Safety and efficacy of tranexamic acid in paediatric cardiac surgery: study protocol for a double-blind randomised controlled trial

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ABSTRACT

Introduction An initial retrospective study suggested that tranexamic acid (TXA) administration increased the incidence of seizures in paediatric patients undergoing cardiac surgery. However, the efficacy of TXA in paediatric cardiac surgery remains unclear owing to the small sample sizes of the studies. Therefore, this study will investigate the efficacy and safety of TXA in paediatric patients undergoing cardiac surgery. We hypothesised that TXA may increase the incidence of postoperative seizures with no effect on postoperative allogeneic transfusion in paediatric patients undergoing cardiac surgery. The pragmatic study will provide important implications for paediatric cardiac surgery.

Methods and analysis This will be a single-centre prospective, double-blind randomised controlled trial. The plan is to enrol in the study 2090 paediatric patients aged 31 days to 7 years who will be undergoing cardiac surgery with cardiopulmonary bypass (CPB). All eligible participants will be randomly assigned to either the TXA or placebo group by using a Web-based randomisation service in a 1:1 ratio. The primary safety end point will be postoperative seizures until hospital discharge, and the primary efficacy end point will be the volume of allogeneic red blood cell transfusion after termination of CPB. All patients will be followed up for 1 year postdischarge. All data will be analysed in accordance with the intention-to-treat principle.

Ethics and dissemination This study was approved by the Institutional review board of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No 20191195). Written informed consent will be obtained from the parents/legal guardian of each patient because all participants will be <18 years of age. The results of the trial will be published in an international peer-reviewed journal.

Trial registration number Chinese Clinical Trial Register (ChiCTR1900024131).

INTRODUCTION

Paediatric cardiac surgery increases the risk of excessive blood loss and subsequent allogeneic transfusion due to the abnormal coagulation in patients with congenital heart disease and the activation of platelets, coagulation and fibrinolysis caused by hemodilution during cardiopulmonary bypass (CPB).1 More than 2090 participants will be recruited to obtain results with high statistical power.

This will be a randomised controlled trial aimed at evaluating the efficacy and safety of tranexamic acid (TXA) in paediatric patients undergoing cardiac surgery, which will provide important implications.

More than 2090 participants will be recruited to obtain results with high statistical power.

The TXA dosage that will be used in this study is appropriate according to a pharmacokinetic study.

This will be a single-centre trial, which can be a limitation of this study.

This study will exclude some high-risk patients, such as neonates and children undergoing total cavopulmonary connection, under the consideration of heterogeneity.
clinical studies on the use of TXA in paediatric cardiac surgery have been limited by their small sample sizes; thus, TXA administration is not explicitly recommended in paediatric cardiac surgery. A large retrospective cohort study and a randomised trial showed that TXA administration was associated with a reduction in the postoperative bleeding volume but not the allogeneic transfusion requirement in paediatric patients undergoing cardiac surgery.

Considering the clinical experience with aprotinin, more attention should be paid to the adverse effects of TXA. Pasquali et al suggested that use of TXA was associated with significantly lower mortality than that of aprotinin in paediatric cardiac surgery. Unfortunately, recent clinical trials and meta-analyses have suggested a dose-dependent association between TXA administration and the risk of seizures in adult patients undergoing cardiac surgery. Moreover, recent studies have suggested that a TXA dose of >100 mg/kg confers a twofold increased risk of seizures when compared with lower doses (30–50 mg/kg). Retrospective studies have revealed that the use of TXA is associated with a significantly increased risk of seizures in paediatric cardiac surgery. Maeda et al found a 0.2% incidence of seizures in the non-TXA group and a 1.6% incidence of seizures in the TXA group among paediatric patients undergoing cardiac surgery (p<0.001). However, the adverse effects to TXA in paediatric cardiac surgery have only been reported in retrospective studies; no prospective studies have been designed or powered to evaluate the incidence of adverse events. Moreover, seizures after cardiac surgery may increase the operative mortality and interfere with the neurodevelopment and quality of life of children.

Therefore, safety evaluations of the use of TXA in paediatric cardiac surgery are important.

On the basis of our preliminary observations in clinical practice, we hypothesised that TXA may increase the incidence of postoperative seizures while having no effect on postoperative allogeneic transfusion in paediatric patients undergoing cardiac surgery. Therefore, although removing TXA from routine treatment may have no effect on perioperative blood protection, this may greatly reduce the risk and cost of surgery and improve the long-term neurodevelopment and quality of life of paediatric patients undergoing cardiac surgery.

To verify our hypothesis, we designed a large randomised controlled trial (RCT) to investigate the efficacy and safety of TXA in paediatric patients undergoing cardiac surgery.

METHODS AND ANALYSIS

Study objective

The aim of our study will be to test the hypothesis that TXA, compared with placebo, increases the incidence of postoperative seizures and has no effect on postoperative allogeneic transfusion in paediatric patients undergoing cardiac surgery.

Study design

The study will be a single-centre, parallel-group, double-blind RCT. The study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials guideline. Patients will first be screened for eligibility and willingness to participate in the trial. Informed consent will then be collected from all the participants. Written informed consent will be obtained from the parents/legal guardian of each patient because all participants will be <18 years of age. All eligible participants will be randomly assigned to either the TXA or placebo group in a 1:1 ratio in a blinded fashion. Randomisation will be performed by using a Web-based randomisation service in Fuwai Hospital. The patients will be closely monitored for the occurrence of postoperative seizures. The times of events will also be assessed. The study flowchart is shown in figure 1.

Study population

We plan to enrol 2090 paediatric patients aged 31 days to 7 years who will be undergoing cardiac surgery with CPB at Fuwai Hospital in Beijing, China. The included patients will be undergoing surgical repair of an atrial or ventricular septal defect, atrioventricular septal defect, or endocardial cushion defect, or a complete repair for tetralogy of Fallot, double-outlet right ventricle, transposition of the great arteries, pulmonary atresia, anomalous pulmonary venous connection, anomalous origin of the left coronary artery from the pulmonary artery, and similar conditions. The patients will be included in the study after their parents/guardian provide written informed consent. The exclusion criteria will be total cavopulmonary connection with CPB, thrombocytopenia or any other known history of a bleeding disorder, thromboembolic disease (history of postoperative or spontaneous pulmonary embolism, spontaneous arterial thrombosis or familial hypercoagulability), previous convulsion or seizure, intellectual or
legal disabilities, severe renal impairment (serum creatinine level of >3.3 mg/dL), allergy or contraindication to TXA injection or its components, and current enrolment in another perioperative interventional study.

**Randomisation and blinding**

Randomisation will be performed using a Web-based randomisation service in Fuwai Hospital. The allocation sequence will be computer-generated, and the randomisation list will not be known to the investigators. All eligible participants will be randomly assigned to either the TXA or placebo group in a 1:1 ratio. The participants, medical staff and investigators will be unaware of the treatment allocation. The drugs will be prepared by nurse anaesthetists, labelled with numbers and then injected by the anaesthesiologist. Data will be collected by trained observers who will not participate in patient care and will be blinded to the patient allocation.

**Interventions**

The participants will be randomised to receive injections using identical syringes labelled with the randomisation number. The syringes will contain a transparent solution (either TXA or saline solution). In infants aged 31 days to 12 months, the medication will be intravenously administered with a pump in a 30 mg/kg bolus over a 15 min period after induction, followed by maintenance at 10 mg/(kg·h) throughout the surgery. In children aged 12 months to 7 years, the medication will be intravenously administered with a pump in a 10 mg/kg bolus over a 15 min period after induction, followed by maintenance at 10 mg/(kg·h) throughout the surgery.

All other perioperative clinical care will be performed in accordance with the standard practice in our centre because this trial is designed to represent real-world clinical practice. Heparinisation for CPB will be based on a bolus dose of 400 IU/kg and maintenance of an activated clotting time of >450 s during CPB, with additional heparin as required. Heparin reversal at CPB completion will be achieved with protamine administration at 4 mg/kg, monitored on the basis of the activated clotting time (<140 s). Other antifibrinolytic therapies such as human fibrinogen, human prothrombin and recombinant VIIa cannot be used before or during CPB; however, these can be used if clinically significant bleeding is present after protamine administration. The study will be guided by a transfusion protocol. The threshold for red blood cell transfusion will be a haemoglobin concentration of <100 g/L in acyanotic patients and <110 g/L in cyanotic patients after CPB termination. The indication for fresh frozen plasma administration will be a haemoglobin concentration of <100 g/L in acyanotic patients and <110 g/L in cyanotic patients after CPB termination. The secondary safety end points will be exposure to allogeneic red blood cell transfusion after CPB termination, volume of and exposure to fresh frozen plasma and platelet transfusions after CPB termination. Additionally, other study variables will be postoperative bleeding (6-hour postoperative bleeding to be measured as the accumulated volume of pericardial and mediastinal fluid collected via a drainage tube during the first 6 hours after surgery and total postoperative bleeding to be measured before removal of the tubes); the rate of reoperation for massive bleeding with a drainage rate of >10% of the total blood volume per hour for up to 2 hours or until the occurrence of cardiac tamponade; mechanical ventilation duration; intensive care unit stay; hospital length of stay; and total hospitalisation cost.

Seizure will be defined as ‘a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain’. Seizures will be usually clinically manifested as tonic, clonic or myoclonic activity of the limb or trunk, or generalised all over the body with or without loss of awareness. All the patients with seizures will undergo serial electroencephalography, which may show epileptiform discharges, or slow waves or normal findings.

Stroke will be diagnosed as a new neurological deficit (paralysis, weakness or speech difficulty) that lasts for >24 hours or that leads to early death and will be confirmed on the basis of the presence of cerebral infarction or haemorrhage on CT or MRI.

Myocardial infarction will be defined as the development of pathologic Q waves on two or more adjacent leads on an ECG, changes indicative of ischemia (ST-segment elevation or depression) on an ECG, and/or a change in the serum level of creatine kinase-muscle/brain of >75 µg/L.

Pulmonary embolism will be confirmed on the basis of clinical symptoms and pulmonary angiography or ultrasonography findings.

Deep venous thrombosis will be confirmed on the basis of clinical symptoms and venous Doppler ultrasonography findings.

AKI will be defined in accordance with the Acute Kidney Injury Network criteria. The ratio of the peak serum creatinine level to the preoperative serum creatinine
level on each postoperative day will be used to define the
timepoint during which the outcome event proves to be rare. A Cox regression
model will be used to analyse the follow-up morbidity and mortality rates. The
number of covariates in the regression model will be decided on the basis of the number of outcome events.

An independent data and safety monitoring board (DSMB) will perform one interim analysis after recruitment of 50% of the 2090 participants. The interim analysis will be adjusted according to the Lan-DeMets alpha spending function for the TXA main effects. For the interim analysis, a single-sided p value <0.0015 will be taken as the stopping rule.

Data and safety monitoring board
The DSMB will consist of a cardiologist (chair), cardiac surgeon, independent statistician, cardiac anesthesiologist with an interest in medical ethics and law, and clinical pharmacologist. The independent DSMB will perform one interim analysis after recruitment of 50% of the 2090 participants, and make recommendations to continue, modify or terminate the study according to the stopping rules and consideration of other evidence relevant to the DSMB.

Study status
The trial will start patient recruitment in December 2019, and the recruitment will continue for 2 years, until December 2021. The 1 year follow-up programme is planned to be continued until December 2022.

Patient and public involvement
No patient or public entity will be involved in the present study. On the completion of this trial, a journal article manuscript will be prepared to present the trial results.

DISCUSSION
To the best of our knowledge, this is currently the first large RCT to evaluate the efficacy and safety of TXA in paediatric cardiac surgery, which will provide important implications for paediatric cardiac surgery. If our hypothesis is proven correct, removing TXA from routine treatment may have no effect on perioperative blood protection but may greatly reduce the risk and cost of surgery and improve the long-term neurodevelopment and quality of life of paediatric patients undergoing cardiac surgery.

Owing to the increased risk of renal failure and mortality reported in adults undergoing cardiac surgery, aprotinin administration should not be considered as a safe option for children. Since withdrawal of aprotinin from the market in 2008, TXA has been widely used as an antifibrinolytic agent. Unfortunately, evidence is limited regarding the safety of TXA in paediatric cardiac surgery. Pasquale et al. performed a large Society of Thoracic Surgeons National Database study of >20 000 paediatric patients undergoing cardiac surgery and found that TXA (vs aprotinin) was associated with significantly reduced mortality/bleeding
limitations of the patients is broad, as is the number of procedures that will be needed in the future. Although the age range related to TXA administration during paediatric cardiac surgery.\textsuperscript{13-15} Martin \textit{et al}.\textsuperscript{13} found 9.6%, 1.8%, 3.5% and 2.6% incidence rates of renal injury, renal failure, seizure and other neurological events, respectively. According to their results, >500 patients per group are needed to evaluate the adverse effects of TXA administration in paediatric cardiac surgery. In fact, according to the findings reported by Maeda \textit{et al},\textsuperscript{15} our planned study of the effects of TXA in a very large number of participants (n=2090) will be powerful enough to explain the safety of TXA in paediatric cardiac surgery. At present, the dosage of TXA recommended for use during paediatric cardiac surgery significantly vary. The loading dose of TXA ranges from 10 to 100 mg/kg, and the maintenance dose ranges from 1 to 15 mg/(kg-h).\textsuperscript{20} The dosage regimens that will be used in our study will be based on pharmacokinetic principles. Multiple in vitro studies have focused on determining the TXA concentration needed to prevent fibrinolysis, inhibit platelet activation or increase thrombin generation. Paediatric cardiac TXA pharmacokinetic studies have shown that a lower plasma concentration of TXA (~10–20 µg/mL) is thought to inhibit ~80% of fibrinolysis and that a high plasmatic concentration of TXA (~100 µg/mL) should completely inhibit fibrinolysis.\textsuperscript{21,22} On the basis of the plasma concentration of TXA obtained from these in vitro models, a low dosage maintaining a low plasmatic concentration of TXA may not achieve the effect of clinical blood protection, while a high dosage may cause adverse events after paediatric cardiac surgery. In a recent paediatric cardiac TXA pharmacokinetic study, Wesley \textit{et al}.\textsuperscript{23} described three different dose regimens based on targeted plasmatic concentrations of 20, 60 and 150 µg/mL. To maintain a plasma concentration of 60 µg/mL, the authors suggested a loading dose of 50, 26 and 13 mg/kg followed by a continuous infusion of 7, 6 and 5.5 mg/(kg-h) in neonates and infants aged <2, 2–12 and >12 months and ≤20 kg in body weight, respectively. An additional priming volume of 60 µg/mL was also suggested. Therefore, on the basis of the existing literature, the present study indicates that a TXA loading dose of 30 mg/kg followed by a continuous infusion of 10 mg/(kg-h) can be used in infants <1 year of age, while a loading dose of 10 mg/kg followed by a continuous infusion of 10 mg/(kg-h) can be used in older patients; this is recommended by Faraoni \textit{et al}.\textsuperscript{23} as an expert opinion.

Limitations

The single-centre nature of this study may limit its generalisability; thus, a multicentre study with a large sample size will be needed in the future. Although the age range of the patients is broad, as is the number of procedures

CONCLUSIONS

The pragmatic study will be the first adequately powered RCT to evaluate the efficacy and safety of TXA in paediatric patients undergoing cardiac surgery, which will provide important implications for paediatric cardiac surgery. If the predicted effects are proven, removing TXA from routine treatment may have no effect on perioperative blood protection, but may greatly reduce the risk and cost of surgery and improve the long-term neurodevelopment and quality of life of paediatric patients undergoing cardiac surgery.

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Contributors YZ, YW and FY conceived the study and initiated the study design. YZ, YJ, JS, SY, RW, ZH, JW, JL, JR, Y-GZ, ZH and JY will be involved in study implementation. YW provided statistical expertise in clinical trial design and will...
REFERENCES

1 Siemens K, Sangaran DP, Hunt BJ, et al. Strategies for prevention and management of bleeding following pediatric cardiac surgery on cardiopulmonary bypass: a scoping review. Pediatr Crit Care Med 2018;19:40–7.

2 Chollette JM, Faraoni D, Goobie SM, et al. Patient blood management in pediatric cardiac surgery: a review. Anesth Analg 2018;127:1002–16.

3 Koster A, Faraoni D, Levy JH. Antifibrinolytic therapy for cardiac surgery: an update. Anesthesiology 2015;123:214–21.

4 Basta MN, Stricker PA, Taylor JA. A systematic review of the use of antifibrinolytics agents in pediatric surgery and implications for craniofacial use. Pediatr Surg Int 2012;28:1059–69.

5 Faraoni D, Willems A, Melot G, et al. Efficacy of tranexamic acid in paediatric cardiac surgery: a systematic review and meta-analysis. Eur J Cardiothorac Surg 2012;42:781–6.

6 Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. Eur J Anaesthesiol 2017:34:332–95.

7 Zhang Y, Zhang X, Wang Y, et al. Efficacy and safety of tranexamic acid in pediatric patients undergoing cardiac surgery: a single-center experience. Front Pediatr 2019;7.

8 Shimizu K, Toda Y, Iwasaki T, et al. Effect of tranexamic acid on blood loss in pediatric cardiac surgery: a randomized trial. J Anesth 2011;25:823–30.

9 Pasquali SK, Li JS, He X, et al. Comparative analysis of antifibrinolytic medications in pediatric heart surgery. J Thorac Cardiovasc Surg 2012;143:550–7.

10 Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med 2017;376:136–48.

11 Lin Z, Xiao Y. Tranexamic acid-associated seizures: a meta-analysis. Seizure 2016;36:70–3.

12 Takagi H, Ando T, Umemoto T, et al. Seizures associated with tranexamic acid for cardiac surgery: a meta-analysis of randomized and non-randomized studies. J Cardiovasc Surg 2017;58:633–41.

13 Breuer T, Martin K, Wilhelm M, et al. The blood sparing effect and the safety of aprotinin compared to tranexamic acid in paediatric cardiac surgery. Eur J Cardiothorac Surg 2009;35:167–71.

14 Martin K, Breuer T, Gertler R, et al. Tranexamic acid versus ε-aminocaproic acid: efficacy and safety in paediatric cardiac surgery. Eur J Cardiothorac Surg 2011;39:892–7.

15 Maeda T, Sasabuchi Y, Matsui H, et al. Safety of tranexamic acid in pediatric cardiac surgery: a nationwide database study. J Cardiothorac Vasc Anesth 2017;31:549–53.

16 Manji RA, Grocott HP, Leake J, et al. Seizures following cardiac surgery: the impact of tranexamic acid and other risk factors. Can J Anaesth 2012;59:6–13.

17 Gaynor JW, Jarvik GP, Gerdes M, et al. Postoperative electroencephalographic seizures are associated with deficits in executive function and social behaviors at 4 years of age following cardiac surgery in infancy. J Thorac Cardiovasc Surg 2013;146:132–9.

18 Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11.

19 Giordano R, Palma G, Poli V, et al. Tranexamic acid therapy in pediatric cardiac surgery: a single-center study. Ann Thorac Surg 2012;94:1302–6.

20 Nishioka DK, Monuteaux MC, Faraoni D, et al. Tranexamic acid use in United States Children's Hospitals. J Pediatr 2015;166:567–72.

21 Gertler R, Gruber M, Grassin-Delyle S, et al. Pharmacokinetics of tranexamic acid in neonates and infants undergoing cardiac surgery. Br J Clin Pharmacol 2017;83:1745–57.

22 Rozen L, Faraoni D, Sanchez Torres C, et al. Effective tranexamic acid concentration for 95% inhibition of tissue-type plasminogen activator induced hyperfibrinolysis in children with congenital heart disease: A prospective, controlled, in vitro study. Eur J Anaesthesiol 2015;32:844–50.

23 Wesley MC, Pereira LM, Scharp LA, et al. Pharmacokinetics of tranexamic acid in neonates, infants, and children undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology 2015;122:746–58.

24 Faraoni D, Rahe C, Cybulski KA. Use of antifibrinolytics in pediatric cardiac surgery: where are we now? Paediatr Anaesth 2019;29:435–40.

25 Lin C-Y, Shuhalber JH, Loyola H, et al. The safety and efficacy of antifibrinolytic therapy in neonatal cardiac surgery. PLoS One 2015;10:e0126514.