Original Article

Risk factors associated with postoperative seizures in patients undergoing cardiac surgery who received tranexamic acid: A case-control study

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ABSTRACT

Antifibrinolytic agents are used during cardiac surgery to minimize bleeding and reduce exposure to blood products. Several reports suggest that tranexamic acid (TA) can induce seizure activity in the postoperative period. To examine factors associated with postoperative seizures in patients undergoing cardiac surgery who received TA. University-affiliated hospital. Case–control study. Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) between January 2008 and December 2009 were identified. During this time, all patients undergoing heart surgery with CPB received TA. Cases were defined as patients who developed seizures that required initiation of anticonvulsive therapy within 48 h of surgery. Exclusion criteria included subjects with preexisting epilepsy and patients in whom the convulsive episode was secondary to a new ischemic lesion on brain imaging. Controls who did not develop seizures were randomly selected from the initial cohort. From an initial cohort of 903 patients, we identified 32 patients with postoperative seizures. Four patients were excluded. Twenty-eight cases and 112 controls were analyzed. Cases were more likely to have a history of renal impairment and higher preoperative creatinine values compared with controls (1.39 ± 1.1 vs. 0.98 ± 0.02 mg/dL, P = 0.02). Significant differences in the intensive care unit, postoperative and total lengths of stay were observed. An association between high preoperative creatinine value and postoperative seizure was identified. TA may be associated with the development of postoperative seizures in patients with renal dysfunction. Doses of TA should be reduced or even avoided in this population.

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INTRODUCTION

Excessive perioperative bleeding is still an important risk of contemporary cardiac surgery under cardiopulmonary bypass (CPB). This bleeding tendency is associated with the surgical procedure itself and is due to the acquired defects in hemostasis resulting from extracorporeal circulation. Different pharmacologic strategies have been used to reduce bleeding and the need for donor-blood transfusion.[1] In many centers, because of its proven hemostatic properties, tranexamic acid (TA), a synthetic antifibrinolytic agent, is now administrated to cardiac surgical patients on a routine basis.[2,3]

A growing body of evidence suggests that TA can induce seizure activity in the early postoperative period.[4-6] In 2008, Martin *et al.* showed an increased seizure rate of 4.6% associated with the use of TA when compared with high-dose aprotinin, with a seizure rate of 1.2%.[7] More recently, Murkin

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et al. reported that use of high-dose TA in older patients in conjunction with CPB and open-chamber cardiac surgery is associated with an increase of seizure rates.[5] Similar results have been observed by Sander *et al.*[6]

TA-induced seizures are a multifactorial phenomenon because the effective cerebrospinal fluid TA concentrations may be increased not only by larger doses but also by alterations in the blood–brain barrier permeability.[8] Also, some conditions often found in patients undergoing cardiac surgery may exacerbate the tendency for seizure activity: renal insufficiency,[9] open-chamber procedures[5,7] and co-administration of other drugs such as cephalosporin antibiotics.[10] Unfortunately, these relationships have been barely studied. The objective of this case–control study was to examine factors associated with the development of postoperative seizures in patients undergoing cardiac surgery who received TA.

MATERIALS AND METHODS

The institutional review board approved the study. Given the retrospective design and that the information was collected from medical records, written informed consent was waived. Using the institutional database that follows the guidelines of the Society of Thoracic Surgery database, all patients undergoing cardiac surgery with CPB from January 1, 2008 to December 31, 2009 were identified. During this time, all patients undergoing heart surgery with CPB in our institution received TA. TA dosing strategy in our institution was based on the work of Dowd *et al*.[11] Low-risk cardiac patients received a 12.5 mg/kg loading dose over 30 min, followed by a maintenance infusion of 6.5 mg/kg/h until the end of the surgery, and an additional 1 mg/kg was added to the pump prime. High-risk cardiac patients received a loading dose of 30 mg/kg over 30 min, followed by a continuous infusion of 16 mg/kg/h until the end of the surgery, and an additional 2 mg/kg was added to the pump prime.

For this study, cases were defined as those patients who developed postoperative generalized convulsive seizures (myoclonic or tonic–clonic) that required initiation of anticonvulsive therapy within 48 h of surgery. Subjects with preexisting seizure history and patients in whom the convulsive episode was secondary to a new ischemic lesion on brain imaging were excluded. As per protocol, in the intensive care unit (ICU), all patients who experienced seizures underwent computerized tomography after the episode as soon as the patient's clinical condition was stable. For each case, four controls who did not experience postoperative generalized convulsive seizures were selected from the initial cohort. Controls were matched based on gender, age (±5 years) and the type of procedure performed.

The medical records of cases and controls were reviewed and potential risk factors for postoperative seizures were abstracted. The following patient-related data were recorded: age, sex, weight, height, body mass index, New York Heart Association functional class, previous cardiac operation, estimated left ventricular ejection fraction, previous myocardial infarction, permanent pacemaker, smoker, heart failure, renal disease, history of clinically severe vascular disease, hypertension, chronic obstructive pulmonary disease, diabetes (insulin dependent or not), other severe underlying noncardiac disease including seizure disorder, preoperative stay in hospital and/or ICU and preoperative medications including antiepileptic drugs, blood chemistry and hematocrit.

The Society of Thoracic Surgeons database collects preoperative serum creatinine (SCr), defined as the last single SCr measurement before surgery. Measurement of preoperative renal function was also based on the estimated glomerular filtration rate (GFR), which is the most reliable index of renal function according to the National Kidney Foundation (NFK) statement.[12] GFR was calculated according to the Modification of Diet in Renal Disease (MDRD) study formula as suggested by the NKF guidelines.[13] The MDRD formula is as follows:

$$GFR = 186.3 \times SCr^{-1.154} \times age^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$$

For descriptive purposes, renal function was classified as normal (GFR > 90 mL/min per 1.73 m^2), mild dysfunction (GFR 60–90 mL/min per 1.73 m^2), moderate dysfunction (GFR 30–59 mL/min per 1.73 m^2), severe dysfunction (GFR < 30 mL/min per 1.73 m^2) and dialysis dependence (regardless of GFR). These cut-points were chosen on the basis of published guidelines.[13]

The following operation-related factors were recorded: type of intervention done, urgency of operation (elective, urgent, emergency), duration of operation, duration of CPB, duration of aortic cross-clamping, use of deep hypothermic circulatory arrest, use of internal mammary artery, number of bypass grafts, type of valve prosthesis, problems weaning off CPB, operative blood loss and units of blood products transfused. The

following postoperative variables were assessed: time on mechanical ventilator, reintubation, reoperation, occurrence and type of complications, need for peritoneal dialysis, need for hemodialysis, duration of ICU stay, postoperative length of stay (LOS) and survival or death until 30 days of surgery.

Antibiotic prophylaxis was given intravenously 30–60 min before skin incision, after 3 h and then in the ICU every 6 h during the first 24 h. Cephazolin, 1 g for patients <70 kg and 2 g for patients >70 kg, was the standard choice, and in the case of penicillin allergy, vancomycin, 1 g every 12 h, was given. All patients received 2 mg oral lorazepam immediately before transfer to the operation theater (OR), and their cardiac medications were continued through the morning of surgery. Anesthetic induction consisted of fentanyl 5–15 μg/kg, propofol 2–3 mg/kg and pancuronium 0.1 mg/kg, followed by maintenance with isoflurane and oxygen before, during and after CPB. Anticoagulation was established with an initial 300 U/kg of heparin; the target kaolin-based activated coagulation time was greater than 400 s, and additional doses of heparin were administered as required during CPB to maintain activated coagulation time greater than 480 s. The bypass circuit was primed with isotonic electrolyte solution and 20% mannitol. During CPB, the pump flow was set at approximately 2.4–2.8 L/min/m^2. Arterial carbon dioxide tension was maintained throughout hypothermic CPB at 30–35 mmHg, uncorrected for temperature, according to alfa-stat blood management. Myocardial protection was achieved using a combination of anterograde and retrograde cold blood cardioplegia, and the systemic temperature was allowed to drift down depending on the surgical procedure. During rewarming, all patients received a continuous infusion of nitroglycerin and were actively rewarmed to 35°C (rectal temperature) before discontinuation of CPB. During the period of the study, there were no major changes in perfusion techniques or in the composition of the cardioplegia solutions. The surgical, anesthetic and ICU protocols remained unchanged during the time period in review.

Data are expressed as mean (SD) when the variables were normally distributed or as median (range) when the variables were not normally distributed. The correlation between preoperative, intraoperative and postoperative variables and postoperative seizures was studied by bivariate analysis using student's *t*-test, a nonparametric test (Mann-Whitney) or Chi-square test (or Fisher's test) for categorical data. Variables that tended to be associated with postoperative seizures ($P < 0.1$) were then analyzed by a model of logistic regression. Independent risk factors were pinpointed by a backward elimination procedure using the multivariate logistic model. A *P*-value of less than 0.05 was considered a significant risk factor. Association between risk factors and postoperative seizures was estimated by the odds ratio (OR) and 95% confidence interval (CI). All statistical tests were performed with SPSS for Windows (version 16, SPSS Inc., Chicago, IL, USA, 2009).

RESULTS

During the time period of this review, 903 patients underwent cardiac surgery with CPB. From this initial cohort, we identified 32 patients with postoperative seizures. Four patients were excluded (one had history of seizure disorder, two had evidence of new cerebral ischemic injury and one developed seizures on the 8th postoperative day); thus, 28 cases and 112 controls were analyzed. There were no statistically significant differences between the groups concerning demographic data [Table 1].

No significant differences were found with regard to past medical history, with the exception of preoperative renal impairment. Cases were more likely to have higher preoperative SCr values, lower estimated GFR and lower hematocrit levels compared with controls. The characteristics of surgical procedures were similar between the groups [Table 2].

There was a significant difference in the ICU LOS between the groups. Case patients had a median time of 4.5 days (range 1–33 days) in the ICU, whereas control patients had a median time in the ICU of 2 days (range 1–15 days) [Figure 1]. The postoperative (exclusive of ICU) LOS, the total postoperative LOS and the total hospitalization LOS were consistently higher in the seizure group compared with the control group [Table 3].

There was a trend for increased mortality in patients with postoperative seizures. The mortality rate was 14.3% (four of 28 patients) in the case group and 3.6%

Table 1: Demographic characteristics

	Seizure (n = 28)	Control (n = 112)	*P*-value
Age (years)	63.5 ± 14.3	63 ± 14.6	0.82
Weight (kg)	65.5 ± 14.4	69.1 ± 11.9	0.17
Height (cm)	162.3 ± 7.5	164.2 ± 9.3	0.31
Male sex (%)	16 (57.1)	69 (59.5)	0.67

Data are presented as mean ± SD and number of patients (percentage)

Table 2: Preoperative and intraoperative data

	Seizure (*n* = 28)	Control (*n* = 112)	*P*-value
Medical history			
Hypertension	16 (57.1)	72 (64.2)	0.48
Myocardial infarction	8 (28.6)	32 (28.6)	0.99
Diabetes mellitus	8 (28.6)	22 (16.7)	0.12
Cerebrovascular disease	2 (7.1)	7 (6.3)	0.9
Dyslipidemia	11 (39.3)	49 (43.8)	0.67
Endocarditis	1 (3.6)	5 (4.5)	0.95
Unstable angina	3 (10.7)	13 (11.6)	0.98
COPD	3 (10.7)	10 (8.9)	0.72
Renal disease	6 (21.4)	7 (6.3)	0.024
Previous cardiac surgery	4 (14.3)	11 (10.9)	0.5
Left ventricular ejection fraction	48 ± 16	49 ± 14	0.83
Preoperative status			0.4
Elective	15 (53.6)	65 (58)	
Urgent	13 (46.4)	43 (38.4)	
Emergency surgery	0	4	
Biochemical data			
Hematocrit (%)	37 ± 7.2	42.9 ± 6.3	0.0004
Creatinine (mg/dL)	1.39 ± 1.1	0.98 ± 0.2	0.02
Estimated GFR (mL/min/m^2)	63.5 ± 25.8	77.6 ± 20.8	0.0028
GFR level (mL/min per 1.73 m^2)			0.0441
Normal (>90)	4 (14.3)	32 (28.6)	
Mild dysfunction (90–60)	13 (46.4)	61 (54.5)	
Moderate dysfunction (59–30)	8 (28.6)	16 (14.3)	
Severe dysfunction (<30)	3 (10.7)	3 (2.7)	
Characteristics of surgical procedure			
Open-chamber cardiac surgery	23 (82.1)	81 (72.3)	0.34
CABG	5 (17.9)	31 (27.7)	
Isolated valve[a]	10 (35.7)	44 (39.2)	
Valve with CABG	11 (39.3)	25 (22.3)	
Other	2 (7.1)	12 (10.7)	
CPB time (min)	125 ± 76.6	115.6 ± 54.1	0.59
Ischemic time (min)	96 ± 63.8	90.1 ± 41.1	0.93

Data are presented as number of patients (percent) and means ± SD, GFR: Glomerular filtration rate, [a]Includes multivalve procedures

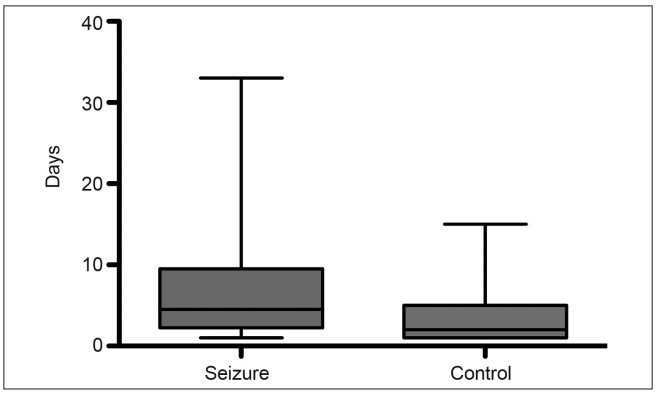

Figure 1: Intensive care unit length of stay. Displayed are the median (solid line), the 25th to 75th percentiles (shaded box) and the lowest and the highest values (whiskers)

(four of 112 patients) in the control group ($P = 0.051$). The 24 surviving patients in the case group made an uneventful neurological recovery after the convulsive episode without presenting permanent neurological deficit or recurrence of seizures. An association between preoperative SCr value, the estimated GFR and postoperative seizure was identified [Table 4].

DISCUSSION

The reported incidence of postoperative seizures in adult patients who did not receive TA during cardiac surgery ranged from 0.4% among patients undergoing coronary bypass surgery[14] to 1.2% in a series of patients undergoing valve, coronary and complex aortic surgery.[15] Our data shows an increased incidence of postoperative convulsive seizures (3.54%) that may be related to the use of TA. Following the STS and SCA guidelines, our hospital used aprotinin as the antifibrinolytic for high-risk patients;[1] this practice ended on December 2007 when aprotinin was

Table 3: Length of stay

	Seizure (*n* = 28)	Control (*n* = 112)	*P*-value
ICU LOS (days)	4.5 (1–33)	2 (1–15)	0.0016
Postoperative – exclusive of ICU – LOS (days)	6 (2–36)	4 (1–52)	0.0121
Total postoperative LOS (days)	10.5 (2–48)	7 (2–59)	0.0020
Total hospitalization LOS (days)	17.5 (3–135)	13 (4–74)	0.035

Data are provided as median (range), ICU: Intensive care unit; LOS: Length of stay.

Table 4: Logistic regression model for predictors of postoperative seizures

Variable	OR	CI (95%)	*P*
Age >70 years	1.9	1.4–3.0	0.05
Serum creatinine >1.29 mg/dL	3.4	1.1–9.2	0.01
MRDR <59 mL/min per 1.73 m^2	1.87	1.14–3.1	0.01

OR: Odds ratio; CI: Confidence interval.

withdrawn from the world market after some studies suggested increased morbidity and mortality compared with the lysine analogues.[16,17] The institution then switched to TA as the only antifibrinolytic agent used in cardiac surgical procedures involving the use of CPB. Several months following the change, it was observed that the incidence of convulsive episodes after cardiac surgery had significantly risen.

Our results are in agreement with recent data from the literature indicating an increased incidence of seizures in patients receiving TA in cardiac surgery.[5-7,18] Laboratory investigations and several case reports have indicated that TA elicits seizure activity if it is applied directly to the central nervous system.[19-22] The exact mechanism by which TA induces seizures is not known, but potential theories have been investigated. Furtmuller *et al.* found that TA directly inhibited activation of ¡-aminobutyric acid (GABA)-A receptors by GABA in membranes from the rat cerebral cortex.[8] GABA is the essential inhibitory neurotransmitter of the central nervous system and acts via GABA receptors: GABA-A, GABA-B and GABA-C. Blockade of GABA-A receptors by TA seems competitive or dose-dependent, and leads to neuronal hyperexcitability that can be observed clinically as convulsive activity.

In the present study, the convulsive crises appeared more frequently in patients with preoperative renal dysfunction. Preoperative renal dysfunction in patients undergoing cardiac surgery has been frequently associated with increased morbidity and mortality.[23-25] However, the occurrence of postoperative seizures in this group of patients is an infrequent event and has been rarely reported.[15] We suggest that the incidence of postoperative seizures in the present study is probably related to an altered metabolism of TA.

Pharmacokinetic studies have shown that excretion of TA depends predominantly on glomerular filtration, and more than 95% of the intravenous administered dose is excreted unchanged in the urine. Renal excretion of TA is about 90% at 24 h after intravenous administration of 10 mg/kg.[26] This dependence on renal excretion makes it probable that patients with major renal impairment could have higher TA concentrations than patients with normal renal function, putting this population at significant risk of complications. Interestingly, we found a strong relationship between preoperative SCr levels and the presence of convulsive crises: patients with a SCr level higher than 1.29 mg/dL had 3.4 times the possibility of developing seizures in the postoperative period. The calculated GFR, a more reliable index of renal function, showed that moderate and severe renal dysfunction raised the risk of developing postoperative seizures 1.87 times compared with patients with normal GFR. These data suggest that the dose of TA should be reduced or that TA should even be avoided in patients with renal impairment. To our knowledge, only one study has been designed incorporating the effects of renal function on TA concentrations.[27] In that study, patients were randomly assigned to receive the authors´ standard TA dosage (bolus of 10 mg/kg plus infusion of 1 mg/kg/h) or a new regimen of a bolus of 6.6 mg/kg plus 40 mg in the CPB circuit and an infusion rate according to the preoperative level of SCr. With the new scheme, they did not reach stable TA target levels of 20 mg/mL on CPB. The small number of patients enrolled limited this study, and the authors did not report the incidence of postoperative seizures.

Another condition that may have contributed to seizures in our study is the concomitant administration of cephazolin.[28,29] Numerous reports suggest that cephalosporins may cause a variety of neurological disturbances, including myoclonus, seizures and status epilepticus. The majority of papers describe this cephalosporin-induced neurotoxicity in patients with renal insufficiency, most likely secondary to an increase in the drug's level, as a result of altered pharmacokinetics.[10] Similar to TA, the main mechanism of cephalosporin neurotoxicity involves ¡-GABA-A

receptor inhibition, although other mechanisms may also be involved.[30,31] It is not known whether the effects of TA and cephazolin are additive or synergistic in patients with renal dysfunction.

In the present study, patients who developed seizures had an increased LOS compared with patients who did not present seizures. The inherent treatment associated with a convulsive episode might be responsible for the longer LOS in the ICU. We also found a trend toward increased mortality in patients with postoperative seizures. The high prevalence of renal dysfunction in this group of patients may be partly responsible for this finding.[25] However, the isolated presence of postoperative seizures has been associated with poor outcomes. Goldstone *et al*.[15] recently reported predictors of seizures and the impact on postoperative outcomes in a cohort of 2,578 consecutive patients undergoing cardiac procedures at a single institution. TA was not used in this series. Postoperative seizures were observed in 1.2% of their patients, and were associated with a significant increase in morbidity and mortality. In their study, multivariate logistic regression identified three risk factors for convulsive episodes: deep hypothermic circulatory arrest, aortic calcification and critical preoperative condition. In our study, the incidence of postoperative seizures was significantly higher (3.54%), and we were not able to find an association with the aforementioned factors. Both studies are difficult to compare due to the differences in the diagnosis of aortic calcification, the definition of critical preoperative condition and, as outlined above, the nonuse of TA in Goldstone's study.

In our series, advanced age was identified as a predictor for postoperative seizures. This association has been previously reported.[5] We suspect that elderly patients may be at higher risk for this complication because of the known age-related decline in creatinine clearance.

Limitations

This study is subject to the methodological limitations of a retrospective case–control study. In addition, the sample size is small. Thus, a type 2 error cannot be excluded for some of the outcomes and risk factors evaluated. The surgical technique varied according to surgeon preference. Even though general patterns were followed as a result of institutional practices, we did not take into account potential confounding factors such as the type of intraoperative cerebral protection. We are aware of the significant dose variation reported in the present study, making it difficult to analyze whether the association between intraoperative administration of TA and postoperative seizures is dose related or not. The dose ranges of TA administered to our patients were based on the pharmacokinetic study of TA during CPB published by Dowd *et al*.[11] The dosing regimen would maintain TA blood concentration between 345 mmol/L and 800 mmol/L (54–126 μg/mL) in order to produce 80–100% reduction of tissue activator activity. This dosage strategy is often used in clinical practice, and has been extensively used in multiple studies.[5,7,17,18]

CONCLUSION

In conclusion, our results suggest an association between conventional doses of TA and the development of postoperative seizures in patients with renal dysfunction. The presence of seizures is associated with an increased ICU, postoperative and total LOS with a trend toward higher mortality. Accordingly, we recommend that doses of TA should be reduced or that TA be even avoided in this population.

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