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High-dose tranexamic acid is related to increased risk of generalized seizures after aortic valve replacement

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Abstract

Objective: To investigate the incidence of postoperative generalized seizures in patients undergoing aortic valve replacement (AVR) under extracorporeal circulation, who received either high-dose tranexamic acid (TXA) or epsilon aminocaproic acid (EACA) as an antifibrinolytic agent. **Methods:** This retrospective analysis comprised 682 consecutive patients undergoing AVR with or without simultaneous coronary artery bypass surgery. Patients operated on before March 2008 were treated intra-operatively with TXA (100 mg kg^{-1}; $n = 341$), patients operated on after March 2008 received EACA (50 mg kg^{-1} loading dose, followed by 25 mg kg^{-1} h^{-1}, and an additional 5 g in the extracorporeal circuit; $n = 341$). **Results:** Clinically diagnosed generalized seizures were observed within the first 24 h postoperatively, more frequently in patients receiving TXA compared with EACA (6.4% vs 0.6%, $p < 0.001$, difference = 5.8%, 95% confidence interval 3.1—8.5%). Besides the antifibrinolytic agent, three other variables differed significantly between patients with and without postoperative seizures: age (mean (SD), 77.0 (5.9) years vs 73.2 (9.0) years, $p = 0.039$), preoperative creatinine clearance (55.4 (16.5) ml min^{-1} vs 72.6 (28.5) ml min^{-1}, $p = 0.002$), and administration of recombinant activated factor VIIa (3 out of 24 patients (12.5%) vs 8 out of 658 patients (1.2%), $p = 0.005$). Logistic regression analysis demonstrated a significant impact of the antifibrinolytic drug, creatinine clearance, and the application of recombinant activated factor VIIa on the occurrence of generalized seizures. **Conclusions:** Our results indicate that high-dose TXA is associated with an increased incidence of postoperative generalized seizures in patients undergoing AVR compared with EACA, especially when suffering from renal impairment. A possible association between recombinant activated factor VIIa and the occurrence of postoperative seizures needs further investigation.

Keywords: Antifibrinolytic agent; Aortic valve replacement; Seizure; Tranexamic acid

1. Introduction

Antifibrinolytics are widely used in patients undergoing cardiac surgery to reduce postoperative blood loss. Although aprotinin seems to be the most effective drug to reduce postoperative blood loss [1,2], its use has been associated with an increased occurrence of unfavorable side effects or increased mortality [1,3—5]. Two alternative substances are currently being used as antifibrinolytic agents: tranexamic acid (TXA) and epsilon aminocaproic acid (EACA). No major differences between TXA and EACA with respect to post-operative bleeding, or other adverse effects have been reported so far [6]. However, recent studies described the occurrence of generalized seizures in patients treated with TXA [7—9]. Martin and Sander observed a more than threefold higher incidence of postoperative seizures in patients who received TXA compared with aprotinin [7,9]. A direct comparison between TXA and EACA with respect to the incidence of postoperative seizures is, however, lacking. Therefore, we performed a retrospective analysis of patients receiving either TXA or EACA as an antifibrinolytic drug. We enrolled patients undergoing aortic valve replacement (AVR), as this cohort seems to be at an increased risk of experiencing postoperative seizures [7].

2. Materials and methods

The study was designed as a retrospective cohort study. We analyzed data from patients 18 years of age or older undergoing AVR due to aortic stenosis with or without

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concomitant coronary artery bypass grafting (CABG). Patients with simultaneous replacement of the ascending aorta, with redo cardiac surgery, or with multiple valve surgery were excluded from the study. The study protocol was approved by the local ethics committee that waived the need for obtaining consent of patients for this retrospective analysis.

TXA was replaced by EACA in our institution in March 2008 as we, and others [7], had the impression that TXA was associated with an increased incidence of seizures. According to the determined sample size, we included 341 consecutive patients who were operated on before March 2008 (antifibrinolytic drug: TXA) and 341 consecutive patients who were operated on after March 2008 (antifibrinolytic drug: EACA). Due to this procedure, the 682 patients included in the study were recruited from a total cohort of 2110 patients undergoing cardiac surgery between January 2007 and June 2009; that is, all patients undergoing AVR during that time period were consecutively enrolled.

Data were retrieved from the electronic hospital information system (Patidok, Professional Clinical Software GmbH, Klagenfurt, Austria) and from the electronic patient database (Metavision, IMDsoft, Tel Aviv, Israel). The patient database has been designed for documentation of clinical events, such as generalized seizures, and the intensive care staff has been trained to manage and validate the data. The electronic patient chart was explicitly reviewed in all patients with a documented neurological event.

All patients underwent a standardized anesthesiological and surgical management. Patients were premedicated with temazepam 10–20 mg orally. Anesthesia was induced with sufentanil, etomidate, and pancuronium or rocuronium, depending on the renal function of the patients and the decision of the anesthesiologist. Anesthesia was maintained with sevoflurane and supplemental sufentanil, as required. Blood pressure measurement was performed via a radial artery catheter. A double-lumen central venous catheter and a 7.5 Fr sheath introducer were inserted via the jugular or subclavian vein. All patients were monitored intra-operatively by transesophageal echocardiography. A pulmonary artery catheter was used in most patients in accordance with hospital policy, and depending on the decision of the anesthesiologist.

Surgery was carried out under normothermic conditions via a median sternotomy. The set-up of the heart–lung machine was identical in all patients, using a roller pump (Stoeckert S3, Sorin Group, Munich, Germany) and a membrane oxygenator (Jostra Quadrox, Maquet, Hirrlingen, Germany). Extracorporeal circulation was performed under normothermic conditions, and cardioprotection was achieved using antegrade blood cardioplegia. De-airing of the left ventricle was performed before termination of extracorporeal circulation via a cannula, which was inserted in the ascending aorta and controlled by echocardiography. The pericardium was closed at the end of surgery in all patients.

Postoperatively, the patients were sedated with a propofol infusion, as clinically required, and were transferred to the intensive care unit (ICU). Patients did not receive any muscle relaxant postoperatively. Piritramid or sufentanil was applied according to the patient's analgesic requirements. Sedation was stopped when the patients were normothermic, hemodynamically stable with sufficient respiratory function, and with no relevant bleeding. The patients were extubated as soon as the neurological status was adequate.

TXA was administered according to the study of Karski et al. at a dose of 100 mg kg^{-1} body weight [10]. Half of the dose was added to the bypass circuit, half of the dose was given over a time interval of approximately 1 h via the central venous access, starting after sternotomy with the administration of heparin.

The dosage of EACA was adopted from the pharmacokinetic study of Butterworth et al. [11]. The patients received 50 mg kg^{-1} EACA as a loading dose over 20 min after sternotomy, together with the administration of heparin, followed by a continuous infusion of 25 mg kg^{-1} body weight h^{-1} until the end of surgery. A loading dose of 5 g EACA was added to the pump prime.

The primary end point was defined as the occurrence of a generalized seizure within the first 24 h postoperatively, after admission to the ICU. Generalized seizures were diagnosed as typical tonic–clonic convulsions by intensive-care physicians and nurses, and were differentiated from phenomena such as shivering. We did not use routine electroencephalogram (EEG) monitoring. Cerebral computer tomography was performed if patients demonstrated focal neurological signs or decreased consciousness on the following day, depending on the decision of the intensivist.

To gain information about the primary purpose of antifibrinolytic drugs, that is, the reduction of postoperative bleeding, we analyzed the mediastinal tube drainage, assessed within 24 h after admission to the ICU, or at the time of removing the drain, if this occurred earlier. A mediastinal drainage $>$ 800 ml was defined as the secondary end point. This cut point represents the 75th percentile of the mediastinal tube drainage, measured in the patient group used for sample size calculation, as described below.

3. Statistical methods

3.1. Sample size calculation

The minimal required sample size was determined using the software G*Power (Department of Experimental Psychology, Heinrich-Heine-University, Düsseldorf, Germany).

Sample size calculation was based on the incidence of postoperative seizures observed in patients undergoing AVR between July and December 2006. TXA was used as an antifibrinolytic agent at that time, and postoperative seizures were observed at a frequency of 5% during the first 24 h after admission to the ICU, in patients undergoing AVR (7 out of 151 patients). According to this data, we determined that 323 patients were required in each group to detect a relative reduction of 80% in the frequency of postoperative seizures between TXA and EACA with alpha of 0.05 (two-sided) and beta of 0.2.

The sample size required to detect the effect of antifibrinolytics on postoperative bleeding was calculated for an estimated effect size of 0.23, according to previous measurements (standard deviation of blood loss of approximately 430 ml, 100 ml expected difference in blood loss between groups). Corrected for the application of the Mann–

Whitney *U* test (minimum asymptomatic relative efficiency of 0.864), we calculated a sample size of 338 patients in each group with alpha of 0.05 (two-sided) and beta of 0.2.

Based on these estimated sample sizes, we included 341 patients in each treatment group, that is, all patients between January 2007 and June 2009 undergoing AVR and adhering to the inclusion criteria described above.

3.2. Statistical analysis

Statistical analysis was performed using commercially available software (Statistical Package for Social Sciences (SPSS) for Windows 16.0., SPSS Inc., Chicago, IL, USA). Normal distribution of data was evaluated by visual assessment of the histograms and the probability plots (Q–Q plots). Data adhering to normal distribution are reported as mean (standard deviation), otherwise as median with 25th and 75th percentiles.

The variables subjected to statistical analysis are presented in Table 1. Categorical variables were compared between patient groups using the chi-square test or Fisher's exact test for cell sizes of less than five. Continuous data were compared by non-parametric (Mann–Whitney *U* test) or parametric tests (Student's two sample *t*-test), as appro-

Table 1. Clinical and demographic characteristics of patients.

	TXA (n = 341)	EACA (n = 341)	p-value
Age (year)	73.0 (9.3)	73.7 (8.5)	0.33
Male	189	184	0.70
Weight (kg)	78.2 (15.4)	76.9 (15.5)	0.73
Height (cm)	168 (9.0)	167 (9.3)	0.55
Preoperative characteristics			
Diabetes	64	74	0.24
Hypertension	259	237	0.33
Chronic obstructive lung disease	11	14	0.47
Peripheral arterial vascular disease	15	20	0.88
Impaired left ventricular function	86	93	0.60
Impaired right ventricular function	18	25	0.27
Stroke/TIA	8	8	1.0
Severe liver disease (cirrhosis)	1	2	0.54
Smoking	62	60	0.98
Creatinine clearance (ml min^{-1})	74.1 (28.3)	70.0 (27.9)	0.04
Preoperative dialysis	0	3	0.25
INR $>$ 1.2	34	32	0.45
Platelets $<$ 150 nl^{-1}	29	45	0.049
Hemoglobin (g dl^{-1})	13.6 (1.6)	13.4 (1.6)	0.06
Preoperative medication			
Aspirin	68	94	0.02
Clopidogrel	11	9	0.65
Heparin	24	25	0.88
Low molecular heparin	22	19	0.63
Coumarin	16	22	0.32
Beta adrenergic blockers	13	19	0.23
ACE inhibitors	163	151	0.36
Antiarrhythmics	13	19	0.28
Calcium channel blockers	47	46	0.91
Digitalis	17	8	0.07
Nitrates	8	15	0.14
Diuretics	161	153	0.95
Type of surgery			0.40
Aortic valve replacement	235	245	
Aortic valve replacement + CABG	106	96	
Intraoperative characteristics			
Extracorporeal circulation (min)	81 (68; 98)	85 (70; 105)	0.006
Extracorporeal circulation $>$90 min	114	152	0.003
Reoperation for bleeding	20	32	0.083
Intra- and postoperative transfusion requirements, drug therapy and mechanical support			
Patients with red cells transfused	249	282	0.002
Patients with platelets transfused	21	59	$<$0.001
Patients with fresh frozen plasma transfused	100	158	$<$0.001
Desmopressin	127	143	0.21
Prothrombin complex concentrate	7	21	0.011
Fibrinogen cryoprecipitate	1	19	$<$0.001
Recombinant activated factor VIIa	4	7	0.55
Vasopressor	300	326	$<$0.001
Positive inotropic drug	93	120	0.026
Inhaled nitric oxide	7	8	0.80
Intra-aortic balloon pump	7	15	0.13
Atrial fibrillation up to 24 h postoperatively	15	20	0.49

EACA, epsilon aminocaproic acid; INR, international normalized ratio; TIA, transitory ischemic attack; TXA, tranexamic acid. Data are reported as number of patients, mean (standard deviation), or median (25th; 75th percentile). Creatinine clearance was calculated by the Cockroft–Gault formula.

Table 2. Unadjusted analysis of the impact of treatment (TXA vs EACA) on the occurrence of generalized seizures and mediastinal drainage > 800 ml within 24 h postoperatively.

	TXA (n = 341)		EACA (n = 341)		p-value	Absolute difference (95% CI) of proportions	Odds ratio (95% CI) TXA versus EACA
	Events	Proportion (%)	Events	Proportion (%)			
Generalized seizure	22	6.4%	2	0.6%	<0.001	5.8 (3.1–8.5)	11.7 (2.7–50.1)
Mediastinal drainage > 800 ml	58	17.0%	95	27.8%	0.001	10.8 (4.6–17.0)	0.53 (0.37–0.77)

CI, confidence interval; EACA, epsilon aminocaproic acid; TXA, tranexamic acid.

priate. All tests were performed as two-sided tests with a significance level of 0.05.

Several independent variables differed between patient groups receiving either TXA or EACA (Table 1). To test the association between these independent variables and the outcome variable, we constructed a logistic regression model. All variables associated with the outcome at alpha <0.1 (two-sided) were included in the model. We selected a logistic regression model with a stepwise forward selection of the variables and deletion of the entered variables that were no longer significant. The significance of each variable was measured using a Wald statistic. The significance levels for entry and removal of variables were set to 0.1. We chose this selection procedure to reduce the number of variables entered in the model in view of the limited number of primary outcomes [12], as discussed later in more detail. The predictive value of the model was assessed by the Hosmer–Lemeshow chi-square test and the concordance-index, calculated by receiver operating characteristic (ROC) curve analysis. Odds ratios with 95% confidence intervals are

Table 3. Characteristics of patients suffering from generalized seizures within 24 h postoperatively.

Gender	Age	Preexisting neurological disorder	Creatinine clearance (ml min^{-1})	Antifibrinolytic agent	F VIIa	Surgery	Cerebral computer-tomography	Postoperative course	ICU stay (days)
M	72	No	51.8	TXA	–	AVR	Not done	Uneventful	1
F	74	No	46.9	TXA	–	AVR	Not done	Uneventful	1
M	72	No	41.8	TXA	–	AVR	Not done	Uneventful	1
M	78	Ischemic cerebral lesions	29.5	TXA	–	AVR, CABG	Multiple preexisting lacunar lesions	Pneumonia, peripheral vascular disease: stenting of a superficial femoral artery occlusion	30
M	68	No	72.8	TXA	–	AVR	Not done	Uneventful	1
M	71	No	82.4	TXA	–	AVR	Not done	Uneventful	1
M	90	No	55.9	TXA	Yes	AVR, CABG	Not done	Delirium for 3 days, complete recovery	4
F	74	No	73.1	TXA	–	AVR	Not done	Uneventful	2
M	81	No	61.3	TXA	–	AVR	Not done	Uneventful	2
F	82	Diabetic polyneuropathia	82.2	TXA	–	AVR	Not done	Prolonged mechanical ventilation, complete recovery	4
F	73	No	52.1	TXA	–	AVR	Not done	Uneventful	1
M	84	No	55.7	TXA	–	AVR	Not done	Uneventful	1
M	73	No	69.9	TXA	–	AVR	Not done	Uneventful	2
M	76	No	67.8	TXA	–	AVR	Not done	Uneventful	2
F	80	No	38.1	TXA	–	AVR	Preexisting lacunar lesion near the left claustrum	Delirium for 2 days, complete recovery	4
F	80	No	63.7	TXA	–	AVR, CABG	Not done	Repeat surgery due to bleeding, complete recovery	6
F	80	No	42.2	TXA	–	AVR, CABG	Not done	Uneventful	2
F	81	No	32.2	TXA	–	AVR, CABG	Not done	Postoperative delirium, respiratory failure, acute renal failure, sepsis, death on day 8	8
F	67	Preexisting hypoxic brain injury: dysarthria	80.4	TXA	–	AVR	Not done	Uneventful	1
F	86	No	38.8	TXA	–	AVR	Not done	Prolonged ventilator support, complete recovery	4
M	72	No	54.0	TXA	Yes	AVR, CABG	Cerebellar hemorrhage (15 × 10 mm)	Respiratory and left ventricular failure, recurrent ventricular fibrillation, death on day 22	10
F	72	No	64.8	TXA	–	AVR	Not done	Uneventful	2
M	80	No	39.5	EACA	–	AVR	Ischemic lesion temporo-occipital left	Postoperative delirium, incomplete neurologic recovery	5
F	83	No	33.2	EACA	Yes	AVR, CABG	No pathological finding	Respiratory failure, renal failure, incomplete recovery	9

AVR, aortic valve replacement; CABG, coronary artery bypass grafting; EACA, epsilon aminocaproic acid; F VIIa, recombinant activated factor VIIa; TXA, tranexamic acid. Creatinine clearance was calculated using the formula of Cockroft–Gault.

reported for the independent variables included in the model.

4. Results

The data of all patients included were analyzed. The demographic characteristics of the patients are reported in Table 1. Several variables differed between the treatment groups: (1) the number of patients with preoperative aspirin therapy was higher in the EACA group; (2) the time of extracorporeal circulation was slightly, but significantly, longer in the EACA group; (3) the number of patients receiving positive inotropic drugs or vasoconstrictors was higher in the EACA group than in the TXA group; and (4) preoperative renal function, assessed as creatinine clearance calculated by the Cockroft–Gault formula, was lower in patients receiving EACA compared with TXA.

Postoperative generalized seizures were observed more frequently in patients receiving TXA compared with patients treated with EACA (6.4% vs 0.6%, $p < 0.001$, Table 2).

Table 3 gives detailed information about the patients suffering from postoperative seizures. All seizures lasted less than 1 min. Sixteen patients suffered an isolated seizure, five patients experienced two seizures, one patient three, one patient four, and one patient five seizures. Clonazepam was administered to 18 patients once or twice. One patient in each treatment group showed persistent major neurological sequelae due to ischemic stroke and intracerebral bleeding, respectively. Ten out of 24 patients showed a complicated postoperative course, and two of them died (Table 3).

Univariate tests identified four variables, which differed between patients with and without postoperative seizures at a significance level of 0.1. These are: age (77.0 (5.9) years vs 73.2 (9.0) years, $p = 0.039$), preoperative creatinine clearance (55.4 (16.5) ml min^{-1} vs 72.6 (28.5) ml min^{-1}, $p = 0.002$), administration of recombinant activated factor VIIa (3 out of 24 patients (12.5%) vs 8 out of 658 patients (1.2%), $p = 0.005$), and the antifibrinolytic agent (22 patients with seizures in the TXA group and two patients with seizures in the EACA group, $p < 0.001$). Logistic regression analysis demonstrated a significant impact of the antifibrinolytic drug, creatinine clearance, and the administration of recombinant activated factor VIIa on the occurrence of generalized seizures (Table 4).

Table 4. Results from logistic regression analysis for the occurrence of generalized seizures within 24 h postoperatively.

	Odds ratio	95% CI	*p*-value
Antifibrinolytic drug (TXA vs EACA)	19.2	4.0–93.2	<0.001
Recombinant activated factor VIIa (yes vs no)	18.9	3.4–104.8	0.001
Preoperative creatinine clearance (ml min^{-1})	0.97	0.95–0.99	0.002

CI, confidence interval; EACA, epsilon aminocaproic acid; TXA, tranexamic acid. Goodness of fit of the logistic regression model: Hosmer and Lemeshow test chi-square = 5.3 with 8 degrees of freedom, $p = 0.73$; concordance index = 0.85.

Table 5. Results from logistic regression analysis for a mediastinal drainage > 800 ml within 24 h postoperatively.

	Odds ratio	95% CI	*p*-value
Antifibrinolytic agent (TXA vs EACA)	0.57	0.39–0.83	0.003
Preoperative aspirin (yes vs no)	1.50	0.98–2.27	0.060
Preoperatively impaired right ventricular function (yes vs no)	2.05	1.06–3.97	0.033
Body weight (kg)	0.97	0.96–0.99	<0.001

CI, confidence interval; EACA, epsilon aminocaproic acid; TXA, tranexamic acid. Goodness of fit of the logistic regression model: Hosmer and Lemeshow test, chi-square = 4.0 with 8 degrees of freedom, $p = 0.86$; concordance index = 0.66.

Postoperative mediastinal drainage was 460 (350; 685) ml (median, 25th and 75th percentiles) in patients receiving TXA and 530 (400; 900) ml in patients receiving EACA ($p < 0.001$). Mediastinal drainage >800 ml was observed in 153 patients (Table 2). Univariate tests identified six variables, which differed between patients with and without increased postoperative bleeding at a significance level of 0.1. These are: body weight (73.2 (13.8) vs 78.8 (15.7) kg, $p < 0.001$), age (74.4 (8.6) vs 73.1 (8.9) years, $p = 0.094$), preoperative creatinine clearance (66.9 (26.7) vs 73.5 (28.6) ml min^{-1}, $p = 0.011$), preoperative treatment with aspirin (45 vs 117 patients, $p = 0.062$), preoperatively impaired right ventricular function (17 vs 26 patients, $p = 0.005$), and the antifibrinolytic agent (58 patients with mediastinal drainage > 800 ml in the TXA group, 95 patients with mediastinal drainage > 800 ml in the EACA group, $p = 0.001$). Logistic regression analysis identified a significant impact of the antifibrinolytic drug, preoperative treatment with aspirin, preoperatively impaired right ventricular function, and body weight on a mediastinal drainage > 800 ml (Table 5).

5. Discussion

5.1. Generalized seizures after AVR

Generalized seizures occurred significantly more often within the first 24 h after AVR in patients receiving TXA than in patients receiving EACA. The incidence of this adverse event was similar to that observed by Martin et al., who investigated a more heterogeneous patient group, which was treated with TXA in a different dosage regimen [7].

Under experimental conditions, TXA exerts convulsive effects when administered intrathecally [13]. Furtmuller et al. reported an antagonistic action of TXA at gamma-amino butyric acid-A (GABA-A) receptors [14], explaining a lowering of the seizure threshold by TXA. This hypothesis is in accordance with our findings that generalized seizures occurred typically during weaning of propofol sedation, a phenomenon that has previously been reported by Murkin et al. [8]. One may hypothesize that the anticonvulsive effect of propofol was diminished during this period. Simultaneously, the seizure threshold may have been lowered by TXA. Obviously, this was a temporary effect, as the majority of patients had one or two seizures followed by an uneventful clinical course. As plasma levels of TXA were not measured, this hypothesis has yet to be proven. On the other hand, the

administration of propofol can be accompanied by seizure-like movements that occur during or after emergence from anesthesia [15]. These events should, however, have been observed irrespective of the treatment with TXA or EACA.

Convulsions under EACA have rarely been observed. Rabinovici et al. reported generalized seizures in a patient with liver failure who received EACA [16], but this observation has not been confirmed by others until now.

TXA and EACA are mainly eliminated by renal clearance [11,17], and it is well known that TXA accumulates in patients with impaired renal function [18,19]. Therefore, it is reasonable to assume, that – in view of the pharmacokinetic properties of TXA – creatinine clearance was significantly associated with the occurrence of generalized seizures in the present study.

The dosage regimens of EACA and TXA, used in our patients, were not equipotent with regard to their antifibrinolytic properties. However, there are no data available indicating that the dose–response relationships of TXA and EACA, regarding their proconvulsive properties, are similar to their antifibrinolytic properties.

There is some controversy about the appropriate dosing of EACA and TXA in the literature. The total dose of EACA administered to our patients was only slightly lower than that used by Fergusson et al. in the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study [1]. The dosage of TXA, on the other hand, was higher than the dose used in the BART study, which did not observe an increased incidence of seizures in the postoperative course. The BART study enrolled high-risk cardiac surgery patients and treated these patients with approximately one-third of the antifibrinolytic dose we used [1].

It is possible that the type of surgery enhanced the convulsive properties of TXA. Martin et al. observed a frequency of seizures comparable to that in our TXA group in patients undergoing valve surgery, but not in patients undergoing other cardiac surgical procedures [7]. Sander et al. noticed a trend toward increased frequency of seizures in patients undergoing open-heart procedures [9]. It is known that valve surgery, as well as aortic atherosclerosis, is associated with an increased risk of cerebral injury, presumably due to gaseous and particulate cerebral microembolism [20]. It may be hypothesized that this effect enhances the vulnerability of the cerebrum to other proconvulsive factors. Cerebral imaging was only performed in patients with persistent neurological sequelae. Thus, it cannot be excluded that minor damages might not have been detected in patients, who showed a clinically uneventful course.

Only a few patients received recombinant activated factor VIIa due to intractable bleeding. Nevertheless, the association with the occurrence of seizures was significant. The 95% confidence interval, however, was very large due to the low number of cases. Treatment with recombinant activated factor VIIa is associated with an increased rate in thrombo-embolic complications [21]. Recent studies also identified recombinant activated factor VIIa as a risk factor for neurological adverse events, such as stroke, in cardiac surgical patients [22]. A similar mechanism may explain the impact of recombinant activated factor VIIa on seizures in our patients. Due to the low number of cases, however, we cannot definitely rule out that other factors, which were not identified, may have contributed to the observed neurological events.

5.2. Mediastinal drainage

Patients receiving TXA showed significantly less mediastinal tube drain than those treated with EACA. This observation may be attributed to the increased prevalence of aspirin in the EACA group. However, multivariable analysis identified also a significant impact of EACA on increased chest drainage (Table 5). Reduced body weight may be interpreted as a sign of poor physical condition, which, *per se*, may have contributed to increased bleeding. Likewise, impaired right-heart function may increase bleeding. However, these hypotheses are not supported by changes in coagulation parameters. The predictive accuracy of the logistic regression model, measured as the area under the ROC curve, was rather low. This model must thus be interpreted cautiously. Furthermore, our dosages of TXA and EACA cannot be regarded as equipotent. TXA is judged to be at least seven times more effective than EACA [23]. The BART trial, as well as a recent meta-analysis, did not report differences in the blood-sparing effect of TXA and EACA [1,24]. However, low-risk procedures, such as AVR, were not included in the BART trial. Another study suggested increased bleeding after EACA compared with TXA in cardiac surgery patients [25]. Obviously, further studies are needed for comparison of the blood-sparing equipotent dosages of antifibrinolytic drugs.

5.3. Potential bias

Although we investigated a clearly defined patient cohort, the groups receiving TXA or EACA differed in several characteristics, as pointed out above. Moreover, a retrospective observational cohort study with a before–after design has certain limitations, such as possible confounding and systematic errors. It is unlikely that a time-trend bias, which indicates a potentially more complicated and prolonged perioperative course in the EACA group (e.g., increased length of extracorporeal circulation, transfusion requirements, and need for vasopressors), contributed to an increased incidence of seizures in patients receiving TXA. A history bias is unlikely, as treatment of patients did not change after March 2008, except for the antifibrinolytic agent used. The surgical technique did not vary among surgeons. Epi-aortic ultrasound was not used to identify aortic atheroma, the surgical field was flooded with carbon dioxide in all patients, and the de-airing technique did not change over time. A selection bias can be excluded, as we analyzed consecutive patients undergoing AVR. The method of documentation on the ICU did not change over time, thus making an ascertainment bias in the identification of seizures unlikely.

We used logistic regression analysis to identify variables, which were associated with the outcome, and to get some information about confounders, which might contribute to time-trend bias. The odds ratios demonstrating the impact of the antifibrinolytic agent or recombinant activated factor VIIa on the occurrence of generalized seizures show large

confidence intervals. This can be explained by the small number of patients experiencing generalized seizures, as well as the small number of patients receiving recombinant activated factor VIIa. We did not expect, when planning the study, that factors other than the antifibrinolytic agent were associated with the occurrence of generalized seizures. Thus, the calculated sample size does not meet the recommended criterion of 10 outcomes per independent variable included in the logistic regression model (i.e., we observed 24 outcomes, but approximately 30 outcomes are recommended for a logistic regression model with three independent variables) [12]. Nevertheless, the regression model confirms the role of TXA suggested by bivariate analysis and initiates a discussion on the contribution of recombinant activated factor VIIa to this phenomenon. We did not adjust for potential confounders between the TXA and EACA groups by constructing a propensity score. This strategy, which compensates for differences in the probability of being assigned to a treatment group, is not adequate for the before-and-after study design of this analysis.

5.4. Limitations

Beside potential bias (as discussed above), this retrospective analysis shows other limitations.

Seizures were diagnosed due to the clinical assessments of experienced intensivists. The majority of patients with seizures had an uneventful clinical course without any persistent neurological deficit. However, it cannot be excluded that sub-clinical seizures were not detected, as the patients were not monitored by EEG postoperatively. The frequency and severity of postoperative neurological impairment, such as delirium, was not assessed by a scoring system, and cannot be reported as a graded index in our cohort.

The dosages of TXA and EACA were not equipotent in their antifibrinolytic properties. There are no data indicating that the proconvulsive properties of TXA and EACA are similar to their antifibrinolytic properties. Due to non-equipotent dosing, the influence of the antifibrinolytic agents on postoperative bleeding has to be interpreted with caution.

6. Conclusion

Our study showed an increased incidence of postoperative generalized seizures in patients receiving high-dose TXA as an antifibrinolytic agent compared with patients receiving EACA, especially when suffering from renal impairment. The possible contribution of recombinant activated factor VIIa to the occurrence of postoperative seizures needs further investigation.

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