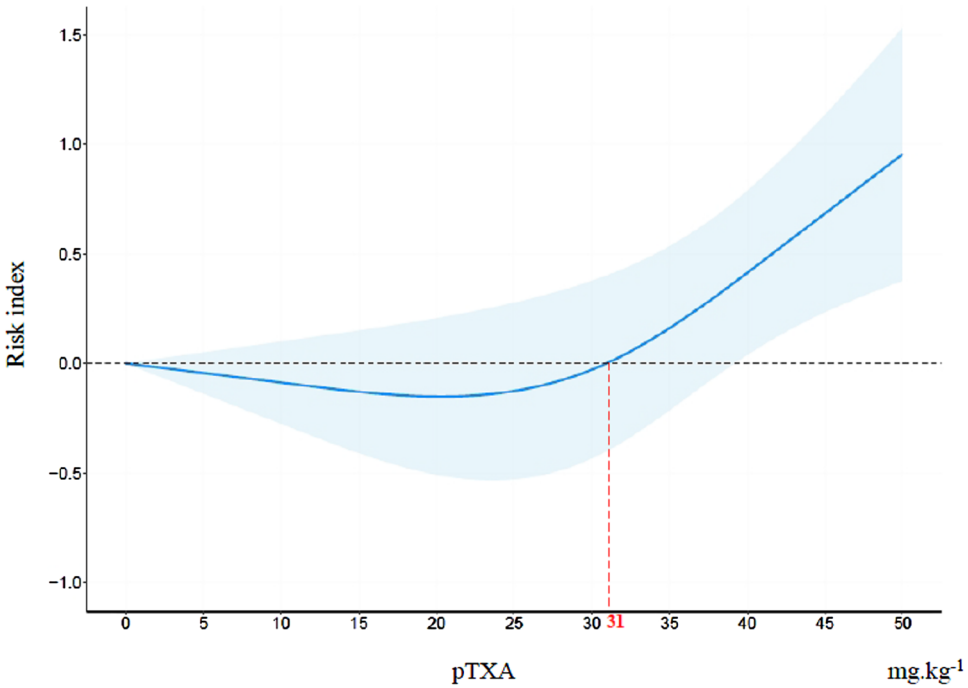

Fig. 2 Relationship between dose of TXA after CPB and the risk of postoperative seizures. The horizontal axis was referred to the dose of TXA (mg kg^{-1}) and vertical axis represented risk index of seizures (log [$risk_{TXA}/risk_{no\text{-}TXA}$])

Table 5 Relationship between dose of TXA after CPB and postoperative seizures

Outcome	Before matching				After matching			
	L-TXA ($n=1081$)	H-TXA ($n=981$)	No-TXA ($n=4236$)	*P* value	L-TXA ($n=1081$)	H-TXA ($n=981$)	No-TXA ($n=2062$)	*P* value
Seizures, *n* (%)	23 (2.1)	33 (3.4)	102 (2.4)	0.153	23 (2.1)	33 (3.4)	46 (2.2)	0.119

on the postoperative seizures in this study, though there was an increasing trend of the incidence of seizures in patients received the high dose of TXA.

Blood product requirements

Among all 6298 patients, 55.9% (3523) received any type of blood products, of whom 40.4% required packed red blood cells; 30.2%, fresh frozen plasma; 14.7%, platelets; and 6.4%, cryoprecipitate. Uni- and multivariate logistic analysis identified the following factors associated with increased risk of requiring any blood product: older age, previous infective endocarditis, history of cardiac catheterization, repeat surgery, higher international normalized ratio, prolonged CPB duration, CABG or combined surgery. These analyses also identified higher hemoglobin level and anticoagulant use as associated with lower risk of requiring any blood product (Table 6). After adjustment for all these factors, TXA after CPB was associated with a reduced risk of requirement of any blood product (OR 0.82, 95% CI 0.73–0.92, $P<0.001$) and more specifically of fresh frozen protein (OR 0.74, 95% CI 0.65–0.83, $P<0.001$), platelets (OR 0.49, 95% CI 0.41–0.59, $P<0.001$) or cryoprecipitate (OR 0.72, 95% CI 0.57–0.91, $P=0.005$; Table 6). However, TXA after CPB did not affect the risk of requirement of red blood cells (OR 1.12, 95% CI 0.99–1.26, $P=0.067$).

Among the subset of 4124 matched patients, 54.7% (2256) received any type of blood products, of whom 40.5% required packed red blood cells; 29.4%, fresh frozen plasma; 12.5%, platelets; and 6.3%, cryoprecipitate. The proportion of patients requiring any type of blood product was significantly smaller in the TXA group (53.1%) than in the no-TXA group (56.3%; OR 0.88, 95% CI 0.78–0.99, $P=0.039$; Tables 2 and 7). Median blood product consumption was also significantly smaller in the TXA group [1.0 (0, 3.5) vs. 1.5 (0, 4.0) units, $P=0.014$; Table 2). Similar trends were found regarding requirements for fresh frozen plasma, platelets and cryoprecipitate. The proportion of patients requiring red blood cells, however, was similar between the TXA and no-TXA groups (Table 2).

Other outcomes

Incidence of surgical re-exploration for hemostasis and length of ICU stay were similar between the TXA and no-TXA groups [21], but length of postoperative hospitalization

Table 6 Assessment of potential risk factors for a requirement for blood products

Variable	Unadjusted		Adjusted[a]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.04 (1.03, 1.04)	< 0.001	1.03 (1.03, 1.04)	< 0.001
Smoking	0.89 (0.80, 0.99)	0.039	0.82 (0.71, 0.93)	0.003
Infective endocarditis	2.59 (1.72, 3.88)	< 0.001	2.30 (1.46, 3.63)	< 0.001
Atrial fibrillation	0.88 (0.80, 0.98)	0.015	0.90 (0.80, 1.02)	0.107
History of cardiac catheterization	2.75 (2.38, 3.18)	< 0.001	1.23 (1.00, 1.51)	0.048
History of repeat cardiac surgery	6.11 (2.60, 14.32)	< 0.001	8.72 (3.48, 21.86)	< 0.001
Respiratory dysfunction	1.96 (1.35, 2.84)	< 0.001	1.40 (0.93, 2.10)	0.105
Stroke	1.28 (0.99, 1.66)	0.058	1.25 (0.94, 1.65)	0.122
Liver dysfunction	1.20 (0.97, 1.49)	0.092	1.25 (0.98, 1.58)	0.069
Gastrointestinal bleeding	2.77 (1.12, 6.86)	0.028	2.28 (0.83, 6.25)	0.110
Beta blockers	1.63 (1.39, 1.92)	< 0.001	1.19 (0.99, 1.43)	0.070
Anticoagulant	1.62 (1.40, 1.88)	< 0.001	0.71 (0.59, 0.86)	< 0.001
Hemoglobin (g dL^{-1})	0.74 (0.72, 0.76)	< 0.001	0.73 (0.70, 0.75)	< 0.001
Platelet ($\times 10^9$ L^{-1})	1.00 (1.00, 1.00)	< 0.001	1.00 (1.00, 1.00)	< 0.001
International normalized ratio	1.44 (1.15, 1.80)	0.001	1.43 (1.12, 1.82)	0.004
Fibrinogen (g L^{-1})	1.26 (1.17, 1.35)	< 0.001	1.06 (0.98, 1.15)	0.134
CABG vs. valve surgery	5.51 (4.28, 7.11)	< 0.001	4.91 (3.42, 7.04)	< 0.001
Combined surgery vs. only valve surgery	3.93 (2.10, 7.37)	< 0.001	2.09 (1.05, 4.16)	0.036
CPB duration (min)	1.01 (1.01, 1.01)	< 0.001	1.01 (1.01, 1.01)	< 0.001

[a]Adjusted by gender, age, history of smoking, hypertension, infective endocarditis, atrial fibrillation, history of cardiac catheterization and repeat surgery, respiratory dysfunction, stroke, diabetes mellitus, liver dysfunction, gastrointestinal bleeding, renal dysfunction, previous history of medicines (beta blockers, anticoagulants, and antiplatelet drugs), preoperative laboratory results (hemoglobin, WBC, platelet, INR, and fibrinogen), surgery type and CPB duration

Table 7 Risk of blood product requirement in the two patient groups, before and after propensity score matching

Outcome	Before matching[a]		After matching	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Requirement for blood products				
Any blood products	0.82 (0.73, 0.92)	< 0.001	0.88 (0.78, 0.99)	0.039
Red blood cell use	1.12 (0.99, 1.26)	0.067	1.10 (0.97, 1.25)	0.120
Fresh frozen plasma use	0.74 (0.65, 0.83)	< 0.001	0.78 (0.66, 0.86)	< 0.001
Platelet use	0.49 (0.41, 0.59)	< 0.001	0.62 (0.52, 0.75)	< 0.001
Cryoprecipitate use	0.72 (0.57, 0.91)	0.005	0.72 (0.56, 0.92)	0.010

[a]Risk of a requirement for blood products was adjusted by age, smoking, infective endocarditis, history of cardiac catheterization, repeat surgery, use of anticoagulants, preoperative hemoglobin, platelet, INR, surgery type and CPB duration

was longer in the TXA group, even after propensity score matching (Table 2).

Discussion

TXA is routinely administered after anesthesia and during CPB at doses of 24–100 mg kg^{-1} to reduce requirement for blood products, but it is associated with a two to sevenfold increase in incidence of postoperative seizures [8, 13, 22]. In our previous study, we found that using TXA after CPB might reduce the risk of postoperative death during hospitalization but was not associated with ischemic or bleeding-related events [21]. The present study provides evidence that administering TXA after CPB at 31 mg kg^{-1} does not increase the risk of postoperative seizures following cardiac surgery, while still reducing the requirement for fresh frozen plasma, platelets and cryoprecipitate, although not necessarily the requirement for packed red blood cells.

In general, postoperative seizures can be induced by focal and generalized lesions [7, 23]. Seizures after cardiac surgery involving arrhythmic movements are believed to result

from generalized lesions, including drug toxicity such as TXA, and diffuse injury such as post-pump encephalopathy and multiple emboli [24]. Seizures occur in 0.1–11.0% of patients after cardiac surgery [8, 10, 13, 23, 25–28], and this wide range may reflect differences in the definition of seizures [23, 29], study populations [30], types of cardiac surgery [7, 9, 31] and administration of TXA [8, 10]. The incidence of postoperative seizures in patients who did not receive any TXA ranged to 0.1–1.2% [8, 9] while that was 2.4% in present study, one of the important reasons was the limitations of the retrospective study. The diagnosis of seizures was highly dependent to clinic observation and many patients suffered related symptoms in ICU which were easily missed or misdiagnosed. Therefore, the incidence of seizures after cardiac surgery might be difficult to calculate authentically. To reduce subjectivity in the observation of seizures in the present study, they were examined according to the definition strictly by a neurologist blinded to whether a patient received TXA or not. The incidence of postoperative seizures in our large cohort was 2.5%. Similar to other reports [25, 32], the independent risk factors for seizures in our study were identified to be male gender, older age, and longer CPB time. Interestingly, we also found that the rate of seizures in patients with CABG (21/518, 4.1%) was higher than that in those who underwent valve surgery or combined surgery (137/5780, 2.4%, $P=0.019$). But, surgery type was not associated with seizures after adjusted by gender, age, atrial fibrillation, history of cardiac catheterization, respiratory dysfunction, beta blockers, surgery type and CPB duration. These findings suggest caution in administering TXA after cardiac surgery to older patients, male patients, and patients who undergo prolonged CPB.

Different with previous conclusions that TXA after anesthesia induction dose-dependently increased the seizures risk [7, 8], present study indicated that TXA at the dose of 15–50 mg kg^{-1} after CPB did not increase seizures. Given these results, we believe that RCT studies are required to distinguish whether the effect of TXA due to its low dosage or the different time window of its administration.

The molecular pathway(s) linking TXA with postoperative seizures is unclear. One link appears to be drug toxicity, i.e., inhibition by TXA of γ-aminobutyric acid (GABA) binding to $GABA_A$ receptors in the central nervous system [33, 34]. Another link may be the formation of microthrombi in the cerebral circulation. The results of the present study suggest that simply changing the TXA administration window can affect risk of postoperative seizures. It may be that TXA increases the risk of microthrombus formation when it is administered before CPB, but not when administered after CPB.

Although TXA is used globally to reduce requirements for blood transfusion, evidence about its efficacy remains controversial. Two randomized controlled trials showed that TXA could reduce exposure to any blood product transfusion as well as the amount of total blood products consumed [5, 8]. On the other hand, one study reported no such reduction [35], while a retrospective study suggested that TXA increased the incidence of fresh frozen plasma transfusion by 19.4% and of platelet transfusion by 68.5% [15]. Our results with TXA administered after CPB are similar to those of the randomized controlled trials of TXA administered before and during CPB [5, 8]: the drug reduced the requirement among our patients for any blood product and specifically for fresh frozen plasma, platelets and cryoprecipitate. These results suggest that TXA exerts similar hemostatic effects regardless of whether it is administered after CPB or after anesthesia induction.

We were slightly surprised to find that TXA in our study did not reduce consumption of red blood cells. One explanation may be that since TXA was administered after CPB in our study, anesthesiologists had the opportunity to decide whether or not to use the drug. They may have tended to use TXA in patients with high risk of bleeding, and this assessment may be quite subjective, as reflected in the significant heterogeneity in TXA use among anesthesiologists [36]. In any event, administering TXA after CPB may help reduce its unnecessary use by giving anesthesiologists the opportunity to observe the complexity of the operation and the amount of bleeding after CPB.

Our study is limited by its reliance on retrospective data, which led to significant differences between the TXA and no-TXA groups at baseline. Therefore, propensity score matching was performed to reduce biases from confounding factors. Furthermore, it is very difficult to distinguish the seizures due to TXA or other reasons, although the same CPB procedure for each patient between the two groups was applied. And because the seizures were only diagnosed retrospectively by the investigators based on postoperative medical records, the authentic incidence of postoperative seizures may be difficult to calculate. Our results are also limited by the fact that they came from a single cardiology center, and that administration of TXA was subjective, because it was based on anesthesiologists' assessment of bleeding in the surgical field. This subjectivity is shared by TXA studies because there is no international consensus on its use. We could not directly compare outcomes when TXA was administered after anesthesia induction or after CPB because of the paucity of patients at our hospital who were given the drug after anesthesia induction. Future RCT studies should examine this parallel comparison to verify and extend our results.

Conclusions

Our results suggest that TXA after CPB reduces blood product requirements without increasing risk of postoperative seizures. Simply changing the TXA administration window

may avoid unnecessary use of TXA and allow the use of lower doses. Further multi-center, randomized, double-blind, controlled studies are warranted to improve patient management through TXA administration during cardiac surgery.

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Declarations

Conflict of interest Jing Liu has no conflict of interest. Changwei Chen has no conflict of interest. Lei Du has no conflict of interest.

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