Comparison of Two Tranexamic Acid Dose Regimens in Patients Undergoing Cardiac Valve Surgery

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Objective: **Tranexamic acid (TA), a synthetic antifibrinolytic drug, has been shown to reduce postoperative bleeding and the need for allogeneic blood transfusion in cardiac surgery. However, the optimal dose regimen of TA is still under debate. The aim of this study was to evaluate whether a lower-dose TA regimen produced equivalent efficacy to its higher-dose counterpart in reducing postoperative bleeding and transfusion needs.**

Design: **A prospective, randomized, double-blind trial.**

Setting: **National Center for Cardiovascular Diseases & University Hospital, Beijing, People's Republic of China.**

Participants: **One hundred seventy-five patients undergoing cardiac valve surgery were enrolled in the study.**

Interventions: **All patients were divided randomly into 2 groups. The lower-dose TA group received a loading dose of 10 mg/kg, maintenance dose of 2 mg/kg/h, and a cardiopulmonary bypass pump prime dose of 40 mg; the higher-dose TA group received a loading dose of 30 mg/kg, maintenance dose of 16 mg/kg/h, and a pump prime dose of 2 mg/kg.**

Measurements and Main Results: **The amount of postoperative bleeding, the amount and frequency of allogeneic transfusion, mortality, and morbidities were recorded. There was no significant difference in the volume of 24-hour postoperative bleeding between the lower-dose group and the higher-dose group. Other measurements also showed no statistical difference between the 2 groups, including the amount and frequency of allogeneic transfusion, mortality, and morbidities.**

Conclusion: **Lower-dose TA regimen was as effective as the higher-dose regimen in reducing postoperative bleeding and transfusion needs in patients undergoing cardiac valve surgery.**

KEY WORDS: tranexamic acid, fibrinolysis, heart valve diseases, hemostasis, hemorrhage

POSTOPERATIVE MASSIVE BLEEDING is still a great challenge for cardiac surgery. It leads to substantial use of allogeneic blood products, which increases mortality and morbidity.[1,2] Because aprotinin increases the risk for renal dysfunction and mortality,[3–8] tranexamic acid (TA) has taken the forefront and has become the antifibrinolytic agent of choice for cardiac surgery in many countries, including China.[3,6–8] TA is a synthetic antifibrinolytic drug that acts by binding to the lysine-binding sites of plasminogen, thus blocking its interaction with specific lysine residues of fibrin, thereby preventing degradation of fibrin and dissolution of clots.[8,9] TA is currently a class I recommendation in many guidelines for blood conservation during cardiac operation.[10,11]

However, the optimal TA dose regimen to achieve and sustain steady therapeutic blood concentration is still under debate.[12–17] Current clinical total dose ranges from 1 g to 20 g, indicating indiscriminate use of TA.[16] Of all regimens, the recommended dose from the BART trial remains most popular for high-risk cardiac surgery. It suggested a loading dose of 30 mg/kg plus an additional 2 mg/kg added to the pump prime, followed by continuous infusion dose of 16 mg/kg/h.[6] With this dose regimen, mean plasma TA concentration was constantly higher than the suggested threshold to achieve 100% inhibition of systemic fibrinolysis and 80% inhibition of tissue plasminogen activator during the surgery and the first 6 postoperative hours.[18] In fact, the plasma TA concentration required to suppress fibrinolysis and plasmin-induced platelet activation is 10 μg/mL and 16 μg/mL, respectively.[19,20] To achieve a steady plasma level of 20 μg/mL, Nuttall et al suggested a dose regimen consisting of a loading dose of 10 mg/kg given over 20 minutes followed by an infusion rate of 2 mg/kg/h and a cardiopulmonary bypass (CPB) prime dose of 40 mg for a 2-L circuit.[21]

This prospective, double-blinded, randomized trial selected the above 2 popular dose regimens to evaluate whether they produce equivalent efficacy in reducing postoperative bleeding and transfusion needs in cardiac valve surgery.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of this hospital, and written informed consent was obtained from all patients. The study has been registered at Clinical Trial.gov (Identifier NCT01191554).

From February 2009 to February 2010, consecutive patients scheduled for elective cardiac valve surgery (replacement or plasty) were enrolled in the study. Exclusion criteria were as follows: Known allergy to the study drug, preoperative anemia (hemoglobin <100 g/L), history of bleeding disorders, previous cardiac surgery, chronic renal insufficiency (serum creatinine >176.8 μmol/L), active chronic

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hepatitis or cirrhosis, under coumadin treatment within 7 days of surgery, and urgent or emergency surgery.

After enrollment in the study, patients were divided randomly into 2 groups: A lower-dose group (loading dose 10 mg/kg, maintenance dose 2 mg/kg/h, and a CPB prime dose of 40 mg) and a higher-dose group (loading dose 30 mg/kg, maintenance dose 16 mg/kg/h, and a CPB prime dose of 2 mg/kg). All drugs were prepared by an anesthesia nurse who was not involved in clinical treatment. Both the loading and the maintenance doses used in the lower-dose group were diluted to the same volume as in the higher-dose group, as was the dose injected into the CPB prime. After anesthesia induction, the loading dose was administered within 15 minutes followed by the maintenance dose. The lower-dose TA group had the same total infusion volume and speed as the higher-dose group to ensure the blindness of the study.

The envelope method with computer-generated random numbers was used. Another independent anesthesia nurse prepared coded infusions with lower dose or higher dose just before the surgery and was not involved directly in the clinical treatment of the patients. Both operating room and intensive care unit (ICU) staff were blinded to the study group.

All patients received premedication of morphine, 0.20 mg/kg IM. The anesthetic technique was standardized, with fentanyl, 30 to 50 μg/kg, midazolam, 0.10 mg/kg, pipecuronium, 0.15 to 0.20 mg/kg, isoflurane, 0.5% to 2.5%, and propofol, 200 to 500 mg/h. All patients were operated through a full median sternotomy. A heparin dose of 400 IU/kg was administered to obtain an activated coagulation time (ACT) >480 seconds. The CPB circuit was primed with 1L of 6% HES and 600 mL of Ringer's lactate solution. Mild hypothermia with core temperatures of 30°C to 32°C was performed. The pump flow was adjusted to maintain a mean perfusion pressure between 50 and 70 mmHg and a flow index of 2.2 L/min/m^2. Myocardial protection was achieved by intermittent antegrade cold blood cardioplegia. The hematocrit was maintained at least 24% throughout the entire CPB. At the end of the CPB, the effect of heparin was neutralized by protamine with a ratio of 1:1, then with the residue blood in the CPB machine retransfused, additional protamine would be used to reach 1:1.5 at most to make the ACT <130 seconds. Intraoperative cell saver was used in cases of significant intraoperative bleeding.

Allogeneic red blood cells (RBCs) were transfused when hemoglobin concentration was <90 g/L or hematocrit value was $<27\%$. Fresh frozen plasma was transfused when prothrombin, time was 1.5 times longer than baseline together with diffused bleeding. Platelets were transfused when there was diffuse bleeding and platelet count $<50 \times 10^9$/L. Surgical re-exploration was considered when the chest tube drainage was >300 mL/h in the first 2 postoperative hours, or >200 mL/h for 4 consecutive hours with normal coagulation data.

Data on transfusion requirements and perioperative complications were recorded and registered concomitantly by an independent blinded research fellow. The primary outcome was the volume of 24-hour postoperative chest tube drainage. The secondary outcomes included the volume of 6-hour postoperative chest tube drainage, and the number and frequency of allogeneic blood products transfusion. Other secondary outcomes included in-hospital all-cause mortality, stroke, myocardial infarction, renal failure requiring dialysis, wound infections, use of intra-aortic ballon pump, seizure, new-onset ventricular arrhythmia, new-onset atrial fibrillation, reintubation, tracheotomy, duration of mechanical ventilation, ICU length of stay, and hospital length of stay. Stroke was defined as focal neurologic deficit confirmed by brain computed tomography imaging. Myocardial infarction was assessed on the basis of clinical symptoms, electrocardiographic changes (new q-waves on electrocardiogram), creatine kinase isoenzyme MB, and troponin I levels. Duration of mechanical ventilation was measured from the end of surgery to the time of tracheal extubation. ICU and hospital length of stay were measured from the end of surgery until ICU or hospital discharge, respectively. The prolonged CPB is defined as ≥ 120 minutes.

Based on a previous retrospective study in which patients received a dose as in the lower-dose TA group, the chest tube drainage 24 hours after surgery was approximately 620 mL, and the standard deviation was approximately ±210 mL. To detect a 15% reduction (about 100 mL) with 80% power and an alpha level of 0.05 in patients receiving higher-dose TA, 81 patients were required in each group. Therefore, the total sample size should have been 162 patients. Considering the loss rate and for the convenience of randomization, the final sample size was increased to 175 patients.

Statistical analysis was performed with SPSS software (Version 17.0; SPSS, Inc, Chicago, IL). For normal distributed data, all data were described as mean ± standard deviation. Nonparametric data were described as medians and interquartile ranges, and categoric data were described as number of patients and relative frequencies. Chi-square tests or the Fisher exact test were used to analyze categoric variables, and the Student's t test was used to analyze normally distributed data. The normality of distribution was assessed with the Shapiro-Wilk test. All tests were two-sided and conducted in an explorative manner. All p values <0.05 were considered significant.

RESULTS

Patient screening, enrollment, and follow-up data are presented in Figure 1. Of the 175 patients randomized, 88 were allocated to the lower-dose group and 87 to the higher-dose group. No patients in the 2 groups were withdrawn from the study. Therefore, all of the 175 patients' data were analyzed.

No differences were detected in baseline demographic data, preoperative variables, and surgical characteristics between the 2 groups, except the total TA dose (Table 1). There was also no significant difference between groups in the 24-hour postoperative hematologic variables (Table 2).

The amount of postoperative bleeding and the need for allogeneic transfusions are shown in Table 3. There was no significant difference in the volume of postoperative bleeding between the 2 groups at 24 hours after operation. Neither were the amount or frequency of allogeneic RBCs and frozen fresh plasma. The difference of postoperative bleeding at 6 hours, although statistically significant, was not clinically important. Platelet transfusion was rare and the difference between the

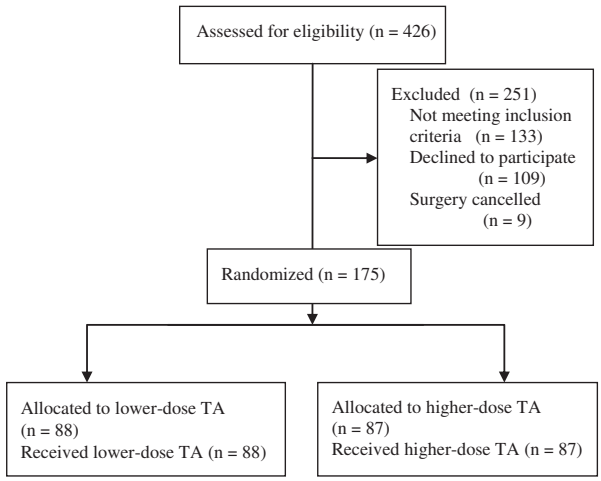

Fig 1. CONSORT diagram showing the flow of participants through each stage of the trial, comparing lower-dose tranexamic acid with higher-dose.