Tranexamic acid versus e-aminocaproic acid: efficacy and safety in paediatric cardiac surgery

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Abstract

Objective: Tranexamic acid (TXA) and e-aminocaproic acid (EACA) are used for antifibrinolytic therapy in cardiac surgery, although data directly comparing their blood sparing effect and their side effects, especially in paediatric cardiac surgical patients, are still missing. Methods: We analysed perioperative data of 234 paediatric patients weighing less than 20 kg undergoing cardiac surgery. In a 5-month period, all patients (n = 114) received TXA (group TXA). During a second 5-month period, all patients (n = 120) were treated with EACA (group EACA). Primary outcome was blood loss at 24 h postoperatively; secondary outcome criteria were transfusion requirement, rate of revision for bleeding, postoperative complications and in-hospital mortality. Results: All descriptive and intra-operative parameters were well comparable. There was no evidence for a difference in blood loss at 24 h postoperatively (TXA 21 ml kg⁻¹ (14–40), p = 0.242), rate of re-operation for bleeding (TXA 9.6% vs EACA 8.3%, p = 0.725) and transfusion of blood products. The incidence of postoperative complications such as seizures (TXA 3.5% vs EACA 0.8%, p = 0.203) and other neurological complications (TXA 2.6% vs EACA 1.7%, p = 0.677), renal injury (TXA 9.6% vs EACA 13.3%, p = 0.378), renal failure (TXA 1.8% vs EACA 4.2%, p = 0.447), low cardiac output syndrome (TXA 12.3% vs EACA 10.8%, p = 0.729), and vascular thrombosis (TXA 4.4% vs EACA 5.0%, p = 0.824), as well as the in-hospital mortality (TXA 2.6% vs EACA 3.3%, p > 0.999) did not show any statistically significant difference. Conclusions: TXA and EACA are well comparable in their effect on perioperative blood loss as well as in major clinical outcome criteria. Although the fourfold risk for seizures using TXA was not significant, we currently use EACA in paediatric cardiac surgery.

Keywords: Tranexamic acid; Aminocaproic acid; Paediatric cardiac surgery; Blood loss; Outcome

1. Introduction

Due to the rise of serious concerns about the safety of aprotinin, the manufacturer suspended this widely used antifibrinolytic agent from worldwide markets (Bayer Healthcare Pharmaceuticals communication (Leverkusen GaWH, CT, USA): www.bayerhealthcare.com/trasylol/en). Today, the two remaining antifibrinolytic medications available to reduce postoperative bleeding are tranexamic acid and e-aminocaproic acid [1], although their blood-sparing effect is considered inferior to that of aprotinin [2]. Both are lysine analogues and competitively inhibit the binding of plasminogen to fibrin. Both have been used for many years, in some institutions as the main antifibrinolytic medications, but, most often, they are used in less-complicated cardiac surgeries where the bleeding risk was felt to be low [3,4]. Up to now, there is just one small trial comparing tranexamic acid and e-aminocaproic acid, according to their efficiency in paediatric cardiac surgery [5], but there is not a single study focussing especially on safety [6]. We previously found that tranexamic acid in comparison to aprotinin in adult patients was associated with cardiac, renal and neurological (seizures) adverse events after open heart surgery [7], whereas in paediatric patients there was a noticeable tendency to an increased rate of seizures [8]. These results encouraged us to change our institutional blood conservation strategy; we completely switched from tranexamic acid to e-aminocaproic acid as our routine prophylactic antifibrinolytic therapy.

After 5 months of continuous use of e-aminocaproic acid, we compared the data of these patients to a cohort consequently treated with tranexamic acid according to
efficacy (blood loss, rate of revision for bleeding and transfusion requirement) and postoperative complications in paediatric patients undergoing cardiac surgery with extracorporeal circulation.

2. Methods

2.1. Study design

The study was approved by the Ethical Committee of the Technical University Munich; the need for parental informed consent was waived by the board. We analysed the perioperative data of a 5-month period of all children (n = 126) weighing less than 20 kg undergoing cardiac surgery with cardiopulmonary bypass (CPB). All received ω-aminocaproic acid (group EACA). This population was compared to a previous cohort of patients that was treated with tranexamic acid (group TXA) (n = 124). All data were prospectively collected in the clinical database as part of the national quality assurance programme in cardiac anaesthesia and surgery. Patients who received no antifibrinolytic therapy or for whom the administered dose of the antifibrinolytic agent was less than 80% of our institutional protocol or patients who received multiple agents were excluded (n = 16). After exclusions, the study cohort contained the data of 234 patients (EACA n = 120; TXA n = 114). If a patient was re-operated for non-bleeding reasons during the same admission, only data from the first operation were included in the analysis.

2.2. Institutional protocol

The institutional protocol for tranexamic acid (Cyklokapron; Pfizer, Karlsruhe, Deutschland) consisted of a bolus of 50 mg kg⁻¹ bodyweight at the beginning and at the end of CPB, and 100 mg 100 ml⁻¹ priming volume was added to the priming fluid of the CPB system. The protocol for ω-aminocaproic acid (Aminocaproic acid, Hospira, Inc., Lake Forest, IL, USA) consisted of a bolus of 75 mg kg⁻¹ bodyweight at the beginning and at the end of CPB, and, additionally, 75 mg 100 ml⁻¹ was added to the priming fluid of the CPB system [9].

In all other aspects, the team of surgeons, anaesthesiologists and paediatric cardiologists, and their protocols remained unchanged. Induction and maintenance of anaesthesia was performed with a standardised total intravenous anaesthesia consisting of midazolam, sufentanil and pancuronium. After induction of anaesthesia, a 24 G cannula was inserted in a radial artery for blood pressure measurement; alternatively, a 22 G or 20 G catheter was placed in the femoral artery. All patients received a central venous line (3–5F) in the vena cava superior (SVC) through the right vena jugularis interna. In addition, patients with a total or partial cavo-pulmonic anastomosis were monitored with a central venous line in the inferior vena cava through a femoral approach. In these patients, the SVC catheter was removed within the first postoperative day. Our standard CPB setting consisted of a membrane oxygenator (≤7 kg Dideco D 901 Littleput I, 7–20 kg Dideco D 902 Littleput II, Sorin, Mirandola Modena, Italy) mounted on a non-pulsatile roller pump (Stöckert 5S, Sorin, Mirandola Modena, Italy). CPB circuit components, set-up and prime were standardised. The circuit was primed with Ringer lactate solution, mannitol (3 ml kg⁻¹) and sodium bicarbonate (10–20 ml). Anticoagulation was established with an initial intravenous bovine heparin dose of 4 mg kg⁻¹; target kaolin-based activated clotting time (ACT) was > 480 s; if necessary, additional heparin was administered during CPB to maintain ACT > 480 s. Packed red blood cells (RBCs) were added to achieve a haematocrit of approximately 30% during CPB initiation. Fresh-frozen plasma (FFP) was added to the prime in a 1:1 ratio compared with RBC to maintain onco tic pressure and concentration of coagulation factors. Cardiac arrest was achieved by infusion of 30 ml kg⁻¹ of cold crystalloid cardioplegic solution (Custodiol®; Köhler Pharma GmbH, Alsbach, Germany). After CPB, protamine was administered with kaolin-based ACT control, starting with an initial dose of 6 mg kg⁻¹. Postoperative care was assumed by our paediatric cardiologists in the paediatric intensive care unit (PICU). Transfusion triggers in the operating room (OR) and the PICU were identical. RBCs were transfused at a haemoglobin level < 140 g l⁻¹ in cyanotic patients and < 100 g l⁻¹ in non-cyanotic patients or if a patient showed clinical signs indicating the need for a higher oxygen delivery. With ongoing bleeding, FFP was transfused for a prothrombin time below 40%, and platelets were transfused at a platelet count below 50 × 10⁹ μl⁻¹. Indication for re-exploration due to bleeding was determined by the attending surgeon. The criterion was significant ongoing bleeding without clinically relevant bleeding disorders or bleedings indicating a massive surgical leakage. The team of surgeons, anaesthesiologists and intensivists, as well as all the protocols remained unchanged during the time period in review.

2.3. Perioperative data and outcome criteria

The perioperative data (Table 1) were investigated to assess the comparability of the study cohorts. Because efficacy is of utmost importance for antifibrinolytic medications, we chose blood loss measured as chest-tube drainage at 24 h after surgery as the primary outcome criterion.

The following listing describes the extensive assessment of secondary outcomes. The amount of transfused allogeneic blood products in the perioperative course (including pump prime) and the need of revision for bleeding was recorded. Postoperative renal injury was defined according to the paediatric modified Risk, Injury, and Failure; and Loss, and End-stage kidney disease (RIFLE) criteria (creatinine clearance decreased by 50%) [10]. The estimated creatinine clearance was calculated using the Schwartz-formula [11]. Renal failure was defined as the need for postoperative dialysis. Neurological complications were divided into seizures and other neurological events, for example, stroke, cerebral oedema and intracranial bleeding. All of them were clinically diagnosed and confirmed by computed tomography (CT) scan or ultrasound. Postoperative low cardiac output syndrome was defined as need for high-dose inotropic support at the end of surgery (at least 0.1 μg kg⁻¹ min⁻¹ epinephrine) [8]. Vascular thrombosis was clinically diagnosed and...
confirmed by CT scan, ultrasound or angiography. In-hospital mortality was recorded.

2.4. Sample size

Estimating a mean blood loss of approximately 20 ml kg\(^{-1}\) at 24 h after surgery [8] in the TXA group, a total sample size of 200 is necessary to detect a 20% difference (with a standard deviation of 10) to EACA patients in a two-sided manner (Power = 0.8, \(p = 0.05\)) (GPOWER for MS-DOS, Franz Faul & Edgar Erdfelder, Bonn, Germany).

2.5. Statistics

Descriptive statistics are given by means and standard deviations for normal distributed data. Skewed distributions are represented by medians and interquartile ranges. Categorical data are subsumed by absolute and relative frequencies, which are displayed by contingency tables. Effect sizes are presented by mean differences and relative risks with 95% confidence intervals. Statistical tests for group comparisons of continuous parameters are given by \(p\)-values by chi-square tests and *Cochran—Armitage trend test, mean deviations for normal distributed data. Skewed distributions are represented by medians and interquartile ranges. Categorical variables were compared between groups by chi-square tests and Fisher’s exact test, depending on the expected cell counts of the corresponding cross tabs. Count data such as the need for several transfusions was compared by Poisson regression analysis. To assess a possible trend difference in the complexity of surgeries, as given by the Risk Adjustment for Congenital Heart Surgery (RACHS) classification, the Cochran–Armitage trend test was computed. All tests were two-sided and conducted in an explorative manner on a 5% level of significance. The statistical analyses were performed by Statistical Package for Social Sciences (SPSS) for Windows 17.0 statistical software package (SPSS Inc., Chicago, IL, USA) and R 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

There was no proof against the comparability of recorded descriptive parameters in the two groups (Table 1). This also holds for the demographics and the pre- and intra-operative data. There was no statistically significant trend in the complexity of the operations as graded by the RACHS classification system [12]. The assumption of similarity for intra-operative risk parameters and transfusion rates of blood products could not be rejected (Table 1).

With regard to the primary outcome criterion, blood loss at 24 h postoperatively, there was no statistically significant difference (TXA 21 ml kg\(^{-1}\) (14–38) (median (interquartile range)) vs EACA 29 ml kg\(^{-1}\) (14–40), \(p = 0.242\)).

This also held for all secondary outcome parameters, namely incidence of revision for bleeding, and transfusion rates of RBC, FFP and platelets (Table 2). There was no verifiable difference in all recorded outcome parameters, namely renal injury, renal failure, vascular thrombosis, seizure, other neurological events, cardiac events, duration of ventilation and ICU stay and in-hospital mortality. A tendency was observed for seizures (TXA vs EACA: Relative Risk 4.21) and renal failure (TXA vs EACA: Relative Risk 0.42),
Data are presented as median (25th—75th percentile) with deviation.

Table 2. Blood loss and transfusion rates of blood products.

<table>
<thead>
<tr>
<th></th>
<th>TXA (n = 114)</th>
<th>EACA (n = 120)</th>
<th>Effect size (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss 24 h (ml kg⁻¹)</td>
<td>21 (14–38)</td>
<td>29 (14–40)</td>
<td>—</td>
<td>0.242</td>
</tr>
<tr>
<td><strong>Intra-operative transfusions</strong></td>
<td></td>
<td></td>
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<tr>
<td>RBC (pts)</td>
<td>107 (93.9%)</td>
<td>107 (89.2%)</td>
<td>RR: 1.05 (0.97; 1.14)</td>
<td>0.199</td>
</tr>
<tr>
<td>FFP (pts)</td>
<td>106 (93.0%)</td>
<td>105 (87.5%)</td>
<td>RR: 1.06 (0.98; 1.16)</td>
<td>0.159</td>
</tr>
<tr>
<td>Platelets (pts)</td>
<td>14 (12.3%)</td>
<td>19 (15.8%)</td>
<td>RR: 0.77 (0.41; 1.47)</td>
<td>0.435</td>
</tr>
<tr>
<td>RBC (U)</td>
<td>1.2 ± 0.6</td>
<td>1.2 ± 0.6</td>
<td>MD: 0.02 (−0.13; 0.17)</td>
<td>0.821</td>
</tr>
<tr>
<td>FFP (U)</td>
<td>1.8 ± 0.8</td>
<td>1.7 ± 1.0</td>
<td>MD: 0.17 (−0.06; 0.39)</td>
<td>0.152</td>
</tr>
<tr>
<td>Platelets (U)</td>
<td>0.1 ± 0.4</td>
<td>0.2 ± 0.4</td>
<td>MD: −0.03 (−0.12; 0.07)</td>
<td>0.589</td>
</tr>
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</table>

**Transfusions within the first 24 h postoperatively**

<table>
<thead>
<tr>
<th></th>
<th>TXA (n = 114)</th>
<th>EACA (n = 120)</th>
<th>Relative risk (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC (pts)</td>
<td>25 (21.9%)</td>
<td>34 (28.3%)</td>
<td>RR: 0.77 (0.49; 1.21)</td>
<td>0.260</td>
</tr>
<tr>
<td>FFP (pts)</td>
<td>83 (72.8%)</td>
<td>73 (60.8%)</td>
<td>RR: 1.20 (0.99; 1.44)</td>
<td>0.052</td>
</tr>
<tr>
<td>Platelets (pts)</td>
<td>6 (5.3%)</td>
<td>8 (6.7%)</td>
<td>RR: 0.79 (0.28; 2.20)</td>
<td>0.651</td>
</tr>
<tr>
<td>RBC (U)</td>
<td>0.3 ± 0.6</td>
<td>0.3 ± 0.6</td>
<td>MD: −0.04 (−0.19; 0.11)</td>
<td>0.565</td>
</tr>
<tr>
<td>FFP (U)</td>
<td>0.9 ± 0.8</td>
<td>1.0 ± 1.5</td>
<td>MD: −0.06 (−0.38; 0.25)</td>
<td>0.694</td>
</tr>
<tr>
<td>Platelets (U)</td>
<td>0.1 ± 0.3</td>
<td>0.1 ± 0.3</td>
<td>MD: −0.01 (−0.09; 0.06)</td>
<td>0.717</td>
</tr>
</tbody>
</table>

Data are presented as median (25th—75th percentile) with p-values by Mann–Whitney U test, incidence (percent) with p-values by chi-square tests, mean ± standard deviation with p-values by Poisson regression. TXA, tranexamic acid; EACA, α-aminocaproic acid; RBC, red blood cells; pts, number of patients; FFP, fresh-frozen plasma, U, units; MD, mean difference; RR, relative risk.

but the hypothesis of equivalency could not be rejected on the 5% level of significance (Table 3). A retrospective power calculation showed that, based on the observed event rates for seizures and by using a two-sided chi-square test on a 5% significance level, a power of 80% can be achieved by the inclusion of 447 patients in each group (SamplePower 2.0, SPSS Inc., Chicago, IL, USA).

4. Discussion

To our knowledge, there is just one published study comparing the blood-sparing effect of TXA and EACA in paediatric cardiac surgery [5], but without a focus on adverse events. Our study is the first one investigating the differences between the two medications with regard not only to postoperative bleeding but also to major clinical outcome. The main result of this analysis is that tranexamic acid and α-aminocaproic acid showed no statistically significant differences either in the effect on postoperative blood loss or in all other measured outcomes such as renal, cardiovascular and neurological complications as well as in-hospital mortality.

4.1. Efficacy

We found no significant difference in postoperative blood loss and its sequelae: the need for perioperative transfusions and re-operation for bleeding, the most hazardous complication of postoperative bleeding; there was no proof against similarity. The blood-sparing effect of both medications versus a control cohort in adult cardiac surgery is well documented [13]. The previously mentioned review on antifibrinolytic therapy in paediatric cardiac surgery [6] showed that most of the conducted studies in this population demonstrate the effectiveness of the lysine analogues compared with control, but only one smaller study compared both medications against each other [5]. Discussing our results in the light of the published reports leads to some major concerns. First, the trials reviewed by Eaton [6] included patients up to the age of 16 years, and, in our opinion, it is questionable whether one can compare the haemostatic system of newborns with that of young adults. A second problem appears with the inconsistent dosages of the antifibrinolytic medications. This is especially important for tranexamic acid where the used dosage regimes range from a single 50 mg kg⁻¹ dose up to two doses of 100 mg kg⁻¹ and an additional bolus of 100 mg kg⁻¹ added to the priming fluid of the CPB system [6]. In comparison to the only head-to-head trial on TXA and EACA [5], our dosage for EACA was a little lower and the TXA dosage much higher than in this study; nonetheless, our results revealed no evidence against the comparability of postoperative bleeding similar to their finding.

4.2. Clinical outcome

A recent review about antifibrinolytic therapy in paediatric cardiac surgery suggested to "assess the relative
likelihood of various infrequent or rare adverse events related to the use of TA and EACA, namely thrombosis, renal failure, stroke or death. The author also states that both substances are distributed as cheap generics and, therefore, no manufacturer will be interested in supporting expensive clinical investigations [6]. As long as these two medications are used in paediatric cardiac surgery without a Food and Drug Administration (FDA) indication, clinicians have to prove the innocence of these lysine analogues.

As a result of the aprotinin story, many investigators criticised that there was a huge number of trials reporting the haemostatic effect of the antifibrinolytic medications; but data about the potentially detrimental side effects, especially of TXA and EACA, are still rare. Even the analysis of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) trial did not compare the two cohorts treated with the lysine analogues [14]. Likewise, safety comparisons between these two medications in paediatric cardiac surgery have not been established in a sufficient manner [15]. In this particular population, clinicians usually have to deal with small patients who have insufficient renal and liver function as well as coagulation disorders due to their cardiac disease. In our mind, conclusions drawn from adult studies should not be compared with issues arising when treating paediatric patients.

A previous investigation at our institution comparing tranexamic acid and aprotinin in adult cardiac surgery detected a significant increase of seizures after the administration of tranexamic acid [7]. Significance was not reached in the analysis of our paediatric patients, but there was a notable tendency (TXA 3.5% vs aprotinin 0%, p = 0.14) [8]. Tranexamic acid is known to cause convulsions by a gamma-aminobutyric acid receptor antagonistic effect [16]. Because both medications are lysine analogues, one would expect the same effect for EACA. We detected just one case of a new-onset seizure after EACA treatment in this paediatric population. Although the incidence of seizures in the TXA group did not reach significance, the fourfold greater risk after TXA should be noted and investigated in the future. A similar analysis of our adult patients undergoing open heart surgery revealed a significantly elevated rate of seizures in tranexamic acid-treated patients compared with EACA (Martin K. unpublished data, 2009). On this account, we are worried about the rate of postoperative seizures after tranexamic acid treatment.

Postoperative renal dysfunction and failure in paediatric cardiac surgery occur frequently [17,18] and lead to a high mortality, if dialysis is required [19,20]. Renal failure was observed in 1.8% of the TXA and in 4.2% of the EACA patients. Several reports about the impact of aprotinin on postoperative renal function in paediatric cardiac surgery mentioned that the incidence of renal injury is about 10–20%, which is independent of aprotinin treatment [17,19]. Our rates of about 10% (TXA 9.6% vs EACA 13.3%) are within the lower range of these reports using similar definitions [19]. Therefore, we assume that both lysine analogues do not decrease renal function in this collective. There is no trial comparing TXA and EACA to each other or placebo with the focus on renal outcome in paediatric cardiac surgery, and, in contrast to TXA and seizures [16], there is only one abstract on renal damage assessed by increased β2-microglobulin concentrations after EACA [21].

Due to the antifibrinolytic effect of both medications, the primary serious risk of the lysine analogues might be vascular thrombosis. Because of their small vessels, prolonged immobility, artificial shunts, low flow states, central venous catheters and high blood viscosity, paediatric patients undergoing cardiac surgery are at a high risk for this kind of complication [22]. In our cohort, the rate of thrombosis was about 5%, without a statistically significant difference between the groups. We could not find any other publication regarding the incidence of thrombosis in a comparable collective.

Although underpowered to detect a difference in the above-mentioned rare events, this study establishes some hypotheses on the adverse effects of lysine analogues in paediatric cardiac surgical patients, for example, seizures and renal failure, which have to be confirmed in further studies. As long as there is not enough evidence with respect to the safety of the lysine analogues, these medications should be restricted to patients at high risk for bleeding, but not be used on a routine basis for patients expected to undergo uneventful surgery.

4.3. Limitations

This trial is not a prospective randomised study, but analysing the perioperative data of two patient cohorts offered the opportunity to create two unselected treatment groups. Therefore, this setting needs no mathematical risk adjustments to compensate for differences in perioperative risk factors. Based on the enrolment of unselected consecutive patients in each of the two treatment groups and the numerous comparable demographic and preoperative data, we assume that the unmeasured underlying variables of the patients were also similar.

Another shortcoming of this analysis is the absence of a placebo group. For both medications, the majority of the studies demonstrated reduced bleeding and transfusion rates when compared with placebo [6]; only one underpowered study did not reach a significant difference compared with placebo [23]. Therefore, we do believe that the blood conservation effect of both medications is well documented. As we make all efforts to avoid allogeneic blood transfusions, especially in paediatric cardiac surgical patients, we feel ethically obligated to use antifibrinolytic prophylaxis on a routine basis on patients we consider at high risk for bleeding and transfusion.

5. Conclusion

In our cohort of 234 paediatric patients weighing less than 20 kg undergoing open heart surgery, there was no statistically significant difference according to postoperative blood loss and, subsequently, in the incidence of revision for bleeding or the amount of allogeneic transfusions. Furthermore, we could not find significant differences in all measured major clinical outcomes, in particular regarding renal, neurological and cardiovascular complications as well as in-hospital mortality. With regard to the fourfold risk for seizures after TXA, we currently use EACA in paediatric cardiac surgery.
References