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Moderate dosage of tranexamic acid during cardiac surgery with cardiopulmonary bypass and convulsive seizures: incidence and clinical outcome

A. Koster[1]*, J. Börgermann[2], A. Zittermann[2], J. U. Lueth[1], T. Gillis-Januszewski[2] and U. Schirmer[1]

[1] Institute for Anaesthesiology and [2] Department of Cardiac and Thoracic Surgery, Heart and Diabetes Centre North Rhine-Westphalia, Bad Oeynhausen, Ruhr-University Bochum, Georgstr. 11, D-32545 Bad Oeynhausen, Germany

* Corresponding author. E-mail: akoster@hdz-nrw.de

Editor's key points

- This is a retrospective data analysis of 4883 patients who underwent cardiac surgery.
- Comparison was made between the use and non-use of tranexamic acid (TA).
- In open-heart surgery, the use of TA was associated with increased mortality.
- The study highlights the need for prospective trials on the safety profile of using TA during cardiac surgery.

Background. Convulsive seizures (CS) occur in ~1% of the patients after cardiac surgery with cardiopulmonary bypass. Recent investigations indicate an up to seven-fold increase in CS in cardiac surgical patients receiving high doses (≥60 mg kg^{-1} body weight) of tranexamic acid (TA).

Methods. In a retrospective data analysis of 4883 cardiac surgical patients, we investigated the incidence of CS in patients receiving a moderate dose of TA (24 mg kg^{-1} body weight) compared with a reference group not receiving TA as a primary endpoint. Secondary endpoints were intensive care unit stay and in-hospital mortality. We performed propensity score (PS)-adjusted logistic regression analysis to test the association between TA use/non-use and clinical outcomes.

Results. Compared with the reference group, the PS-adjusted odds ratio (OR) for CS in the TA group was 1.703 [95% confidence interval (CI): 1.01–2.87; P=0.045; incidence 2.5% *vs* 1.2%]. Log-ICU-stay was significantly longer (P=0.004) and PS-adjusted relative in-hospital mortality risk was significantly higher for the TA group compared with the reference group (OR=1.89; 95% CI: 1.21–2.96; P=0.005). Both the TA-associated CS incidence and the in-hospital mortality risk were only significant in patients undergoing open-heart surgery (OR=2.034, 95% CI: 1.07–3.87; P=0.034 and OR=2.20, 95% CI: 1.32–3.69; P=0.003, respectively) but not in patients undergoing coronary artery bypass grafting (OR=1.21, 95% CI: 0.49–3.03; P=0.678 and OR=1.13, 95% CI: 0.42–3.02; P=0.809, respectively).

Conclusions. In open-heart surgery, even moderate TA doses are associated with a doubled rate of CS and in-hospital mortality. Prospective trials are needed to further evaluate the safety profile of TA in cardiac surgery.

Keywords: blood, coagulation; brain, convulsions; cardiopulmonary bypass; neurological outcome

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After aprotinin was removed from the market, tranexamic acid (TA) has become the mainstay pharmacological blood conservation of antifibrinolytic therapy in cardiac surgery. Although such use of TA has been under investigation for more than 20 yr, dosing regimens vary greatly and no standard regimen has been established yet.[1 2]

The administration of TA in cardiac surgery has not been associated with severe adverse events. However, current studies and case series reports mention an increased incidence of seizures after administration of high TA doses (60–260 mg kg^{-1} body weight).[3–7] In addition, one recent small retrospective analysis associated high TA doses (100 mg kg^{-1} body weight) with an increased mortality risk in patients undergoing open-heart procedures when compared with aprotinin.[3]

At our institution, we use a protocol with a more moderate (~25 mg kg^{-1} body weight) dose, which approximates the suggested dose for achieving an effective inhibition of fibrinolysis during cardiac surgery.[8–10]

We herein report our single-centre experience with this moderate dose of TA on convulsive seizures (CS) and other clinical outcome parameters in a large cohort of cardiac surgery patients.

Methods

Patients and study design

This study was a retrospective, single-centre, cohort study. The institutional database was analysed over a 2 yr period

between January 2008 and December 2009. Out of 6201 consecutive patients who underwent cardiopulmonary bypass (CPB) surgery at the Heart and Diabetes Centre North Rhine-Westphalia, Germany, 4883 patients were finally included in the data analysis (Fig. 1). The database consisted of perioperative data which were prospectively collected. All cardiac surgical patients were asked to give their general written permission before the operation in the scientific analysis and possible publication of anonymized data. The local Ethics Committee had approved this approach. The study was performed according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement for cohort studies (www.strobe-statement.org).

Data collection

All clinical data were collected using the digital patient data management system PDMS (COPRA, Sasbachwalden, Germany). In total, 21 parameters were retrieved for each patient. Among them, 19 patients and surgery characteristics [age, sex, weight, left ventricular ejection fraction, concomitant diagnoses such as stroke, diabetes mellitus, cardiovascular disease, pulmonary disease, peripheral arterial occlusive disease, and hypertension, estimated glomerular filtration rate (eGFR), previous thoracic surgery, aspirin use, open-heart surgery, aortic cross clamp time, duration of CPB, transfusion requirement, and catecholamine requirement], two event categories (CS and in-hospital mortality), and two other outcome parameters [duration of mechanical ventilatory support and intensive care unit (ICU) stay] were assessed.

Primary endpoint

The primary endpoint was the rate of CS observed on the ICU. A CS was considered to have occurred in the case of sudden clonic movement of the patient. The suspicion of the occurrence of a CS was immediately reported from the specially trained nursing staff to the responsible physician who confirmed the diagnosis. Only in the case of re-occurrence or the suspicion of persisting neurological damage, a specialized neurologist was involved and further diagnostics (CT scan and electroencephalogram) were performed.

Secondary endpoints

Secondary endpoints were the duration of mechanical ventilatory support, duration of ICU stay, and in-hospital mortality.

Biochemical analyses

Preoperative creatinine was measured using the Architect autoanalyzer (Abbott, Wiesbaden, Germany). Then, GFR was estimated using the creatinine-based modification of diet in renal disease formula.

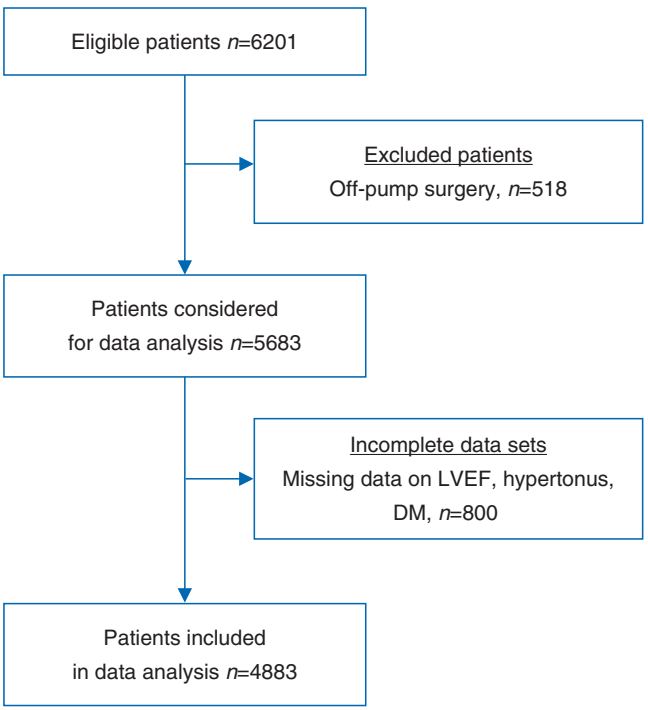

Fig 1 Study flow chart for inclusion of patients into the final analysis according to the STROBE statement. Off-pump, without cardiopulmonary bypass; LVEF, left ventricular ejection fraction; DM, diabetes mellitus.

Anaesthesia, CPB, and vasoactive drugs

Anaesthesia was typically performed as a balanced anaesthesia with midazolam, fentanyl, etomidate, pancuronium-bromide, and vaporization of sevoflurane. Antibiotic prophylaxis was performed with 2 g cephazolin (Fresenius Kabi, Bad Homburg, Germany). In all cases except for aortic arch procedures, the operation was performed under CPB support with open CPB circuits, mild hypothermia with core temperatures of 32–34°C and warm blood cardioplegia. In case the eGFR value decreased below 40 ml min^{-1}, we performed intraoperative haemofiltration. We used this strategy to prevent hyperkalaemia due to potassium-containing cardioplegia and to remove excessive volume.

The target mean arterial pressure during CPB was 50–60 mmHg. If this pressure was not achieved by increasing the pump flow to ~120% target cardiac index of 2.5 litre m^{-2} body surface area, a continuous infusion of norepinephrine was used as a vasoconstrictor (adjusted from 0.05 to 0.4 μg kg^{-1} min^{-2}). In the very rare event that this therapy failed to achieve the target arterial pressure, increasing dosages of vasopressin (1–4 IU h^{-1}) were continuously infused. Dopamine and dobutamine were inotropic drugs of first choice. In patients with congestive heart failure, milrinone (0.25–0.5 μg kg^{-1} min^{-2}) was added. If this approach did not result in an adequate cardiac index of >2.5 litre m^{-2} body surface area, epinephrine was added (0.05–0.2 μg kg^{-1} min^{-2}). In the case of failure of this approach, temporary mechanical support was established.

TA administration

The recommended dose from the German package insert of TA is a bolus of 1000 mg for the patient and 500 mg for the CPB circuit followed by a continuous infusion of 400 mg h^{-1} during surgery. The dosing regimen used at our clinic is slightly lower with the same boluses but a continuous infusion rate of 200 mg h^{-1} limited to the time during CPB. It is suggested that this dose achieves an effective inhibition of fibrinolysis during CPB.[8–10] A dose adjustment in patients with impaired renal function was not performed due to the use of intraoperative haemofiltration in patients with a GFR of <40 ml min^{-1}. There was no strict institutional protocol regarding TA administration. The use of TA was at the discretion of the surgeon and the anaesthesiologist. Typical indications for TA were active anti-platelet therapy, re-operations, and complex procedures with an expected CPB time exceeding 90 min. TA was given after systemic heparinization.

Statistics

We report categorical variables as observational percentages. Continuous variables are presented as mean (SD). We tested normal distribution of the data using the Kolmogorov–Smirnov test. The patient characteristic and clinical parameters of patients who received or did not receive TA were compared with Student's *t*-test, Mann–Whitney test, or Fisher's exact test as appropriate. We tested the association between TA use/non-use and clinical outcomes using univariable and multivariable binary logistic regression analysis. Results are presented as odds ratio (OR) with a 95% confidence interval (CI). The group not receiving TA was used as the reference group. Since the number of variables that can be included for multivariable testing equals ~10% or the square root of the number of events,[11] in the present study, the multivariable regression analysis could only contain up to 2–4 covariates. We therefore performed a propensity score (PS) adjustment, which prevented us from over-parameterizing the model.[12] The risk score derivation model was constructed with multivariable logistic regression, with the TA group as the binominal-dependent variable and the variables listed in Table 1 as predictor variables. The model's reliability and predictive ability were

Table 1 Characteristics of the study groups. Continuous data are presented as mean (SD), unless otherwise stated. TA, tranexamic acid; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting

Parameter	Reference group (*n*=3854)	TA group (*n*=1029)	*P*-value
Age mean (range)	69.5 (18–96)	70.3 (18–96)	0.010
Gender (% males)	58.2	59.9	0.336
Diabetes mellitus (%)	24.6	26.2	0.298
Body weight (kg)	79.3 (14.9)	80.0 (15.3)	0.177
Coronary heart disease (%)	69.4	73.6	0.010
Peripheral arterial occlusive disease (%)	19.9	23.5	0.045
Pulmonary disease (%)	20.5	24.0	0.030
Hypertension (%)	87.2	85.7	0.217
Neurological complications (%)	13.3	11.4	0.103
Preoperative anti-platelet agents (%)	8.8	20.4	<0.001
LVEF >55 (%)	71.8	64.3	<0.001
eGFR (ml min^{-1})	64.3 (24.9)	66.6 (22.6)	0.008
Type of cardiac surgery			
CABG (%)	44.4	38.2	<0.001
Valve surgery (%)	37.1	36.5	0.744
Combined CABG and valve surgery (%)	18.5	25.3	<0.001
Open-heart surgery (%)	55.6	61.8	<0.001
Redo (%)	19.3	55.6	<0.001
Catecholamine requirement (%)	43.0	65.8	<0.001
Transfusions (%)	54.0	63.9	<0.001
Aortic cross-clamp time (min)	45.8 (24.3)	54.9 (32.4)	<0.001
Duration of CPB (min)	88.6 (31.3)	100.0 (43.2)	<0.001

measured with the Hosmer–Lemeshow test and the *c*-index, respectively. The risk score ranged from a low of 0.0483 to a high of 0.9450. The model was reliable (the Hosmer–Lemeshow test $P=0.525$) and moderately discriminate (*c*-index=0.680, range 0.661–0.700). In addition, to test the robustness of the association, we performed sensitivity analyses adjusting for age. Because of potential non-linear associations between continuous variables such as age and seizures, age was added to the model as a categorical variable [age classified as: <50, 50–59.9, 60–69.9 (reference category), 70–79.9, and ≥80 years]. Because the type of cardiac surgery may be in the causal pathway between TA administration and seizures, we developed models with CABG-only surgery or open-heart surgery procedures. In additional models, we restricted the analysis to the TA group and assessed the association between seizures and parameters potentially related to TA bioavailability such as the total TA dose, body weight, and eGFR. Finally, we performed an analysis where we used the excluded patients in the logistic regression analysis. For evaluating the association of TA administration with secondary endpoints such as the duration of mechanical ventilatory support and ICU stay, we used a two-factor analysis of covariance (ANCOVA) with the aforementioned patients and surgery characteristics as covariates. Because the secondary endpoints were non-normally distributed, these data were logarithmically transformed before being analysed by ANCOVA. *P*-values <0.05 (two-tailed test) were considered statistically significant. The software package PASW Statistics (Predictive Analysis Soft Ware, Chicago, IL, USA), version 18, was used to perform the analyses.

Results

Baseline characteristics

Basic patient characteristics are presented in Table 1. The two study groups were comparable with respect to gender distribution, body weight, and prevalence of diabetes mellitus, hypertension, and preoperative neurological complications. However, in comparison with the reference group, patients in the TA group were older and slightly heavier, had a slightly higher prevalence of pulmonary disease and peripheral arterial occlusive disease, were more often undergoing re-do procedures, were less likely to have a preoperative ventricular ejection fraction of >55%, suffered more frequently from coronary heart disease, and were more often using aspirin, but had slightly higher eGFR values. CABG surgery was performed less often and combined CABG and valve surgery more often in the TA group than in the reference group. In addition, the duration of CPB and aortic cross clamp time were significantly higher in the TA group than in the control group. Further, patients in the TA group required more blood transfusions and pharmacological inotropic support with catecholamines than patients of the reference group. In the TA group, the mean (SD) administered TA dose was 24.0 (5.5) mg kg^{-1} body weight. The total TA dose was 1833 (144) mg.

Table 2 Postoperative outcome parameters in the tranexamic acid group and the reference group. Continuous data are presented as mean (SD). TA, tranexamic acid

Parameter	Reference group (*n*=3854)	TA group (*n*=1029)	*P*-value
Primary endpoint			
Convulsive seizures (%)	1.2	2.5	<0.001
Secondary endpoints			
Duration of mechanical ventilation support (h)	22.3 (92.1)	37.2 (123.0)	<0.001
Intensive care unit stay (h)	66.5 (136.0)	104.9 (199.2)	<0.001
In-hospital mortality (%)	1.5	4.1	<0.001

Primary endpoint

In total, 73 CS occurred. The incidence of CS was 2.5% in the TA group and was approximately twice as high compared with the reference group (Table 2). Unadjusted OR of CS was significantly higher in the TA group than in the reference group: OR 2.10 (95% CI: 1.29–3.41; $P=0.003$). Results were attenuated in the PS-adjusted model but remained significant: OR=1.704 (95% CI: 1.01–2.87; $P=0.045$). Sensitivity analyses demonstrate that results did not change substantially when age was entered to the fully adjusted model of seizures as a categorical variable [OR for TA group=1.71 (95% CI: 1.02–2.87; $P=0.044$)]. However, in the subgroup of patients with CABG-only surgery ($n=2104$), the OR of CS for the TA group was only 1.21 (95% CI: 0.49–3.03; $P=0.678$). This contrast to the results of the subgroup of patients with open-heart surgery ($n=2779$), where the OR of CS for the TA group was 2.034 (95% CI: 1.07–3.87; $P=0.034$). When we restricted the analysis to the TA group, CS risk decreased by 2.2% (SE: 0.9%) for each ml min^{-1} increment in preoperative eGFR ($P=0.012$), but was unrelated to body weight or total TA dose (data not shown).

In the 1318 patients who were excluded from data analysis, 295 patients received TA. In the entire group of excluded patients, 12 CS occurred (incidence: 0.91%). When the excluded patients were included in the logistic regression analysis, the OR of CS remained significantly higher in the TA group than in the reference group (OR=2.25, 95% CI: 1.45–3.51; $P<0.001$).

Secondary endpoints

Results of the secondary endpoints are presented in Table 2 according to the study group. Log-duration of mechanical ventilatory support and log-ICU stay were significantly longer in the TA group than in the reference group, even after adjustments were made for the potential preoperative and perioperative confounders listed in Table 1 ($P=0.004$ and 0.008).

Before discharge, 98 patients died. PS-adjusted relative in-hospital mortality risk for the TA group was 1.89 (95% CI: 1.21–2.96; $P=0.005$). Results did not change substantially when the postoperative presence or absence of CS was added to the PS-adjusted model (data not shown). Likewise, results remained unchanged when age or eGFR entered the model as a continuous or categorical variable (age: according to the aforementioned age groups; eGFR: according to chronic kidney disease stages I–IV; data not shown).

We also investigated the effect of CS on clinical outcome. In both the TA and the reference groups, the duration of mechanical ventilatory support, ICU stay, and in-hospital mortality was significantly higher in patients experiencing CS compared with CS-free patients (Table 3).

Because the type of cardiac surgery also may be in the causal pathway between TA administration and in-hospital mortality, we used statistical models to test potential associations. Again, in the subgroup of patients with CABG-only surgery ($n=2104$), the OR of in-hospital mortality for the TA group was not statistically significant: OR=1.13 (95% CI: 0.42–3.02; $P=0.809$). This is in contrast again to the results of the subgroup of patients with open-heart surgery ($n=2779$), where the OR of in-hospital mortality for the TA group was 2.20 (95% CI: 1.32–3.69; $P=0.003$). In the TA group, the total TA dose was slightly but significantly higher in the subgroup of patients with open-heart surgery compared with the subgroup of CABG-only surgery [1872 (149) *vs* 1770 (109) mg; $P<0.001$]. Table 4 outlines the study endpoints according to the surgical procedure in the TA and reference groups.

In Table 5, the TA dose and some perioperative data are presented according to the occurrence or absence of seizures in patients with and without open-heart surgery.

Discussion

The present large retrospective data analysis from a single centre demonstrates that even moderate TA doses of on average 24 mg kg^{-1} are associated with an increased risk to experience CS, which after PS adjustment was attenuated, but still 70% higher compared with the reference group. However, this risk was less pronounced in patients undergoing CABG-only surgery compared with patients undergoing open-heart surgery. In addition, TA use was an independent

Table 3 Postoperative secondary endpoints in the tranexamic acid group and the reference group according to the occurrence or absence of seizures. Continuous data are presented as mean (SD). TA, tranexamic acid

Parameter	Without seizures	With seizures	*P*-value
Reference group			
Duration of mechanical ventilation support (%)	20.5 (85.7)	165.5 (286.1)	<0.001
Intensive care unit stay (h)	64.1 (130.9)	261.8 (302.1)	<0.001
In-hospital mortality (%)	1.4	6.4	0.030
TA group			
Duration of mechanical ventilation support (%)	34.6 (113.1)	139.7 (302.5)	<0.001
Intensive care unit stay (h)	98.8 (175.5)	329.2 (575.0)	0.052
In-hospital mortality (%)	3.7	19.1	<0.003

Table 4 Primary and secondary endpoints according to surgical procedure in the tranexamic acid and reference group. Continuous data are presented as mean (SD). CABG, coronary artery bypass grafting; TA, tranexamic acid

Parameter	Reference group, CABG ($n=1707$)	TA group, CABG ($n=397$)	*P*-value
Primary endpoint			
Convulsive seizures (%)	1.2	1.8	0.322
Secondary endpoints			
Duration of mechanical ventilation support (h)	18.7 (82.3)	21.9 (71.1)	0.024
Intensive care unit stay (h)	60.4 (133.7)	77.2 (186.6)	0.039
In-hospital mortality (%)	1.1	1.5	0.446
	Reference group, open heart ($n=2143$)	**TA group, open heart ($n=636$)**	***P*-value**
Primary endpoint			
Convulsive seizures (%)	1.3	3.0	0.004
Secondary endpoints			
Duration of mechanical ventilation support (h)	25.1 (99.2)	47.0 (144.9)	<0.001
Intensive care unit stay (h)	71.4 (137.6)	122.5 (205.1)	<0.001
In-hospital mortality (%)	1.7	5.7	<0.001

Table 5 Perioperative data according to the occurrence or absence of seizures in patients with and without open heart surgery. Continuous data are presented as mean (SD)

Parameter	Without seizures, CABG ($n=386$)	With seizures, CABG ($n=7$)	*P*-value
Tranexamic acid dose kg body weight^{-1} day^{-2} (mg)	22.1 (4.0)	23.9 (4.0)	0.246
Aortic cross-clamp time (min)	31.1 (17.2)	38.4 (34.2)	0.592
Duration of CPB (min)	80.7 (31.8)	110.0 (65.0)	0.279
Transfusions (%)	53.4	85.7	0.130
Catecholamine requirement (%)	53.6	71.4	0.459
	Without seizures ($n=617$)	**With seizures ($n=19$)**	***P*-value**
Tranexamic acid dose kg body weight^{-1} day^{-2} (mg)	25.2 (6.0)	25.9 (6.1)	0.601
Aortic cross-clamp time (min)	69.7 (30.8)	65.2 (30.7)	0.527
Duration of CPB (min)	112.1 (45.0)	98.6 (37.0)	0.198
Transfusions (%)	69.7	84.2	0.211
Catecholamine requirement (%)	73.1	73.7	>0.999

predictor of in-hospital mortality, especially in patients with open-heart surgery procedures.

The incidence of CS after cardiac surgery is consistently reported to be within the range of 0.9–1.2%.[13 14] Several recent investigations have described a dramatically increased CS rate in patients on TA administration, reaching 2.7–7.6%.[3–7] In our investigation, the CS rate in the TA group was 2.5% and thus at the lower end of the aforementioned range. The fact that TA promotes CS has been known for 20 yr. An increased CS rate was first observed in a neurosurgical animal model where fibrin glue that contained TA was administered topically.[15] The underlying biochemical mechanism appears to be a γ-aminobutyric acid A receptor antagonist effect.[16] Compared with the patients of our data analysis, much higher TA doses have been used in the aforementioned earlier studies, that is, 70, 100, and 60–260 mg kg^{-1}, respectively.[3–7] Although in our investigation, kidney function was related to CS risk, the fact that the total TA dose and body weight were not related to CS risk indicates that there may be no strong relationship between TA bioavailability and CS risk. However, note that we do not adjust the TA dose to renal function because we perform intraoperative haemofiltration in case eGFR values decrease below 40 ml min^{-1}. The higher transfusion requirement in the TA group compared with the reference group can reliably be explained by their higher risk profile including increased preoperative medication with anti-platelet agents and more complex surgery.

It was another important finding of our study that the CS risk was only enhanced in open-heart surgery but not in CABG-only surgery. Our results confirm earlier findings by Murkin and colleagues.[5] The underlying causes for the aforementioned differences in the incidence of CS are unknown at present. It is well known that changes in blood–brain barrier permeability caused by ischaemia, certain proteins, or inflammatory substances play a pivotal role in a large number of diseases of the central nervous system (CNS).[17 18] Those changes may lead to increased permeability for TA and toxic cerebral TA concentrations. Diffuse cerebral air-embolism in open-heart surgery, an increased systemic inflammatory response due to prolonged CPB, and severe electrolyte imbalances in patients with renal impairment might cause such disturbances of blood–brain barrier permeability.

Another significant and unexpected observation of this investigation was that in-hospital mortality was approximately twice as high in the total TA group compared with the reference group, even after PS adjustment was performed. Once more, it was an important finding that this association was restricted to patients with open-heart surgery. These results are comparable with an earlier investigation by Sander and colleagues.[3] In that study, compared with aprotinin administration, TA administration was associated with a doubling of the mortality risk in the subgroup of patients undergoing open-heart surgery. However, it is noteworthy that mortality risk remained significantly enhanced in our investigation, even when the postoperative presence or absence of CS was added to the PS-adjusted model. This suggests a TA effect on mortality which is independent of the presence of CS. Nevertheless, it is also noteworthy that our results support earlier findings of an impaired clinical outcome in patients experiencing CS.[13] In both the TA and reference groups of our study, in-hospital mortality was ~4.5–5.0 times higher in the subgroups of patients experiencing CS compared with patients without CS. The in-hospital mortality of 19.1% in patients receiving TA and experiencing CS is unacceptably high and cannot be explained by a transient antagonistic effect on a receptor of the CNS. The high mortality rate of up to 19.1% in open-heart surgery does not justify the use of TA in this patient group.

Our investigation has some limitations. First, the observational nature of the study design precludes us from concluding that there is a causal relation between TA administration and clinical outcome. Although we used a PS-adjusted model which considered various pre- and intraoperative parameters, residual confounding may still exist. Secondly, the CS were only evaluated clinically by the specially trained nursing staff and the physician on duty on the ICU. This has to be attributed to the fact that in our specialized

hospital, no 24 h day^{-1} specialized neurological service is established. A neurologist, who could confirm the clinical diagnosis and perform an EEG analysis, was only involved in the case of multiple incidences of seizures or persistent neurocognitive dysfunction. However, others have used similar methods to assess seizures.[3–5] In addition, as this procedure applied for all patients, any potential errors should be equally distributed between the two study groups observed. Thirdly, we did not review the charts of our patients with respect to the event of stroke. The association of CS with stroke in a cardiac surgery ICU is unknown at present. In a large prospective investigation assessing the incidence of CS after stroke, only 8.9% of the patients exhibited a single event or repetitive CS after stroke.[19] In another large retrospective analysis of 6044 stroke patients, the overall incidence was 3.1% with 8.4% in patients with haemorrhagic stroke and 2.4% in patients with ischaemic stroke.[20] Due to this rare association, even the evidence of a stroke in a patient receiving TA would not have ruled out that TA provoked the CS. Fourthly, we assessed CS only in the ICU. A CABG-only patient would be in an ICU setting for less time and the chance of being witnessed is lower than in a higher risk patient, for example, a patient with open-heart surgery. However, since we compared the TA group with a reference group not receiving TA, the aforementioned aspect should not influence our results systematically. It is also noteworthy that the occurrence of TA-induced CS is rather unlikely after discharge from the ICU.

In conclusion, this large set of data indicates that even moderate dosages of TA are associated with a nearly doubled rate of CS and detrimental clinical outcome of cardiac surgery patients. Particularly, patients undergoing open-heart surgery procedures are at an increased risk. The findings can hardly be explained by a temporary antagonistic pharmacological TA effect on a special receptor in the CNS. Even moderate dosages of TA should be used with caution in patients undergoing open-heart procedures. The new insights into clinically significant side-effects of TA and the potentially increased risk for in-hospital mortality show that large controlled prospective clinical trials are needed to further evaluate the safety profile of TA.

Declaration of interest

None declared.

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