Original Article
Epsilon aminocaproic acid reduces blood transfusion and improves the coagulation test after pediatric open-heart surgery: a meta-analysis of 5 clinical trials

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Abstract: Background: Excessive postoperative blood loss after cardiopulmonary bypass is a common problem, especially in patients suffering from congenital heart diseases. The efficacy of epsilon aminocaproic acid (EACA) as a prophylactic treatment for postoperative bleeding after pediatric open-heart surgery has not been determined. This meta-analysis investigates the efficacy of EACA in the minimization of bleeding and blood transfusion and the maintenance of coagulation tests after pediatric open-heart surgery. Methods: A comprehensive literature search was performed to identify all randomized clinical trials on the subject. PubMed, Embase, the Cochrane Library, and the Chinese Medical Journal Network were screened. The primary outcome used for the analysis was postoperative blood loss. Secondary outcomes included postoperative blood transfusion, re-exploration rate and postoperative coagulation tests. The mean difference (MD) and risk ratio (RR) with 95% confidence intervals (CI) were used as summary statistics. Results: Five trials were included in this meta-analysis of 515 patients. Prophylactic EACA was associated with a reduction in postoperative blood loss, but this difference did not reach statistical significance (MD: -7.08; 95% CI: -16.11 to 1.95; P = 0.12). Patients treated with EACA received fewer postoperative blood transfusions, including packed red blood cells (MD: -8.36; 95% CI: -12.63 to -4.09; P = 0.0001), fresh frozen plasma (MD: -3.85; 95% CI: -5.63 to -2.08; P < 0.0001), and platelet concentrate (MD: -10.66; 95% CI: -18.45 to -2.87; P = 0.007), and had a lower re-exploration rate (RR: 0.46; 95% CI: 0.23 to 0.92; P = 0.03). Prophylactic EACA also improved coagulation tests 6 hours after open-heart surgery. Conclusions: Prophylactic EACA minimizes postoperative blood transfusion and helps maintain coagulation in pediatric patients undergoing open-heart surgery. Therefore, the results of this study indicate that adjunctive EACA is a good choice for the prevention of postoperative blood transfusion following pediatric cardiac surgery.

Keywords: Epsilon aminocaproic acid, EACA, blood transfusion, bleeding, pediatric, open-heart surgery, cardiac surgery

Introduction

Excessive postoperative blood loss is a common complication of cardiac surgery. The cardiopulmonary bypass (CPB) procedure itself can lead to coagulation disorders during open-heart surgery via fibrinolysis initiation, platelet count reduction, and complement and neutrophil activation [1, 2]. Patients with cyanotic congenital heart disease (CHD) are at an even higher risk of severe blood loss after open-heart surgery because CHD is accompanied by increased fibrinolysis and platelet dysfunction [3].

A high percentage of CHD patients undergoing open-heart surgery require postoperative blood transfusion. Blood transfusion is beneficial for recovery, but it is not without risk. Transfusion also increases postoperative care costs. Specifically, blood transfusions are associated with an increased risk of transmitted viral or
EACA reduces blood transfusion and improves the coagulation test

Figure 1. Trial selection flow chart. The process used for the selection of relevant randomized clinical trials for inclusion in the current meta-analysis is shown.

Infectious agents and the initiation of various immune-related events, such as hemolytic reactions and transfusion-associated graft-versus-host diseases. Unfortunately, the surgical treatment of CHD often requires multiple-staged operations over several years, which exposes these pediatric patients to multiple blood transfusions composed of components from several different donors. Moreover, excessive postoperative hemorrhage can necessitate surgical re-exploration, which is associated with a high prevalence of cardiovascular morbidity and mortality [1-3].

Prophylactic use of antifibrinolytic therapeutic agents has emerged as a promising approach to reducing postoperative blood loss in pediatric patients undergoing open-heart surgery. Three antifibrinolytic agents are currently available-aprotinin, tranexamic acid (TA), and epsilon aminocaproic acid (EACA)-and they have been applied clinically with varying results. The use of aprotinin in cardiac surgery patients effectively reduces blood loss, but it is strongly correlated with serious adverse events, including renal dysfunction and cardiocerebrovascular events [4, 5]. TA and EACA are as effective as aprotinin in reducing blood loss and blood transfusion rates in pediatric open-heart surgery [6-8]. Several studies of TA demonstrated that it does not produce significant adverse events [9-11]. However, TA is cost prohibitive in some patient populations, and EACA is significantly more economical. In addition, study results of EACA efficacy in pediatric open-heart surgery patients are inconsistent [12-17]. One nested case-control study of pediatric cardiac surgery patients found that prophylactic EACA decreased intraoperative blood loss but did not significantly diminish postoperative chest tube output or the rate of blood product transfusion [12]. Several other clinical randomized controlled trials found that prophylactic EACA treatment preserved coagulation function, as evidenced by reduced postoperative blood volume loss, fewer blood transfusions, and improved coagulation test results [13-17]. However, not all of the results were consistent during these randomized controlled trials, and evidence for the efficacy of EACA as a prophylactic treatment for postoperative bleeding and blood transfusion after pediatric open-heart requires further evaluation.

To this end, we performed an updated meta-analysis of prophylactic EACA postoperative use in pediatric CHD patients to obtain a more precise estimation of the clinical efficacy of EACA as measured based on postoperative blood loss, blood transfusion and re-exploration rates as well as coagulation test results.

Materials and methods

Eligibility and search strategy

A computerized search of the PubMed, Embase, Cochrane Library, and Chinese Medical Journal Network literature databases was performed to identify all published trials that compared EACA treatment with placebo therapy in pediatric patients undergoing open-heart surgery up to August 2013. The following Medical Subject Headings (MeSH) terms were used: “((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo [tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals [mh] NOT humans[mh]) AND ((epsilon aminocaproic acid) OR (eaca) OR (6-aminocaproic acid)) AND ((cardiac surgery) OR (cardiac operation) OR (thoracic surgery) OR (cardiac surgical procedures) OR (cardiopulmonary bypass) OR (CPB) OR (congenital heart disease) OR (open-heart surgery)) NOT (adults NOT ((child) OR (children) OR (pediatric patients) OR (newborn) OR (neonatal) OR (baby) OR (neonate) OR (neonates) OR (infant) OR (infants) OR (pediatric)))”.

The reference lists of all identified trials were manually searched to identify any additional
Table 1. Characteristics of the trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Author/year Country</th>
<th>Sample Size (EACA vs. Placebo)</th>
<th>Cardiac Disease</th>
<th>Drug Dose</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandeep 2004 India</td>
<td>50 vs. 50</td>
<td>Cyanotic CHD</td>
<td>100 mg/kg after anesthetic induction, 100 mg/kg in the CPB pump prime and 100 mg/kg after protamine reversal of heparin</td>
<td>Postoperative blood loss, Postoperative blood transfusion, Coagulation tests</td>
</tr>
<tr>
<td>Sandeep 2000 India</td>
<td>60 vs. 80</td>
<td>Cyanotic CHD</td>
<td>100 mg/kg after anesthetic induction, 100 mg/kg in the CPB pump prime, and 100 mg/kg on weaning from CPB over 3 hours</td>
<td>Postoperative blood loss, Postoperative blood transfusion, Coagulation tests</td>
</tr>
<tr>
<td>Rao et al. 2000 India</td>
<td>85 vs. 85</td>
<td>Cyanotic CHD</td>
<td>100 mg/kg after anesthetic induction, 100 mg/kg in the CPB pump prime, and 100 mg/kg on weaning from CPB over 3 hours</td>
<td>Postoperative blood loss, Postoperative blood transfusion, Coagulation tests</td>
</tr>
<tr>
<td>Yang 2003 China</td>
<td>15 vs. 15</td>
<td>Acyanotic CHD</td>
<td>300 mg/kg in total</td>
<td>Postoperative blood loss, Fibrinolytic system change</td>
</tr>
<tr>
<td>Anju 2013 India</td>
<td>38 vs. 37</td>
<td>Cyanotic CHD</td>
<td>100 mg/kg after anesthetic induction, 100 mg/kg in the CPB pump prime, and 100 mg/kg on weaning from CPB over 3 hours</td>
<td>Postoperative blood loss, Postoperative blood transfusion, Coagulation tests</td>
</tr>
</tbody>
</table>

CHD, congenital heart disease; CPB: cardiopulmonary bypass.
EACA reduces blood transfusion and improves the coagulation test

**Table 2.** Baseline characteristics of the trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>EACA (n = 248)</th>
<th>Placebo (n = 267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5.0 years</td>
<td>4.9 years</td>
</tr>
<tr>
<td>Range</td>
<td>2 months - 14 years</td>
<td>2.4 months - 14 years</td>
</tr>
<tr>
<td>Sex, Male/Female</td>
<td>160/88</td>
<td>173/94</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>9.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>0.40</td>
<td>0.36</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>79.8</td>
<td>80.4</td>
</tr>
</tbody>
</table>

CPB: cardiopulmonary bypass.

potentially relevant studies. No language restrictions were used. Study populations based on non-humans or adults and study designs involving non-randomized clinical trials, such as reviews, letters, case reports and case-control studies, were excluded.

**Study selection and data extraction**

Potentially relevant trials were selected for inclusion in the meta-analysis if they met the following criteria: 1) random allocation to the EACA treatment or placebo control groups; 2) exclusively involving pediatric patients, younger than 14 years old, undergoing open-heart surgery; and 3) clinical outcomes composed of postoperative blood loss (mL×kg⁻¹×24 h⁻¹), blood transfusion (mL×kg⁻¹×24 h⁻¹), or coagulation tests (seconds). Two authors (Jun Lu and Haoyu Meng) independently reviewed the full texts of the potentially relevant trials according to the inclusion criteria. Any disagreements were resolved by discussion to reach a consensus.

The following information was extracted from all selected studies: drug dosage, mean age, age range, sex ratio, body surface area, weight, and CPB time. Attempts were made to contact the study’s authors in cases of incomplete or unclear data. All data were considered with respect to the intention-to-treat principle.

Methodological quality was assessed using the Review Manager (RevMan v5.0.0) software, which classifies items related to an individual study’s randomization, allocation concealment, blinding, and dropout rates according to three potential responses: yes, no, and unclear [18]. The methodological quality of the study was deemed acceptable if a study received more than one “No” response or no more than two “Unclear” responses.

**Clinical outcomes**

The primary clinical outcome was postoperative blood loss, which was recorded in milliliters. The following secondary clinical outcomes were used: postoperative blood transfusions, including packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelet concentrate (PC); the proportion of patients who underwent re-exploration; and postoperative coagulation test results six hours following cardiac surgery, which included platelet count, activated clotting time (ACT), fibrinogen, fibrin degradation products (FDP), as well as activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT).

**Statistical analysis**

Statistical analyses were performed using the RevMan v5.0.0 program and SPSS v15.0 software package (SPSS Inc., Chicago, IL, USA). For categorical variables, the risk ratio (RR) and 95% confidence interval (CI) were calculated using a fixed-effects model with the Mantel-Haenszel test. The calculated RR was further assessed using the DerSimonian-Laird random-effects model in cases where significant heterogeneity existed across studies to account for the inter-study differences [19]. For continuous variables, the mean difference (MD) and 95% CI were calculated using the inverse variance weighting method to minimize the variance of the sum. Statistical heterogeneity was evaluated using the Q statistic with a p-value less than 0.10. For all the other tests, a 2-sided p-value < 0.05 was considered statistically significant.

**Results**

**Eligible studies**

Fifty-nine potentially relevant articles were identified in the initial literature search. A total of 54 articles were excluded after retrieval and review of the summary or abstract based on the following factors: meta-analysis design (n =
EACA reduces blood transfusion and improves the coagulation test

Table 3. Risk of publication bias graph

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Was the allocation sequence adequately generated?</th>
<th>Was allocation adequately concealed?</th>
<th>Was knowledge of the allocated intervention adequately prevented during the study?</th>
<th>Were incomplete outcome data adequately addressed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandeep 2004</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sandeep 2000</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rao et al. 2000</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yang 2003</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anju 2013</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Unclear: Insufficient information from one article regarding the process to permit a ‘Yes’ or ‘No’ response.

![Figure 2](image)

Figure 2. Prophylactic EACA and postoperative blood loss. Data are expressed as MD and 95% CI. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. EACA, epsilon aminocaproic acid; MD, mean difference.

5); reviews (n = 13); study population based on non-relatives, non-humans or adults, and study design with a non-randomized clinical trial (n = 36). The data from trials by McClure et al. were reported without standard deviations (SD) [20]. Because we were unable to acquire these values from the primary authors, this trial was also excluded from the meta-analysis due to the incomplete data. Therefore, a total of five articles met all of the inclusion criteria for the meta-analysis, providing data for a total of 515 patients. The restrictive selection process for trials included in the meta-analysis is presented in Figure 1.

The characteristics of the selected studies are summarized in Table 1, and baseline patient characteristics are listed in Table 2. A total of 248 (48.2%) of the 515 patients in the five studies had been randomly assigned to the EACA treatment group, and 267 (51.8%) patients had been assigned to the placebo-treated control group. There were no significant differences between the two treatment groups in mean age, age range, sex ratio, body surface area, weight, or CPB time. The methodological quality assessment suggested that all five trials were of acceptable quality (Table 3).

Primary clinical outcome

Postoperative blood loss

Data were available from all five trials in the meta-analysis [13-17]. Funnel plot analysis indicated that no publication bias existed among the five studies in the meta-analysis, which was confirmed by a negative Egger test (P > |t| = 0.92). The heterogeneity test indicated high heterogeneity (P < 0.00001), and the sensitivity analysis revealed that the heterogeneity was caused by the article by Rao et al. [15]. However, a careful reading of the article by Rao et al. [15] revealed no apparent differences from the two studies by Sandeep et al.. Therefore, we chose not to eliminate this article from further analyses based solely on the sensitivity test. Data from the five articles were analyzed using the random-effects model because of the presence of heterogeneity. Figure 2 shows that prophylactic EACA was associated with a reduction in postoperative
EACA reduces blood transfusion and improves the coagulation test

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean difference IV, random, 95%CI</th>
<th>Mean difference IV, random, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anju 2013</td>
<td>54.35</td>
<td>27.42</td>
<td>38</td>
<td>69.86</td>
<td>23.91</td>
<td>37</td>
<td>10.2% -15.51 [-27.14, -3.88]</td>
<td>-</td>
</tr>
<tr>
<td>Rao BH 2000</td>
<td>10.7</td>
<td>7.8</td>
<td>85</td>
<td>21.8</td>
<td>7.1</td>
<td>85</td>
<td>37.0% -11.10 [-13.34, -8.86]</td>
<td>-</td>
</tr>
<tr>
<td>Sandeep 2000</td>
<td>214.0</td>
<td>19.0</td>
<td>60</td>
<td>18.0</td>
<td>12.0</td>
<td>80</td>
<td>24.6% -4.00 [-9.48, 1.48]</td>
<td>-</td>
</tr>
<tr>
<td>Sandeep 2004</td>
<td>13.0</td>
<td>11.0</td>
<td>50</td>
<td>19.0</td>
<td>12.0</td>
<td>50</td>
<td>28.2% -6.00 [-10.51, -1.49]</td>
<td>-</td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>233</td>
<td>252</td>
<td>100.0%</td>
<td>-8.36</td>
<td>[-12.63, -4.09]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 11.52; \chi^2 = 9.16, df = 3 (p = 0.03); I^2 = 67%$
Test for overall effect: $Z = 3.84 (p = 0.0001)$

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean difference IV, random, 95%CI</th>
<th>Mean difference IV, random, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anju 2013</td>
<td>27.6</td>
<td>16.36</td>
<td>38</td>
<td>42.98</td>
<td>13.91</td>
<td>37</td>
<td>6.7% -15.38 [-22.25, -8.51]</td>
<td>-</td>
</tr>
<tr>
<td>Rao BH 2000</td>
<td>21.5</td>
<td>7.7</td>
<td>85</td>
<td>23.5</td>
<td>7.6</td>
<td>85</td>
<td>59.6% -2.00 [-4.30, 0.30]</td>
<td>-</td>
</tr>
<tr>
<td>Sandeep 2000</td>
<td>24.0</td>
<td>12.0</td>
<td>60</td>
<td>28.0</td>
<td>12.0</td>
<td>80</td>
<td>19.5% -4.00 [-8.02, 0.02]</td>
<td>-</td>
</tr>
<tr>
<td>Sandeep 2004</td>
<td>21.0</td>
<td>13.0</td>
<td>50</td>
<td>27.0</td>
<td>11.0</td>
<td>50</td>
<td>14.2% -6.00 [-10.72, -1.28]</td>
<td>-</td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>233</td>
<td>252</td>
<td>100.0%</td>
<td>-3.85</td>
<td>[-5.63, -2.08]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 14.12, df = 3 (p < 0.003); I^2 = 79%$
Test for overall effect: $Z = 4.25 (p < 0.0001)$

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean difference IV, random, 95%CI</th>
<th>Mean difference IV, random, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rao BH 2000</td>
<td>6.2</td>
<td>3.2</td>
<td>85</td>
<td>22.0</td>
<td>6.7</td>
<td>85</td>
<td>35.7% -15.80 [-17.38, -14.22]</td>
<td>-</td>
</tr>
<tr>
<td>Sandeep 2000</td>
<td>12.0</td>
<td>17.0</td>
<td>60</td>
<td>23.0</td>
<td>18.0</td>
<td>80</td>
<td>30.1% -11.00 [-16.94, -5.16]</td>
<td>-</td>
</tr>
<tr>
<td>Sandeep 2004</td>
<td>15.0</td>
<td>7.0</td>
<td>50</td>
<td>20.0</td>
<td>9.0</td>
<td>50</td>
<td>34.2% -5.00 [-8.16, -1.84]</td>
<td>-</td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>195</td>
<td>215</td>
<td>100.0%</td>
<td>-10.66</td>
<td>[-18.45, -2.87]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 43.60; \chi^2 = 36.65, df = 2 (p < 0.00001); I^2 = 95%$
Test for overall effect: $Z = 2.68 (p = 0.007)$

Figure 3. Prophylactic EACA and blood transfusion. Data are expressed as MD and 95% CI. The following blood transfusion types were assessed: PRBC (top panel), FFP (middle panel), and PC (bottom panel). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. CI, confidence intervals; EACA, epsilon aminocaproic acid; FFP, fresh frozen plasma; MD, mean difference; PC, platelet concentrate; PRBC, packed red blood cells.

Secondary clinical outcomes

Postoperative blood transfusion

Data were available from four of the trials in the meta-analysis. Data for all types of transfusions (PRBC: $P = 0.03$; FFP: $P = 0.003$; PC: $P < 0.00001$) displayed significant heterogeneity, which necessitated analysis using the random-effects model. Figure 3 shows that prophylactic EACA was associated with a significant reduction in PRBC (MD: -8.36; 95% CI: -12.63 to -4.09; $P = 0.0001$), FFP (MD: -3.85; 95% CI: -5.63 to -2.08; $P < 0.0001$) and PC (MD: -10.66; 95% CI: -18.45 to -2.87; $P = 0.007$).

Re-exploration rate

Data were available from four of the trials. No heterogeneity was found ($P = 0.27$), and the fixed-effects model was applied. Figure 4 shows that prophylactic EACA was associated with a significantly lower re-exploration rate compared to the placebo treatment (RR: 0.46; 95% CI: 0.23 to 0.92; $P = 0.03$).

Coagulation tests 6 hours after operations

Data on platelet counts were available from four of the trials. No heterogeneity was found ($P = 0.12$), but this difference did not reach statistical significance. Subgroup analyses were performed to identify the effectiveness of EACA on acyanotic or cyanotic heart diseases. Neither the cyanotic nor acyanotic group had a significantly different postoperative blood loss than the placebo control group (cyanotic: MD: -8.08; 95% CI: -18.54 to 2.38; $P = 0.13$; acyanotic: MD: -3.00; 95% CI: -7.9 to 1.96; $P = 0.24$).
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Data on ACT, fibrinogen and FDP were available from three of the trials [13-15]. No heterogeneity was observed for the ACT ($P = 0.28$) data, which allowed for the use of the fixed-effects model. Data on fibrinogen ($P < 0.00001$) and FDP ($P = 0.09$) displayed significant heterogeneity, which necessitated the use of the random-effects model for analysis. Prophylactic EACA was associated with a significantly lower ACT (MD: -2.66; 95% CI: -4.62 to -0.70; $P = 0.008$) and FDP (MD: -4.20; 95% CI: -4.72 to -3.68; $P < 0.00001$) and significantly higher fibrinogen (MD: 36.95; 95% CI: 28.13 to 45.77; $P < 0.00001$) compared to the placebo treatment.

Data on aPTT, PT and TT were available from two of the trials. Heterogeneity was observed ($P < 0.10$), and the random-effects model was applied. No significant difference was found for aPTT (MD: -0.68; 95% CI: -3.83 to 2.47; $P = 0.67$), PT (MD: -0.95; 95% CI: -2.97 to 1.07; $P = 0.36$) or TT (MD: -1.25; 95% CI: -2.51 to 0.01; $P = 0.05$) between the EACA-treated and placebo groups.

Discussion

Our meta-analysis found that pediatric CHD surgery patients receiving prophylactic EACA required fewer PRBC, FFP, and PC transfusions than their counterparts receiving placebo treatment. Moreover, prophylactic EACA was associated with a preservation of coagulation, as evidenced by coagulation test results six hours after open-heart surgery. Our findings are similar to those of two previous meta-analyses of EACA effectiveness in adult cardiac surgery patients. A large, blinded, multicenter study demonstrated that EACA increased “clinical value” in high-risk cardiac surgery compared to TA and recommended EACA as the preferred antifibrinolytic medication for this type of surgery [23]. However, two other trials concluded that EACA and TA were equally effective at reducing perioperative blood loss and transfusion requirements in pediatric cardiac surgery, but EACA was much more economical than TA because of its lower cost. Collectively, these studies support the utility of prophylactic EACA in adult and pediatric patients undergoing open-heart surgery.

EACA is a synthetic derivative of the amino acid lysine, which acts as an effective inhibitor of fibrinolysis. EACA binds reversibly to plasminogen to block fibrin binding, which inhibits plasminogen activation and its transformation into plasmin [16]. EACA also inhibits the proteolytic activity of plasmin and preserves the structural and functional integrity of the platelet receptor [26]. Fibrinolytic activity increases dramatically immediately after sternotomy and reaches a maximal intensity during and at termination of the CPB procedure, which can persist for one to two hours postoperatively. Administration of an EACA bolus before skin incision followed by a postoperative regimen of EACA is commonly recommended in clinical practice. Chauhan et al. reported the clinical efficacy of a 100 mg/kg EACA infusion after anesthesia induction (in the pump prime) and upon weaning from CPB for congenital cyanotic heart disease patients [14]. McClure et al. used a regimen of a 75 mg/
kg loading dose in the first hour and 15 mg/kg/h thereafter in pediatric patients to achieve a significant reduction in blood loss [20]. Another study estimated that the total administration dose of EACA for pediatric children undergoing open-heart surgery ranged from 5 to 30 g [16]. Whether the effectiveness of EACA is dose dependent is not clear, but Anju’s study of children undergoing corrective cardiac surgery on CPB for TOF demonstrated that a dose regimen of 75 mg/kg after induction, followed by a maintenance infusion of 75 mg/kg/h until chest closure and an additional 75 mg/kg upon initiation of CPB, was more effective than traditional methods (100 mg/kg after anesthetic induction, 100 mg/kg in the CPB pump prime, and 100 mg/kg on weaning from CPB over 3 hours) in reducing postoperative blood loss and transfusion requirements [17].

One of the major risks of antifibrinolytic therapy is that it may induce thrombosis-related complications. No published evidence suggests that prophylactic EACA treatment after open-heart surgery is unsafe, and no cases of a hypercoagulability state related to EACA administration have been reported. However, two trials demonstrated that EACA and TA might be safely administered to reduce blood loss [6, 7]. Similarly, a meta-analysis by Munoz et al. found that prophylactic EACA was not associated with the incidence of postoperative myocardial infarction or overall mortality [21]. A more recent meta-analysis by Brown et al. also concluded that prophylactic EACA did not significantly increase the risk of myocardial infarction, stroke, renal failure, or overall mortality [22]. However, two cases of fatal thrombosis after EACA therapy and deep hypothermic circulatory arrest have been reported [27]. A retrospective analysis revealed that EACA patients had a higher incidence of postoperative renal dysfunction, but the incidence of acute kidney injury in children administered EACA was significantly lower than that in children administered aprotinin [28]. Therefore, it was recommended that use of EACA should be restricted to patients at high risk for bleeding [29]. Despite these previous studies and our current meta-analysis, further clinical trials with a large sample size must be performed to more precisely estimate the safety of prophylactic EACA in pediatric patients undergoing open-heart surgery.

Limitations

There are several limitations to this study. First, as with all meta-analyses, heterogeneity among trials cannot be absolutely excluded. Therefore, a random-effects model was applied in some of our results. Second, only five articles were included in our meta-analysis, and the sample size was not large enough to provide conclusive evidence. Therefore, more multicenter, placebo-controlled, and randomized clinical trials are required to more precisely assess the effectiveness and safety of EACA for the optimization of coagulation function in pediatric patients undergoing open-heart surgery. Despite these potential limitations to our study, our findings provide insights into the utility and efficacy of EACA in clinical practice for pediatric cardiac surgery.

Conclusions

Prophylactic EACA minimizes postoperative blood transfusion and helps maintain coagulation in pediatric patients undergoing open-heart surgery. Adjunctive EACA should be recommended for the prevention of postoperative blood transfusion in pediatric cardiac surgery.

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Disclosure of conflict of interest

None.

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References

EACA reduces blood transfusion and improves the coagulation test


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