Can J Anesth/J Can Anesth (2012) 59:6–13
DOI 10.1007/s12630-011-9618-z

REPORTS OF ORIGINAL INVESTIGATIONS

Seizures following cardiac surgery: the impact of tranexamic acid and other risk factors

Crises convulsives après chirurgie cardiaque: impact de l'acide tranexamique et d'autres facteurs de risque

Rizwan A. Manji, MD, PhD · Hilary P. Grocott, MD · Jill Leake, CRA · Rob E. Ariano, PharmD · Jacqueline S. Manji, PhD · Alan H. Menkis, MD · Eric Jacobsohn, MBChB

Received: 10 February 2011 / Accepted: 19 October 2011 / Published online: 8 November 2011

Abstract

Background *Seizures after cardiac surgery are a serious complication. The antifibrinolytic agent tranexamic acid (TA), which has known proconvulsant properties, may be associated with postoperative seizures. We sought to determine the association between TA and other risk factors for seizures after cardiac surgery.*

Methods and results *We analyzed a database of consecutive cardiac surgery patients (April 2003 to December 2009) using multivariable logistic regression analysis to assess for seizure risk factors. Seizures occurred in 56 of 5,958 patients (0.94%). TA use was associated with an increased risk of seizures (odds ratio 7.4, 95% confidence interval 2.8–19.3; $P < 0.001$). Multivariable logistic regression analysis revealed that the following factors were significantly associated with seizures: TA exposure; Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II score > 20; preoperative cardiac arrest; preoperative neurological disease; open chamber surgery; cardiopulmonary bypass time > 150 min; and previous cardiac surgery. Seizures occurred at a median of 5.3 hr (interquartile range 2.4–15.1 hr) after the end of surgery. In all, 58.1% were grand mal, 14.5% were associated with a stroke, and 58.1% recurred in hospital. Altogether, 48.3% of the patients were able to discontinue anticonvulsant medications prior to discharge. Compared to the non-seizure group, seizure patients had an increased rate of postoperative neurological complications, defined as delirium and/or stroke (3.2% vs 19.6%, $P < 0.001$), increased intensive care unit (ICU) length of stay (1.0 vs 4.7 days, $P < 0.001$), and increased ICU mortality (1.4 % vs 9.7 %, $P = 0.001$).*

Conclusions *Our data suggest that multiple risk factors, including TA, are associated with seizures after cardiac surgery. Thus, the TA dose may be a readily modifiable risk factor for postoperative seizures.*

This article is accompanied by an editorial. Please see Can J Anesth 2012; 59(1).

R. A. Manji, MD, PhD · A. H. Menkis, MD
Department of Surgery, University of Manitoba, Winnipeg, MB, Canada

R. A. Manji, MD, PhD · J. Leake, CRA · J. S. Manji, PhD · A. H. Menkis, MD
Cardiac Sciences Program, Winnipeg Regional Health Authority, St. Boniface Hospital, Winnipeg, MB, Canada

H. P. Grocott, MD · E. Jacobsohn, MBChB
Department of Anaesthesia, University of Manitoba, Winnipeg, MB, Canada

R. E. Ariano, PharmD
Department of Pharmacy, St. Boniface Hospital, University of Manitoba, Winnipeg, MB, Canada

R. A. Manji, MD, PhD (✉)
I.H. Asper Clinical Research Institute, St. Boniface Hospital, CR3014 – 369 Tache Avenue, Winnipeg, MB R2H 2A6, Canada
e-mail: rmanji@sbgh.mb.ca

Résumé

Contexte *La survenue de crises convulsives après chirurgie cardiaque peut être une complication grave. L'acide tranexamique (AT), un antifibrinolytique aux propriétés proconvulsivantes connues, peut être associé aux crises convulsives postopératoires. Nous avons cherché à déterminer s'il existait une association entre l'AT et les autres facteurs de risque de convulsions après chirurgie cardiaque.*

Méthodes et résultats *Nous avons analysé une base de données de patients consécutifs ayant subi une chirurgie cardiaque (d'avril 2003 à décembre 2009) au moyen d'une*

analyse de régression logistique multifactorielle pour évaluer les facteurs de risque de crise convulsive. Des crises convulsives sont survenues chez 56 des 5958 patients (0,94 %). L'utilisation d'AT a été associée à une augmentation du risque de convulsions (rapport de cotes: 7,4; intervalle de confiance à 95 %: 2,8–19,3; P < 0,001). L'analyse de régression logistique multifactorielle a révélé que les facteurs suivants étaient associés de façon significative aux crises convulsives: exposition à l'AT; score APACHE II (physiologie aiguë, âge et évaluation de la santé chronique ou Acute Physiology, Age, and Chronic Health Evaluation) > 20; arrêt cardiaque préopératoire; maladie du système nerveux avant l'intervention; chirurgie à cœur ouvert; durée de circulation extracorporelle > 150 min et antécédent de chirurgie cardiaque. Les crises convulsives sont survenues dans un délai médian de 5,3 h (intervalle interquartile: 2,4–15,1 h) après la fin de l'intervention chirurgicale. Parmi l'ensemble des cas, 58,1 % des crises ont été généralisées (grand mal), 14,5 % ont été associées à un accident vasculaire cérébral (AVC) et 58,1 % ont récidivé pendant l'hôpitalisation. Globalement, on a pu cesser le traitement anticonvulsivant avant le congé de l'hôpital chez 48,3 % des patients. Comparé au groupe sans crises convulsives, les patients ayant présenté des convulsions ont eu davantage de complications neurologiques postopératoires: delirium et/ou AVC (3,2 % contre 19,6 %, P < 0,001), durée de séjour prolongée aux soins intensifs (1,0 contre 4,7 jours, P < 0,001), et augmentation de la mortalité aux soins intensifs (1,4 % contre 9,7 %, P = 0,001).

Conclusions *Nos données suggèrent que de multiples facteurs de risque, dont l'AT, sont associés aux crises convulsives après chirurgie cardiaque. La dose d'AT pourrait donc être un facteur de risque de convulsions facilement modifiable.*

The overall prevalence of acute seizures in patients > 60 yr of age is estimated to be 0.1%.[1,2] Traditionally, the causes of seizures in elderly patients include acute stroke (50%), metabolic encephalopathy (6–30%), and various drug side effects, infection, and trauma (5–20%).[3,4] The incidence of seizures after cardiac surgery is not well studied.[5,6] There have been recent reports, however, of postoperative seizures in adult patients who had been given tranexamic acid (TA) as antifibrinolytic therapy.[7-10] Although the reported seizures were generally easily treated, the implications of a seizure diagnosis in this age group are significant, including restrictions on normal activities (e.g., driving) that may affect the patient's quality of life, independence, and self-confidence.[11]

We recently observed what appeared to be an increase in postoperative seizures after cardiac surgery. Prior to January 2007, our antifibrinolytic strategy involved ε-aminocaproic acid (and rarely TA) for patients at low risk for bleeding (e.g., uncomplicated first-time coronary artery bypass surgery) and aprotinin for high-risk patients (e.g., redo cardiac surgery, aortic surgery, multivalve operation). In 2007, the Blood Conservation Using Anti-fibrinolytics in a Randomized Trial (BART) showed an increased morbidity and mortality associated with the use of aprotinin.[12] Partly as a result of this trial, the use of aprotinin was removed from clinical practice. Many institutions, including our own, changed their use of antifibrinolytic agents to TA alone. Tranexamic acid can cross the blood-brain barrier (BBB), especially in circumstances where the BBB has been compromised. This property had previously been exploited in neurosurgery to decrease the risk of rebleeding following subarachnoid hemorrhage. However, its use in neurosurgery was subsequently discontinued after TA was shown to be associated with increased cerebral vasospasm, ischemia, hydrocephalus, and seizures.[13] Tranexamic acid binds competitively, in a dose-dependent fashion, to γ-aminobutyric acid (GABA) type A receptors, which results in reduced inhibitory activity and increased neuronal excitation.[14] There are reports of TA causing seizures when in direct contact with the central nervous system in animals[15,16] and humans.[17,18] It is therefore mechanistically plausible that TA is associated with seizures after cardiac surgery.

We sought to determine the risk factors for seizures after cardiac surgery and to characterize them. We specifically examined TA as a potentially modifiable factor.

Methods

We conducted a historical cohort study using data collected in our cardiac surgery, perfusion service, and intensive care unit (ICU) databases. These databases collect information on all consecutive cardiac surgery cases performed at our institution. Each database undergoes random audits to ensure validity. The perfusion service database collects detailed operative variables (including the antifibrinolytic agent that was used during surgery). The cardiac surgery and ICU databases collect demographic and co-morbidity variables along with postoperative complications, duration of ventilation, and lengths of ICU and hospital stays. A concurrent pharmacy database maintains information related to the inventory of drugs dispensed to various clinical services, including anesthesia for cardiac surgery. The University of Manitoba Research Ethics Board approved the study and waived the requirement for patient consent.

A seizure was deemed to have occurred if the attending physician documented the occurrence and a prescribed intervention occurred. Our databases were searched for the occurrence of postcardiac surgery seizures from April 2003

(when the perfusion service database was available) until December 2009. A further chart review of the patients with seizures was then undertaken to identify factors associated with seizures (e.g., preoperative stroke, preoperative medications), the characteristics of the seizure, and the in-hospital treatment and outcome. Patients with seizures were compared to those without seizures to determine the factors associated with seizures.

The potential contribution of TA was assessed in two ways. First, TA was examined as a dichotomous variable in a multivariable logistic regression analysis to determine its association with seizures. Second, a dose–response relation for TA was examined. The TA dose was calculated per case based on pharmacy dispensing records of the amount of TA dispensed divided by the number of patients receiving TA. Prior to 2007, our institutional policy was to administer 1–2 g of TA per patient (for those prescribed TA). With the BART results,[12] our institutional policy changed in 2007 to a 30 $mg \cdot kg^{-1}$ bolus followed by 16 $mg \cdot kg^{-1} \cdot hr^{-1}$ for the duration of cardiopulmonary bypass (CPB). Although we did not have the exact dose per patient available for all patients (owing to inconsistencies in recording dosing in the anesthesia record), when we cross-referenced these institutional standards with our pharmacy dispensing records (amount of TA dispensed divided by the total cases performed in which TA was prescribed), the doses were remarkably similar, giving us confidence in the dosing data.

Statistical analysis was performed using SPSS 17.0 (SPSS, Chicago, IL, USA). The preoperative characteristics of the two groups (seizure, non-seizure) were compared using Student's two-sample *t* test (for normally distributed data), the Mann-Whitney U-test (for non-normally distributed data), and Pearson's Chi-squared test (for categorical variables). Multivariable logistic regression, using a forward stepwise approach, was performed on all clinically relevant and statistically significant variables available from the initial bivariate analysis (Table 1) to determine factors associated with seizures after cardiac surgery. The variables examined in the regression analysis included the following: TA use; age > 70 yr; history of preoperative neurological disease; preoperative cardiogenic shock; preoperative cardiac arrest; Acute Physiology, Age, and Chronic Health Evaluation (APACHE) score > 20; peripheral vascular disease; preoperative renal insufficiency; preoperative aortic valve disease; preoperative mitral valve disease; preoperative aortic disease; previous cardiac surgery; CPB time > 150 min; open chamber procedure. All reported *P* values are two-tailed.

Results

There were 56 patients with seizures documented among the 5,958 cases (0.94%). The baseline rate of 0.19% for the period April 2003 to December 2006 went up 8.1-fold to 1.54% for the period January 2007 to December 2009 ($P < 0.001$). Table 1 demonstrates that patients who experienced seizures were older and had more preexisting neurological disease, arrhythmias, cardiac arrests, congestive heart failure, previous cardiac surgery, and renal dysfunction, in addition to having higher APACHE II scores. They also had more open-chamber procedures, longer cross-clamp and CPB times, and were more frequently prescribed TA. Table 2 shows the unadjusted odds ratio (OR) and the final multivariable model with the adjusted ORs demonstrating that TA use, preoperative cardiac arrest, APACHE II score > 20, preoperative neurological disease, open-chamber procedure, CPB time > 150 min, and previous cardiac surgery were significant factors for postoperative seizure (Nagelkerke pseudo $R^2 = 0.27$, $P < 0.001$).

The Figure demonstrates the changes in TA dosing over time and the change in the seizure rate over time. From April 2003 to December 2006, patients who were given TA received 1.4–1.7 g per case, and the seizure rate during that period was 0–0.3%. From January 2007 to December 2009, patients given TA received 5.1–5.8 g per case, and the seizure rate was 1.2–1.8%. Our initial analysis at the end of 2009 showed that patients who had seizures received 80.9 ± 24.2 $mg \cdot kg^{-1}$ (mean ± SD) of TA *vs* 63.9 ± 24.1 $mg \cdot kg^{-1}$ of TA ($P < 0.001$) for the patients who did not have seizures. Therefore, an institutional policy change was implemented wherein the total amount of TA prescribed was decreased to < 45 $mg \cdot kg^{-1}$ per case. This number was chosen based on a pharmacokinetic modeling study done by Dowd et al.[19] that suggested adequate antifibrinolytic activity with a 12.5 $mg \cdot kg^{-1}$ bolus, an infusion of 6.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ and 1 $mg \cdot kg^{-1}$ in the pump prime (i.e., 26.5 $mg \cdot kg^{-1}$ for an average 80-kg patient on CPB for 2 hr), and the BART protocol[12] (which would give 64 $mg \cdot kg^{-1}$ to an 80-kg patient on CPB for 2 hr). By averaging the two protocols, we arrived at the administered TA dose of 45 $mg \cdot kg^{-1}$. The Figure shows a reduction in the TA dosing to an average of 3.1 g per case (from January to September 2010) and a simultaneous reduction in the seizure rate from 1.8% to 0.8%. Importantly, from January 2007 to December 2009 compared to January 2010 to September 2010, the APACHE II score (14.0 ± 4.8 *vs* 14.1 ± 4.3), preoperative cardiac arrest rate (0.5% *vs* 0.7%), preoperative neurological disease rate (13% *vs* 14%), and previous cardiac surgery rate (1.8% *vs* 2.3%) did not change. Furthermore, the number of open-chamber procedures increased (from 32.5% to 37.5%) as did the CPB time (108.8 ± 58.6 *vs* 113.0 ± 63.6 min); the increase in open-chamber procedures was clinically and statistically significant ($P = 0.01$). This suggests that the reduction in seizures was likely related to a reduction in the TA dose, not a change in the other significant factors from the multivariable model.

Table 1 Bivariate analysis of potential predictors of seizure after cardiac surgery: April 2003 to December 2009

Variable	No Seizure Group	Seizure Group
Total no. of patients	5902	56
Preoperative variables		
Age (yr), mean (SD)	64.7 (15.7)	70.9 (11.6)§§
Female sex	1,544/5,893 (26.2%)	18/56 (32.1%)
Weight (kg), mean (SD)	84.3 (18.4)	80.8 (19.8)
Neurological disease*	682/5,500 (12.4%)	15/51 (29.4%)§§
COPD	442/5,457 (8.1%)	6/51 (11.8%)
Pulmonary hypertension	65/5,417 (1.2%)	1/50 (2.0%)
Hypertension	3,853/5,489 (70.2%)	38/51 (74.5%)
Hyperlipidemia	3,407/5,460 (62.4%)	24/51 (47.1%)§§
Diabetes mellitus	1,595/5,500 (29.0%)	15.51 (29.4%)
Myocardial infarction	2,648/5,494 (48.2%)	16/51 (31.4%)§§
Brady/tachyarrhythmia	761/5,475 (13.9%)	17/51 (33.3%)§§
Cardiogenic shock	173/5,406 (3.2%)	1/50 (2%)
Cardiac arrest	21/5,250 (0.4%)	3/51 (5.9%)§§
Congestive heart failure	558/5,471 (10.2%)	13/51 (25.5%)§§
Previous cardiac surgery	101/5,611 (1.8%)	6/51 (11.8%)§§
Endocarditis	50/5,556 (0.9%)	0/56 (0.0%)
Peripheral vascular disease	887/5,475 (16.2%)	13/51 (25.5%)
Renal dysfunction†	489/5,494 (8.9%)	10/51 (19.6%)§§
APACHE II score, mean (SD)	14.4 (4.6)	20.8 (7.1)§§
APACHE II > 20	443/5,538 (8.0%)	24/51 (47.1%)§§
Intraoperative variables		
Tranexamic acid used	3,292/5,796 (56.8%)	49/54 (90.7%)§§
Open chamber procedure‡	1,509/5,487 (27.5%)	36/51 (70.6%)§§
Aortic valve procedure§	864/5,503 (15.7%)	20/51 (39.2%)§§
Mitral valve procedure‖	505/5,489 (9.2%)	9/51 (17.7%)
Aortic procedure**	183/5,546 (3.3%)	8/51 (15.7%)§§
Cross-clamp time (min), median (IQR)	62.0 (44.0–94.0)	74.5 (50.3–130.0)§§
CPB time (min), median (IQR)	99.0 (73.0–141.0)	151.0 (86.3–213.8)§§

The results are the number of patients/total available unless otherwise stated

*Neurological disease = preoperative history of cerebrovascular disease, seizure disorder, alcohol abuse, brain tumour, or multiple sclerosis

†Renal dysfunction = preoperative renal insufficiency or chronic renal failure

‡Open-chamber procedure = any procedure where the cardiac chamber or aorta was opened

§Aortic valve procedure = aortic valve surgery ± coronary artery bypass graft (CABG) ± mitral valve surgery ± tricuspid valve surgery ± redo sternotomy; no aortic cases

‖Mitral valve procedure = mitral valve surgery ± CABG ± tricuspid valve procedure, ± redo sternotomy; no aortic valve or aortic cases included. **Aortic procedure = surgery on ascending/arch/descending aorta ± aortic valve surgery ± CABG ± mitral valve surgery ± tricuspid valve surgery ± redo sternotomy. APACHE = Acute Physiology, Age, and Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; IQR = interquartile range. §§$P < 0.05$ *vs* No Seizure Group

To investigate the impact of TA on seizures further, we performed two additional analyses. First, we examined the data for all of the patients who were given TA and all who were not and determined the seizure rate differences between the two groups. The seizure rate in patients not receiving TA was 0.2% (similar to the baseline rate of 0.1% in patients > 60 yr),[1,2] and the seizure rate in patients receiving TA was almost sevenfold higher, at 1.47% ($P < 0.001$). Second, we examined the data for patients with none of the other six risk factors from our model for seizures (patients with no previous neurological history, no prior cardiac arrest, no previous cardiac surgery, and no open-chamber procedure but with an APACHE score < 20 and a CPB time ≤ 150 min). This produced a sample size of 2,786 patients, 1,596 of whom had been given TA (three seizures occurred in this group) and 1,190 who had not

Table 2 Logistic regression analysis of cardiac surgery patients having seizures: April 2003 to December 2009

Variable	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Tranexamic acid used	7.46 (2.97–18.24)	<0.001	7.35 (2.80–19.34)	<0.001
Preoperative cardiac arrest	16.30 (4.70–56.42)	<0.001	31.41 (6.16–160.18)	<0.001
APACHE II score > 20	10.13 (5.80–17.71)	<0.001	7.99 (4.34–14.72)	<0.001
Previous cardiac surgery	7.12 (2.97–17.06)	<0.001	5.78 (2.13–15.69)	<0.001
Open chamber procedure	6.34 (3.46–11.6)	<0.001	4.28 (2.14–8.56)	<0.001
CPB time > 150 min	4.02 (2.37–6.82)	<0.001	1.97 (1.01–3.59)	0.05
Preoperative neurological disease*	2.94 (1.60–5.40)	<0.001	2.31 (1.20–4.46)	0.01

*Preoperative history of cerebrovascular disease, seizure disorder, alcohol abuse, brain tumour, or multiple sclerosis

OR = odds ratio; CI = confidence interval

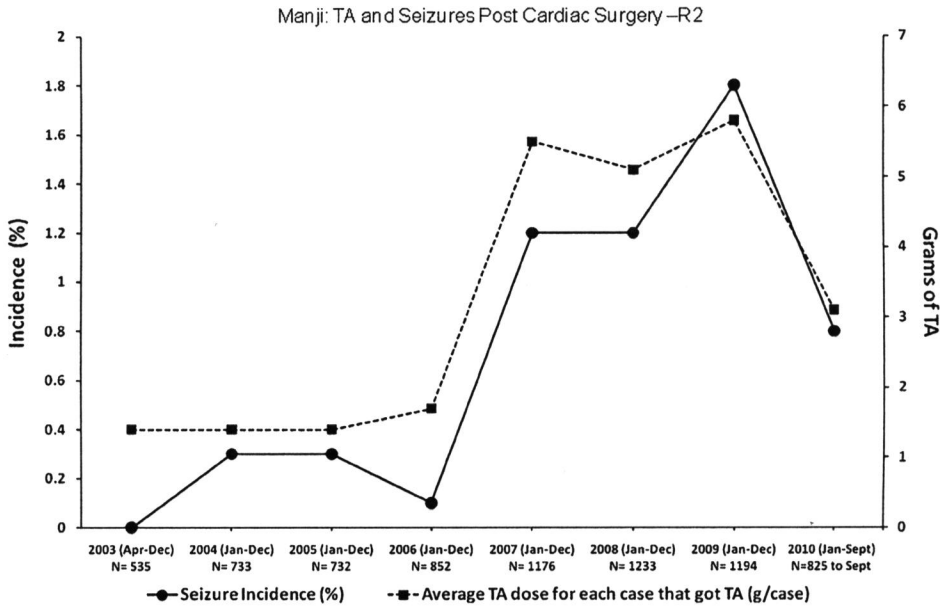

Figure Change in seizure incidence and in tranexamic acid (TA) dosing over time. The TA dose was calculated per case based on the pharmacy records and number of patients given TA. N = the total number of cardiac surgery cases done during that time period. The graph shows the increase in the incidence of seizures after cardiac surgery starting in 2007 correlated with the increase in TA dosing. Note the subsequent drop in the seizure rate in 2010 when the TA dose was decreased

(zero seizures occurred in this group). Our data suggest that TA may influence the probability of seizures after cardiac surgery independent of the other risk factors.

Table 3 shows the characteristics of the 61 patients who had seizures (56 before December 31, 2009 and five thereafter). Most seizures occurred within 6 hr of surgery and were grand mal in nature; 58% recurred during the hospital stay. However, almost half of the patients had their anticonvulsant medications discontinued within 3 days. The incidence of postoperative neurological complications, defined as delirium and/or stroke, were higher in the seizure group (19.6% *vs* 3.2%, $P < 0.001$), as were ICU length of stay [4.7 (2.0–7.8) *vs* 1.0 (0.8–2.0) days, $P < 0.001$] and ICU mortality (9.7% *vs* 1.4%, $P = 0.001$). Interestingly, the three patients who had seizures and only had TA as a seizure risk factor (i.e., none of the other six risk factors) did not have neurological complications, a prolonged ICU length of stay, or any mortality.

Discussion

In this large single-center study, we found an association between the occurrence of seizures after cardiac surgery and the following factors: TA use, preoperative cardiac arrest, high APACHE II score, preoperative neurological disease, open-chamber procedure, long CPB time, and previous cardiac surgery. We also demonstrated a dose–response relationship that suggests an increase in seizures with an increase in TA dose and a decrease in seizures after a decrease in TA dose per case. Although the absolute difference in TA dosing between the seizure and non-seizure groups was not large, it is possible that the circulating and brain levels of TA were much higher in the seizure group because that group was older and had renal dysfunction (reducing TA elimination).

It is noteworthy that most of the seizure events were within hours of arriving in the ICU, and most were grand

Table 3 Characteristics of patients with seizures after cardiac surgery (56 patients before TA dose change; 5 patients after TA dose decrease)

Total no. of patients	61
Time from end of surgery to first seizure (hr), median (IQR)	5.3 (2.4–15.1)
Seizure type	
Grand mal	36 (59.0%)
Focal	12 (19.7%)
Type unclear/mixture	14 (23.0%)
CT of the head findings	
Minor stroke (old or new) lacunar/ischemic demyelination	30 (49.2%)
Major stroke (old or new) watershed/large-vessel territories	9 (14.8%)
New stroke (minor or major)	9 (14.8%)
Ongoing seizure activity on EEG at the time EEG was done	6 (9.8%)
Recurrence of seizure during hospital stay	36 (59.0%)
Anticonvulsant stopped during hospital stay	29 (47.5%)
Duration of treatment before in-hospital discontinuation of anticonvulsant (days), median (IQR)	3.0 (0.6–5.0)
Total hours ventilated, median (IQR)	119.0 (50.0–188.8)
Total ICU length of stay (days), median (IQR)	4.7 (2.0–7.4)
Readmission to ICU after initial transfer to ward	8 (13.1%)
Total length of stay from surgery to discharge/death (days), median (IQR)	15.0 (10.0–31.0)
In-hospital mortality	13 (21.3%)
Discharge location: home	36 (59.0%)

Results are the number of patients unless otherwise stated

TA = tranexamic acid; CT = computed tomography; ICU = intensive care unit; EEG = electroencephalography

mal in nature. This timing likely represents the relatively high plasma levels of TA (which we did not measure) present at that time, resulting in reduced GABA-A receptor activity. This, combined with the weaning of sedative drugs to allow early extubation, structural brain abnormalities in some patients (as demonstrated by computed tomography of the head), and possible BBB abnormalities due to intracerebral embolic events from the open-chamber procedure, may have allowed the proconvulsant properties of TA to be unmasked. Even though many patients had recurrent seizures, almost half of the patients were able to discontinue anticonvulsant medication use prior to discharge. This further supports the notion that transient factors (e.g., TA) play an important role in precipitating seizure activity in susceptible patients. It appears that TA may precipitate seizures in patients who have other significant risk factors for seizure.

Clinically, the problem of TA-associated seizures can be addressed in several ways. First, TA could be withdrawn from use during cardiac surgery until it is subjected to large clinical trials versus placebo to assess its effect on all-cause mortality and morbidity. The BART[12] found increased mortality and morbidity with aprotinin versus TA, leading to the removal of aprotinin from clinical practice. However, the question remains whether TA, in adequately powered clinical studies versus placebo, improves all-cause outcomes. The second option would be to continue using TA until such a large outcome trial is performed but to minimize the risk of TA-induced seizures. Although reducing the TA dose appears prudent, what constitutes an effective TA dose is unclear. It is possible that TA has a relatively flat dose–response curve or that the dosing of TA is clinically relevant only in patients at risk for seizure based on the other factors found in our model. Some limited pharmacokinetic data suggest that a minimum therapeutic TA plasma concentration of 127 μM is required.[19] Dowd *et al.*[19] used a TA regimen of 12.5 $mg \cdot kg^{-1}$ given over 30 min, a maintenance infusion of 6.5 $mg \cdot kg^{-1} \cdot hr^{-1}$, and 1 $mg \cdot kg^{-1}$ in the CPB prime, which maintained a TA concentration > 345 μM in most patients. The BART protocol[12,19] was predicted to give a TA concentration of > 800 μM using this same pharmacokinetic modeling study. Fox[20] reported a dosing regimen of a 5.4 $mg \cdot kg^{-1}$ load followed by 5 $mg \cdot kg^{-1} \cdot hr^{-1}$ with 20 $mg \cdot L^{-1}$ in the CPB pump prime, with no reported seizures and adequate antifibrinolytic activity as measured by thromboelastography. Santos *et al.*[21] performed a double-blinded randomized control trial in cardiac surgery patients with very low dose TA (10 $mg \cdot kg^{-1}$ load followed by 1 $mg \cdot kg^{-1} \cdot hr^{-1}$ for 5 hr) versus no antifibrinolytic agent and found that D-dimer levels were significantly higher in the control group than in the TA group, but there was only a modest decrease in blood loss (approximately 300 mL less blood per case in the TA group at 24 hr postoperatively).

With the uncertainties that exist regarding the effective TA dose, modifying the perioperative course could be considered in some at-risk patients (as described by the regression model). This could include further minimizing the TA dose, being meticulous about cardiac de-airing, minimizing aortic manipulation, and potentially continuing sedative medications during the postoperative period until TA blood levels are predicted to be low. Similarly, in situations where a higher dose of TA is deemed required (e.g., redo sternotomy, thoracic aortic surgery, complex cardiac surgical procedures, surgery requiring hypothermic circulatory arrest), higher doses of GABA agonists could be considered during and immediately after surgery.

Our findings support those currently in the literature and add important new information. In three studies[7,22,23] that primarily investigated the hemostatic effects of aprotinin versus TA, patients receiving aprotinin had fewer seizures

(0–1.2%) than those having received TA (2.7–4.6%).[7,22,23] It is noteworthy that seizures were not reported by the BART investigators, although seizure was not an a priori defined endpoint in that trial.[12] There have been two recent reports that have specifically examined TA and seizures after cardiac surgery. Murkin *et al.* described seizures in 669 cardiac surgery cases in London, Ontario and Cambridge, UK.[10] Their baseline seizure rate of 1.3% increased to 3.8% when higher TA dosing was adopted. The TA dose varied in each of the centres: 61–259 $mg \cdot kg^{-1}$ and 71–258 $mg \cdot kg^{-1}$, respectively. Similar to our experience, when the TA dose was reduced (in their case, to that of the BART protocol),[12] the seizure rate decreased. As in our series, most of the patients were elderly, seizures were predominantly grand mal in nature, they occurred within hours of surgery, and most of the patients had open-chamber procedures. There was documented evidence of stroke in 12% of their patients; but unlike our series, no recurrent seizures were reported. In another series, Bell *et al.* reported seven patients with seizures after cardiac surgery.[9] Their baseline seizure rate of 0% increased to 0.66% with high-dose TA (60 $mg \cdot kg^{-1}$ bolus followed by 5 $mg \cdot kg^{-1} \cdot hr^{-1}$ or a 30 $mg \cdot kg^{-1}$ bolus followed by 15 $mg \cdot kg^{-1} \cdot hr^{-1}$). The patients were elderly, all patients underwent open-chamber procedures, and the seizures were grand mal in nature. All of the seizures occurred within 24 hr, and there were no recurrences after 24 hr. The reason for the high recurrence rate of seizures in our population is unclear at this point but warrants further investigation.

There were some limitations to our study. There are the inherent problems related to database and chart reviews. We did have some missing data (5–10% of random variables); however, this degree of missing data is comparable to that of other retrospective studies and would be unlikely to affect the conclusions of our study. We reviewed the charts of the patients who had a seizure in detail and did not find any biochemical abnormality or medications (e.g., lidocaine, bupivacaine, cephalosporins, others) or evidence of central nervous system infection or trauma that could readily explain the seizures. All patients were given standard preoperative antibiotics (usually 1–2 g of cefazolin), which has been the routine for years; thus, it is likely that this was not the reason for the increased seizures. For logistical reasons, we could not do a detailed review of the charts of the several thousand patients who did not have seizures to determine their biochemical and medication profiles. With all the patients being managed by a homogeneous single-center group of clinicians, and the fact that the seizure rate dropped after decreasing the TA dose, it seems unlikely that other biochemical derangements or medications explained the initial increase and subsequent decrease in the seizure rate.

Ideally, one would have documented seizure activity by electroencephalography (EEG) in all these patients to confirm that the movements seen were indeed seizures and not nonseizure movement. Most seizures lasted only a few minutes, thus precluding the ability to perform an urgent confirmatory EEG during the seizure activity. However, the nursing and medical staff working in the ICU, all experienced practitioners, were accustomed to seeing the common nonseizure involuntary movements after surgery (e.g., shivering) and were therefore likely accurate in their clinical diagnoses. Additionally, the same nursing and medical staff were working in the ICU after the TA dosing was reduced (without them being informed of the dosing change), and the subsequent incidence of seizures was reduced.

Tranexamic acid was used less frequently before 2007 but was the sole agent used from 2007 onwards. Our analysis examined two time periods (2003–2006 and 2007–2009). Thus, it is possible that our study may have biases associated with before/after studies (e.g., selection, history, information bias). However, we do not think the probability of this is high as other groups have reported results similar to ours,[10] with higher TA doses leading to increased seizures. It was not possible to examine the role of TA from 2007 to 2009 as all patients received TA thereby eliminating a no-TA group for comparison. Our dose–response relation to seizure rates attempts to compensate for this limitation.

In conclusion, we have addressed risk factors associated with seizures after cardiac surgery. Notably, TA may be a significant and readily modifiable factor in patients with other risk factors for seizure. We suggest that because of the association of TA with seizures one should use TA in the lowest possible antifibrinolytic dose, particularly in patients with other risk factors for seizure. For patients deemed to be at high risk for seizures, as determined by our multivariate model, but in whom high-dose TA may be necessary, consideration should be given to infusing GABA agonists (propofol or midazolam) during the initial high-risk period.

Funding sources Internal departmental.

Disclosures or conflicts of interest None declared.

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