Int J Clin Exp Pathol 2015;8(7):7978-7987
www.ijcep.com /ISSN:1936-2625/IJCEP0009039

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

Jun Lu[1*], Haoyu Meng[2*], Zhaoyi Meng[3], Ying Sun[2], John P Pribis[4], Chunyan Zhu[4], Quan Li[1*]

[1]*Department of Anesthesiology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China;* [2]*First Clinical Medical College of Nanjing Medical University, Nanjing, China;* [3]*Department of Surgery, Xinyi People's Hospital, Xinyi, China;* [4]*Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.* [*]*Equal contributors.*

Received April 13, 2015; Accepted April 29, 2015; Epub July 1, 2015; Published July 15, 2015

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

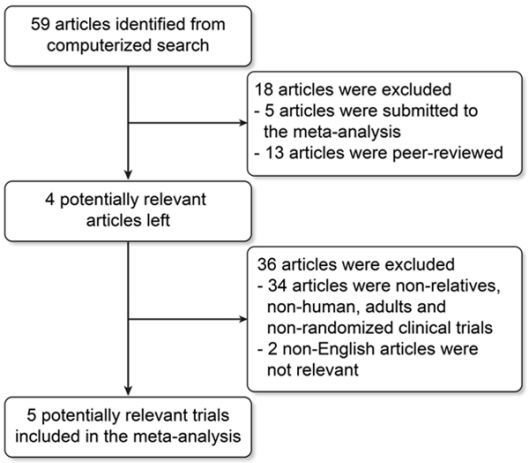

Figure 1. Trial selection flow chart. The process used for the selection of relevant randomized clinical trials for inclusion in the current meta-analysis is shown.

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 (heart surgery) OR (heart 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

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

CHD, congenital heart disease; CPB: cardiopulmonary bypass.

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

Variable	EACA (n = 248)	Placebo (n = 267)
Age, years		
Mean	5.0 years	4.9 years
Range	2 months -14 years	2.4 months -14 years
Sex, Male/Female	160/88	173/94
Weight, kg	9.5	9.5
Body surface area, m^2	0.40	0.36
CPB time, min	79.8	80.4

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 ($mL \times kg^{-1} \times 24\ h^{-1}$), blood transfusion ($mL \times kg^{-1} \times 24\ h^{-1}$), 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 =

Table 3. Risk of publication bias graph

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

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

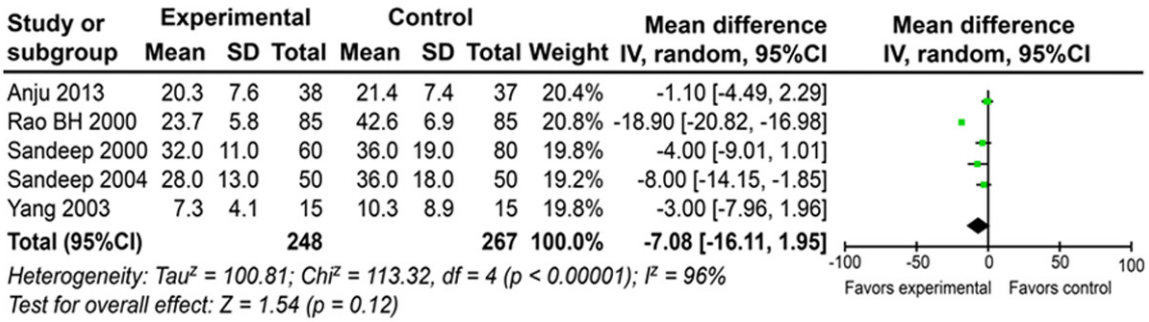

Figure 2. Prophylactic EACA and postoperative blood loss. Data are expressed as MD and 95% CI. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. CI, confidence intervals; EACA, epsilon aminocaproic acid; MD, mean difference.

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

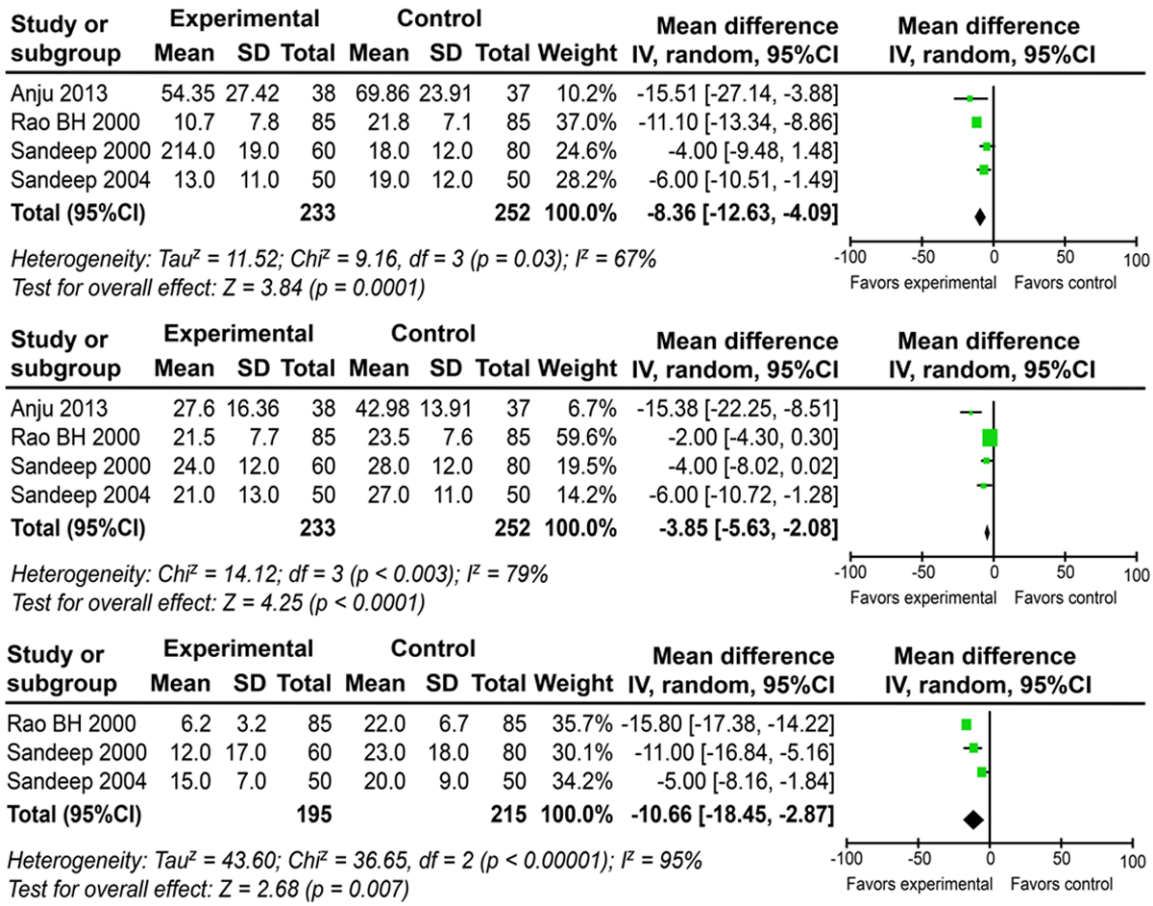

Figure 3. Prophylactic EACA and blood transfusion. Data are expressed as MD and 95% CI. The following blood transfusion types were assessed: PRBC (top panel), FFP (middle panel), and PC (bottom panel). The size of the data markers (squares) is approximately proportional to the statistical weight of each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

blood loss compared to the placebo treatment (MD: -7.08; 95% CI: -16.11 to 1.95; *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*).

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*

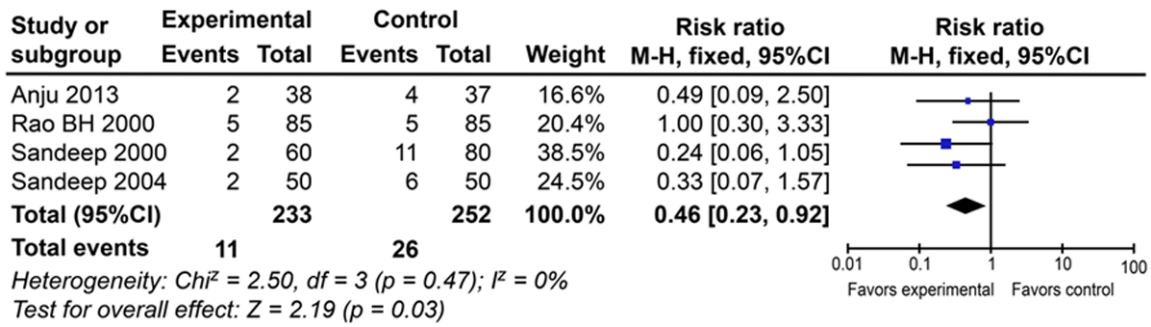

Figure 4. Prophylactic EACA and re-exploration rate. Data are expressed as RR and 95% CI. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. CI, confidence intervals; EACA, epsilon aminocaproic acid; RR, risk ratio.

= 0.20), and the fixed-effects model was applied. Prophylactic EACA was associated with a significantly higher platelet count (MD: 4.18; 95% CI: 1.35 to 7.01; $P = 0.004$).

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: -2.97-1.07; $P = 0.36$) or TT (MD: -1.25; 95% CI: -2.51-0.01; $P = 0.05$) 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.

Acknowledgements

We thank Dr. Yu Bai (Shanghai Changhai Hospital) for guidance in this meta-analysis. This study was partially supported by the Shanghai Natural Science Foundation [10411951400] (to Quan li), [11ZR1428100] (to Quan li). We also thank all authors of the enrolled trials in this study for tracking the required data.

Disclosure of conflict of interest

None.

Address correspondence to: Quan Li, Department of Anesthesiology, Shanghai East Hospital, Tongji University. School of Medicine, 150 Jimo Road, Pudong New Area Shanghai 200120, China. Tel: 86-21-38804518; E-mail: liquandoc@163.com

References

[1] Kern FH, Morana NJ, Sears JJ and Hickey PR. Coagulation defects in neonates during cardiopulmonary bypass. Ann Thorac Surg 1992; 54: 541-546.

[2] Guay J and Rivard GE. Mediastinal bleeding after cardiopulmonary bypass in pediatric patients. Ann Thorac Surg 1996; 62: 1955-1960.
[3] Tempe DK and Virmani S. Coagulation abnormalities in patients with cyanotic congenital heart disease. J Cardiothorac Vasc Anesth 2002; 16: 752-765.
[4] Mangano DT, Tudor IC, Dietzel C; Multicenter Study of Perioperative Ischemia Research Group and Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006; 354: 353-365.
[5] Mangano DT, Miao Y, Vuylsteke A, Tudor IC, Juneja R, Filipescu D, Hoeft A, Fontes ML, Hillel Z, Ott E, Titov T, Dietzel C, Levin J; Investigators of The Multicenter Study of Perioperative Ischemia Research Group and Ischemia Research and Education Foundation. Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. JAMA 2007; 297: 471-479.
[6] Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, McClelland B, Laupacis A and Fergusson D. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2007; CD001886.
[7] Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson and Ker K. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011; CD001886.
[8] Schouten ES, van de Pol AC, Schouten AN, Turner NM, Jansen NJ and Bollen CW. The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis. Pediatr Crit Care Med 2009; 10: 182-910.
[9] Adler Ma SC, Brindle W, Burton G, Gallacher S, Hong FC, Manelius I, Smith A, Ho W, Alston RP and Bhattacharya K. Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2011; 25: 26-35.
[10] Schindler E, Photiadis J, Sinzobahamvya N, Döres A, Asfour B and Hraska V. Tranexamic acid: an alternative to aprotinin as antifibrinolytic therapy in pediatric congenital heart surgery. Eur J Cardiothorac Surg 2011; 39: 495-499.
[11] Martin K, Breuer T, Gertler R, Hapfelmeier A, Schreiber C, Lange R, Hess J and Wiesner G. Tranexamic acid versus -aminocaproic acid: efficacy and safety in paediatric cardiac surgery. Eur J Cardiothorac Surg 2011; 39: 892-897.
[12] Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.
[13] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-187.
[14] McClure PD and Izsak J. The use of epsilon-aminocaproic acid to reduce bleeding during cardiac bypass in children with congenital heart disease. Anaesthesiol 1974; 40: 604-608.
[15] Munoz JJ, Birkmeyer NJ, Birkmeyer JD, O'Connor GT and Dacey LJ. Is epsilon-aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery?: a meta-analysis. Circulation 1999; 99: 81-89.
[16] Brown JR, Birkmeyer NJ and O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation 2007; 115: 2801-2813.
[17] Raghunathan K, Connelly NR and Kanter GJ. ε-Aminocaproic acid and clinical value in cardiac anesthesia. J Cardiothorac Vasc Anesth 2011; 25: 16-19.
[18] Martin K, Breuer T, Gertler R, Hapfelmeier A, Schreiber C, Lange R, Hess J and Wiesner G. Tranexamic acid versus -aminocaproic acid: efficacy and safety in paediatric cardiac surgery. Eur J Cardiothorac Surg 2011; 39: 892-897.
[19] Martin K, Gertler R, Sterner A, MacGuill M, Schreiber C, Hörer J, Vogt M, Tassani P and Wiesner G. Comparison of blood-sparing efficacy of ε-aminocaproic acid and tranexamic acid in newborns undergoing cardiac surgery. Thorac Cardiovasc Surg 2011; 59: 276-280.
[20] Chen RH, Frazier OH and Cooley DA. Antifibrinolytic therapy in cardiac surgery. Tex Heart Inst J 1995; 22: 211-215.
[21] Fanashawe MP, Shore-Lesserson L and Reich DL. Two cases of fatal thrombosis after aminocaproic acid therapy and deep hypothermic circulatory arrest. Anaesthesiol 2001; 95: 1525-1527.
[22] Leyvi G, Nelson O, Yedlin A, Pasamba M, Belamarich PF, Nair S and Cohen HW. A comparison of the effect of aprotinin and epsilon-aminocaproic acid on renal function in children undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2011; 25: 402-406.
[23] Martin K, Knorr J, Breuer T, Gertler R, Macguill M, Lange R, Tassani P and Wiesner G. Seizures after open heart surgery: comparison of ε-aminocaproic acid and tranexamic acid. J Cardiothorac Vasc Anesth 2011; 25: 20-25.
[24] Williams GD, Bratton SL, Riley EC, Ramamoorthy C. Efficacy of epsilon-aminocaproic acid in children undergoing cardiac surgery. J Cardiothorac Vasc Anesth 1999; 13: 304-308.

[25] Chauhan S, Das SN, Bisoi A, Kale S and Kiran U. Comparison of epsilon aminocaproic acid and tranexamic acid in pediatric cardiac surgery. J Cardiothorac Vasc Anesth 2004; 18: 141-143.

[26] Chauhan S, Kumar BA, Rao BH, Rao MS, Dubey B, Saxena N and Venugopal P. Efficacy of aprotinin, epsilon aminocaproic acid, or combination in cyanotic heart disease. Ann Thorac Surg 2000; 70: 1308-1312.

[27] Rao BH, Saxena N, Chauhan S, Bisoi AK and Venugopal P. Epsilon aminocaproic acid in paediatric cardiac surgery to reduce postoperative blood loss. Indian J Med Res 2000; 111: 57-61.

[28] Yang XW, Guo LJ, Li DQ, Zhang Y, Li ZY and Fu Y. Comparison of the effects of epsilon-aminocaproic acid and aprotinin on fibrinolytic system in children undergoing cardiopulmonary bypass. Chinese Remedies and Clinics 2003; 3: 32-35.

[29] Sarupria A, Makhija N, Lakshmy R, Kiran U. Comparison of different doses of epsilon-Aminocaproic Acid in children for tetralogy of Fallot surgery: clinical efficacy and safety. J Cardiothorac Vasc Anesth 2013; 27: 23-29.