Comparison of the in-vivo Effect of Two Tranexamic Acid Doses on Fibrinolysis Parameters in Adults Undergoing Valvular Cardiac Surgery with Cardiopulmonary Bypass - A Pilot Investigation

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Abstract

Background: The blood saving efficacy of TXA in cardiac surgery has been proved in several studies, but TXA dosing regimens were varied in those studies. Therefore, we performed this study to investigate if there is a dose dependent in-vivo effect of TXA on fibrinolysis parameters by measurement of fibrinolysis markers in adults undergoing cardiac surgery with CPB, which has not been systematically elucidated.

Methods: A double-blind, randomized, controlled prospective trial was conducted from February 11, 2017 to May 05, 2017. Thirty patients undergoing cardiac valve surgery were identified and randomly divided into a placebo group, low-dose group and high-dose group by 1: 1: 1. Fibrinolysis parameters were measured by plasma levels of D-Dimers, plasminogen activator inhibitor-1 (PAI-1), thrombin activatable fibrinolysis inhibitor (TAFI), plasmin-antiplasmin complex (PAP), tissue plasminogen activator (tPA) and thrombomodulin (TM). Those proteins were measured at five different sample times: preoperatively before the TXA injection (T_1), 5 min after the TXA bolus (T_2), 5 min after the initiation of CPB (T_3), 5 min before the end of CPB (T_4) and 5 min after the protamine administration (T_5). A Thrombelastography (TEG) and standard coagulation test were also performed.

Results: Compared with the control group, the level of the D-Dimers decreased in the low-dose and high-dose groups when the patients arrived at the ICU and on the first postoperative morning. Over time, the concentrations of PAI-1, TAFI, and TM, but not PAP and tPA, showed significant differences between the three groups (p <0.05). Compared with the placebo group, the plasma concentrations of PAI-1 and TAFI decreased significantly at the T3 and T4 (p <0.05); TAFI concentrations also decreased at the T5 in low-dose group (p <0.05). Compared with the low-dose group, the concentration of TM increased significantly at the T4 in high-dose group. No significant differences were observed in the levels of the coagulation proteins at any points between the groups.

Conclusions: The vivo effect of low dose TXA is equivalent to high dose TXA on fibrinolysis parameters in adults undergoing valvular cardiac surgery with cardiopulmonary bypass, and we recommend a low dose TXA regimen for those patients.

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Key Points Summary

Question: TXA dosing regimenns vary in adults undergoing cardiac surgery, but the in-vivo effect of two tranexamic acid doses on fibrinolysis parameters has not been systematically elucidated.

Findings: The vivo effect of low dose TXA is equivalent to high dose TXA on fibrinolysis parameters in adults undergoing valvular cardiac surgery with cardiopulmonary bypass.

Meaning: We recommend a low dose TXA regimen for those patients.

Background

Perioperative bleeding induced by cardiopulmonary bypass (CPB) is a major complication of cardiac surgery[1]. Various factors contribute to CPB-induced coagulation dysfunction, and hyperactivation of fibrinolysis is one of the important causes [2]. Tranexamic acid (TXA) is the anti-fibrinolytic drug that is most commonly used during cardiac surgery (Class II, Level A evidence) since aprotinin was withdrawn due to issues with clinical safety[3]. The blood saving efficacy of TXA in cardiac surgery has been proved in several studies [4–6], but the TXA dosing regimenns vary in those studies.

The most commonly used TXA dosing regimenns are the low-dose regimenn reported by Horrow et al.[7] and higher-dose regimenn described by Dowd et al.[8]. Horrow et al. [7] proposed a small-dose dosing regimenn according to one early pharmacokinetic study[9] that confirmed TXA concentrations of 10 ug/ml could provide effective inhibition of fibrinolysis. On the other hand, Dowd et al. believed that TXA concentrations should be greater than 126 ug/ml to achieve 100% inhibition of fibrinolysis, and they proposed a high-dose dosing regimenn. A recent systematic review concluded that TXA concentrations of 10–15 mg/l could lead to a substantial inhibition fibrinolysis[10], but of the 21 included studies, 20 were in vitro and only one was in vivo. This vivo study only enrolled children undergoing cardiac surgery with either continuous or discontinuous TXA schemes[11].

The dose of TXA is potentially important because TXA also increases seizure risk[12]. However, the in-vivo effects of TXA on fibrinolysis parameters in patients undergoing cardiac surgery with cardiopulmonary bypass remain poorly investigated. Therefore, we performed this study to investigate if there is a dose dependent in-vivo effect of TXA on fibrinolysis parameters by measurement of fibrinolysis markers in adult patients undergoing cardiac surgery with CPB, which has not been systematically elucidated.

Methods

This study was approved by The Ethics Committee of Second Affiliated Hospital of Zhejiang University (IRB: 2016-049) and written informed consent was obtained from all subjects participating in the trial. Study protocol was presented as supporting information and the trial was registered prior to patient enrollment at clinicaltrials.gov. A double-blind, randomized, and controlled prospective trial was conducted from February 11, 2017 to May 05, 2017. Inclusion criteria were patients undergoing elective valvular cardiac surgery with CPB, an age greater than 18 years and normal preoperative haemoglobin level (hemoglobin > 120 g/dl for men and > 110 g/dl for women). Exclusion criteria were a history of cerebral infarction, the presence of arterial or venous thrombosis, a history of myocardial infarction in the previous 7 days, preoperative chronic kidney disease [CKD] (serum creatinine (Cr) by 1.6 mg/dL for men and > 1.4 mg/dL for women or needing for renal replacement therapy), preoperative chronic liver disease (grade B or C of the Child-Pugh classification), a previous history of endocarditis, anemia(< 120 g/dl for men and < 110 g/dl for women), hyperlipidemia, heart failure, preoperative shock, treatment with preoperative coagulation medication within 5 days of surgery (warfarin, aspirin, antifibrinolytic or

thrombolytic treatment), preoperative coagulopathy (international normalized ratio (INR) > 1.5, platelet count < $100 \times 10^3/mm^3$, fibrinogen < 1 g/L), previous sternotomy, emergency procedures, endocarditis, complex surgeries (combined with coronary artery bypass graft surgery, aortic surgery, carotid surgery, other nonvalvular surgery, experienced deep hypothermic circulatory arrest), allergy or contraindication to tranexamic acid, pregnancy, and participation in another study.

Thirty patients were identified and randomly divided into a placebo group, low-dose TXA group and high-dose TXA group by 1:1:1 using numbered sealed envelopes. Patients, surgical team, and data investigators were unaware of the group assignments. Intra-operative TXA (Conba Bio-Pharm.Co.,Ltd., Jin-hua Zhe-jiang, 0.5 g/100 ml) was injected into the central vein until the wound dressings were placed by the anesthesiologist. The low-dose scheme was adapted from Horrow et al[7]. and the high-dose method was based on the dosing regimenn reported by Dowd et al[8]. In the low-dose TXA group, patients received a loading dose of 10 mg/kg 15 min after intubation, followed by a 1 $mg_*kg^{-1}{}_*h^{-1}$ infusion. In the high-dose TXA group, a 30 mg/kg bolus was administered, followed by continuous infusion of 16 $mg_*kg^{-1}{}_*h^{-1}$. Additional TXA doses of 1 mg/kg and 2 mg/kg were added to the venous reservoir of the low-dose and high-dose groups, respectively, during CPB. An independent investigator generated the random allocation sequence and informed another independent nurse who prepared the study drug with a 100 ml isotonic solution for bolus administration (TXA concentration: low dose = 0.1 $mg_*kg^{-1}{}_*h^{-1}$; high dose = 0.3 $mg_*kg^{-1}{}_*h^{-1}$) 10 min before administration of TXA. A 50 ml isotonic solution a was continuously infused at a rate of 5 ml/h during the operation (TXA concentration: low dose = 0.2 $mg_*kg^{-1}{}_*h^{-1}$; high dose = 3.2 $mg_*kg^{-1}{}_*h^{-1}$) and a 20 ml syringe contained the priming solution in the venous reservoir (TXA concentration: low dose = 0.05 $mg_*kg^{-1}{}_*h^{-1}$; high dose = 0.1 $mg_*kg^{-1}{}_*h^{-1}$). Other perioperative anesthesia management, blood transfusions strategy and post-operative management strategy was consistent with our previous published study[13].

Blood samples were collected into tubes containing 3.8% sodium citrate from the internal jugular vein at the following sample points: (i) preoperatively before TXA injection (baseline), (ii) 5 min after the administration of the TXA bolus (bolus), (iii) 5 min after the onset of CPB (CPB), (iv) 5 min before the end of CPB (end of CPB) and (v) 5 min after the protamine injection (protamine). The tube was immediately placed in a 4 °C refrigerator, centrifuged for 20 min at 3000 rpm at 4 °C within 1 h, and then stored at -80 °C until further testing.

Primary outcome

Intraoperative plasma levels of the following coagulation proteins were measured: plasminogen activator inhibitor-1 (PAI-1), thrombin activatable fibrinolysis inhibitor (TAFI),plasmin-antiplasmin complex (PAP), tissue plasminogen activator (tPA), and thrombomodulin (TM). An independent investigator assayed the plasma concentrations of those coagulation proteins with enzyme immunoassays according to the manufacturer's instructions (ELISA; Shanghai Jianglai Biotech, Shanghai, China). The details of those coagulation proteins are presented in supplemental Table 1. The changes in the concentrations of

coagulation proteins caused by hemodilution were corrected using the following formula: corrected concentration = (sample blood concentration × baseline blood hematocrit)/sample blood hematocrit [14].

Secondary outcome: Intra-operative standard coagulation test and TEG tests were performed. Postoperative laboratory data was collected when arriving at ICU and in the first post-operative morning. Demographic and surgical data was also collected.

Statistical Methods

Given that there are no published studies to guide a power calculation, which investigate in-vivo effect of two tranexamic acid doses on fibrinolysis parameters in adults undergoing cardiac surgery. One-way analysis of variance (ANOVA) was applied and the type I error was assumed by 0.05, we estimated that 7 patients were required for each group to provide 95% power to detect an effect of different doses of TXA on successively changing 33% of the activity of the fibrinolytic system when the standard deviation of coagulation proteins concentration was limited to within 20%. A target sample size of 30 was chosen based in this pilot investigation.

The variables with a normal distribution are reported as means ± standard deviations (SD), and continuous variables with a non-normal distribution are reported as medians (interquartile ranges). ANOVA followed by the Bonferroni test were used to compare continuous variables with a normal distribution, and Welch's test was adopted when variance existed between the groups and the different time points. The homogeneity of variance was analyzed using Mauchly's test of sphericity and corrected with the Greenhouse-Geisser test if variance existed. Differences in the concentrations of coagulation proteins between the groups measured at the same time points were analyzed using two-way ANOVA followed by the Bonferroni test. The Kruskal-Wallis H test was applied to continuous variables with a non-normal distribution. The Chi-squared or Fisher's exact test followed by the Bonferroni test was used to analyze categorical data. All reported *P* values were two sided, and *P* values less than 0.05 were considered significant. Missing data was less than 10% and was not replaced. Intention to treat analysis was used and analysis was performed with SPSS version 18 (IBM, Armonk, NY) and G-Power (version 3.1; Informer Technologies, Inc.).

Results

Baseline Parameters and Operative Characteristics

Of 146 patients who underwent cardiac surgery with CPB, 30 patients participated in and completed the follow- up of this study, and 116 patients met the exclusion criteria as shown in Fig. 1. The basic clinical features of the three groups are presented in Supplemental Table 2 and no difference was observed.

The average age of the participations was 58 years, 60% were female, 93.3% had ASA (American Society of Anesthesiologists) class III and the other patients had ASA grade IV, 20% had NYHA (New York Heart

Association) grade III and 6.7% had grade IV. The average score of the European Cardiovascular Surgery Risk Factor Scoring System (EuroSCORE) was 1.6, and the average score for the bleeding risk was only 0.8. 36.7% of patients underwent aortic valve surgery, 23.3% underwent mitral valve surgery, 36.7% underwent surgery on multiple valves, and only one patient underwent simple tricuspid valve surgery.

Perioperative Fibrinogen, D-Dimers and TEG test

Compared with the control group, the level of the D-Dimers decreased in the low-dose and high-dose groups when the patients arrived at the ICU and on the first postoperative morning, but no differences were observed in other measurement points. Compared with the control group, fibrinogen measured on the first post-operative morning was increased in high-dose groups, but no differences were observed in other measurement points. Significant differences in intra-operative standard coagulation tests and TEG analysis were not observed (Table 1 and Supplemental Table 3).

Intra-operative levels of coagulation proteins involved in thrombin generation and the fibrinolytic response

Over time, the plasma concentrations of PAI-1, TAFI, and TM, but not PAP and tPA, showed significant differences between the three groups ($p < 0.05$) (Table 2).

Compared with the placebo group, the plasma concentrations of PAI-1 (Fig. 2A) and TAFI (Fig. 2B) decreased significantly at the T3 and T4 sample points ($p < 0.05$); TAFI concentrations also decreased at the T5 sample point in the low-dose group ($p < 0.05$). No significant differences were observed in the levels of the coagulation proteins at any other sample points between the three groups (Fig. 2C for PAP and Fig. 2D for tPA). Compared with the low-dose group, the plasma concentration of TM (Fig. 2E) increased significantly at the T4 sample point in the high-dose group ($p < 0.05$) (Table 2).

Postoperative clinical data and Standard coagulation test

Compared with the low-dose group, a lower hematocrit was observed when patients in the high-dose group arrived at the ICU ($p < 0.05$), but a significant difference was not observed on the first postoperative morning. No differences were observed in other clinical data and standard coagulation test (Supplemental Table 4).

Discussion

In this study, we found that the vivo effect of low dose TXA is equivalent to high dose TXA on fibrinolysis parameters in adults undergoing valvular cardiac surgery with cardiopulmonary bypass with a low bleeding risk. Our study support previous studies [4, 5], which showed that low dose TXA is equivalent to high dose TXA in efficacy. Furthermore, the increasing TM produces in the high dose TXA regimen, which raises the potential concern on the safety of high-dose TXA.

D-dimer is a fragment of fibrin produced after hydrolysis by a fibrinolytic enzyme. Compared with the placebo group, we found that the D-dimer level, was significantly decreased in patients receiving both the two TXA doses upon their arrival at the ICU and on the first postoperative morning. We also noticed that although no difference of D-dimer was found between the two TXA doses, it seemed that there was a dose dependent effect of TXA on D-dimer. Although fibrinogen measured on the first post-operative morning was increased in high-dose groups as compared to control group, no difference was found between the two TXA doses. We speculated that TXA would not achieve greater inhibition of fibrinolytic activity when TXA exceeds a certain plasma concentration. This finding may support the hypothesis proposed in a previous study of a platform effect of TXA on inhibiting fibrinolysis[15], and a higher TXA dose should be used with caution in clinical practice.

This small sample study did not observe dose-dependent changes in the levels of tPA and PAP between groups treated with the two TXA doses regimens. The plasmin that was produced during CPB mainly interacted with α2-antiplasmin (α2-AP) to form PAP[2], which would conversely inactivate plasmin. According to another previous study, aminocaproic acid does not inhibit the formation of active plasmin and reduce PAP levels[16], and the peak PAP concentration was detected during the postoperative period[17]. The concentration of tPA increased immediately after CPB began and continued to increase throughout the entire surgical period. However, tPA levels were similar in the groups treated with the two TXA doses and placebo. A previous study examining the kinetics of aprotinin-mediated inhibition of plasmin reported similar results showing similar tPA levels in the aprotinin and placebo groups[18]. However, the authors noticed that tPA concentrations mainly increased during CPB, but PAI-1 concentrations gradually increased after CPB, which is inconsistent with the findings of our study [18]. We noticed that the levels of proteins that promote (tPA and PAP) and inhibit fibrinolysis (PAI-1 and TAFI) were both increased 5 min after CPB began, and then they reached new balanced levels. This discrepancy might due to the analysis of participants with a low bleeding risk and a relatively low degree of intra-operative fibrinolytic activity. Therefore, the participants with a pre-operative normal coagulation function likely readily reached a new fibrinolytic balance.

Many possible factors may also explain the different results. First, although the active tPA and plasmin levels increase approximately 5-fold during CPB, approximately one third of patients might not show any change[19]. Second, the effect of TXA is mediated by many proteins involved in the coagulation process including kallikrein, activated protein C, and thrombin[20]; therefore, different TXA doses may reduce bleeding through different mechanisms. Third, the difference also might due to a relatively low degree of fibrinolytic activity during CPB in adults with a low bleeding risk who are undergoing cardiac valvular surgery. Compared with the levels measured before CPB, the concentrations of tPA and other coagulation proteins during CPB were approximately 1.5 times higher in this study, which differ from a previous study reporting that the active tPA concentration increases approximately 5 times[21]. This effect might be due to the improved compatibility of CPB materials and improved CPB and surgical technologies, which would minimize fibrinolytic activation during CPB, thereby preventing the excessive consumption of coagulation proteins, fibrinogen, and platelets. We speculated that the effect of intraoperative TXA-

mediated tPA inhibition on fibrinolysis may be overestimated, and this effect on inhibiting fibrinolytic activity may occur after protamine antagonism or during the postoperative period.

A randomized, controlled, prospective trial showed that TXA (100 mg/kg) suppressed fibrinolysis by inhibiting tissue plasminogen activator (tPA) and plasmin activity, however, TXA did not affect other important fibrinolytic inhibitors, such as plasminogen activator inhibitor-1 (PAI-1) and α_2-antiplasmin[22]. Similar to the changes in tPA levels, PAI-1 levels do not change in approximately one-third of patients after surgery[23]. PAI-1 prevents plasmin formation. PAI-1 levels increase 15-fold only 2 h after surgery[24], and the levels are maintained until the first postoperative day.

TXA preserves the size and strength of the thrombus in a rat model of a simulated arterial aneurysm [25]. So we also measured TM, a marker of vascular endothelial function[26], increases in TM in patients with coronary atherosclerosis[27]. Compared with the low TXA group, we found that TM increased significantly at 5 minutes after CPB in the high-dose group. Thrombotic complications tend to form when endothelial dysfunction exists. TXA increases the risk of thrombus formation in a dose-dependent manner both in vitro and in vivo. This finding differs from aprotinin, which inhibits thrombus formation[28]. TXA not only reduces the carotid artery occlusion time but also increases the stiffness of the thrombus in a rat model of ferric chloride-induced thrombosis[29]. Increased thrombosis has been observed after treatment with different TXA doses (30,100 and 300 $mg_{*}kg^{-1}{}_{*}h^{-1}$) in vitro and in vivo animal models designed to evaluate fibrinolysis and thrombus formation[30]. Importantly, fibrinolysis decreases after surgery. Furthermore, individual variability in the response to CPB was another reason why the prediction of patients at risk for bleeding or thrombosis is difficult to determine. The increasing TM produces in the high dose TXA regimen in this study, which raises the potential concern on the safety of high-dose TXA.

Our results were consistent with previous studies[15] that standard coagulation test and TEG test did not reflect a difference in the effects of the two TXA doses on inhibiting fibrinolysis in patients undergoing cardiac surgery with CPB. Previous study found that a ROTEM examination could only detect significant fibrinolysis[31].

Hemodilution may mask potential changes in the levels of those proteins during CPB[32]. CPB decreases the plasma concentrations of all factors by approximately 30–40% (including coagulation factors, thrombin inhibitors, and coagulation activation markers)[33]. The basic rates of changes in the levels of those factors were difficult to determine and evaluate when those data were used. Most studies used the corresponding sample marker concentration as activation data without considering the effects of hemodilution and all proteins were diluted equally during CPB.

Limitations

This study has several limitations. First, the total sample was relatively small. It is impossible to know if the differences reported in term of biomarkers would translate into a clinically meaningful difference in

term of bleeding and transfusion, and other outcomes. This pilot investigation study was aimed to compared the in-vivo effect of two TXA doses on fibrinolysis parameters in adults undergoing valvular cardiac surgery and the blood saving efficacy of TXA in cardiac surgery has been proved in several studies [4–6]. As shown in this study, the vivo effect of low dose TXA is equivalent to high dose TXA on fibrinolysis parameters and no further improvement was observed for high dose TXA. So we suggested a low dose TXA regimen for those patients with a low bleeding risk. Second, the plasma TXA concentration was not monitored at different sample points during the study. However, many previous studies have investigated plasma TXA concentrations in patients treated with different TXA doses[34]. Third, this study evaluated postoperative coagulation function only by performing a standard coagulation test and failed to monitor postoperative levels of coagulation proteins, which require further exploration in a future study.

Conclusions

The vivo effect of low dose TXA is equivalent to high dose TXA on fibrinolysis parameters in adults undergoing valvular cardiac surgery with cardiopulmonary bypass. Furthermore, the increasing TM produces in the high dose TXA regimen, which raises the potential concern on the safety of high-dose TXA. We recommend a low dose TXA regimen for those patients with a low bleeding risk.

List Of Abbreviations

Not applicable

Declarations

Ethics approval and consent to participate:

This study was approved by The Ethics Committee of Second Affiliated Hospital of Zhejiang University (IRB2016-049) and written informed consent was obtained from all subjects participating in the trial.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Availability of data and materials:

All data analysed during this study are included in this published article [Additional file].

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Authors' contributions:

ZZf and YM: Those authors helped design the study and wrote the paper. ZW and SK: Those authors helped perform statistical analysis. YLn, SLh and XXf: Those authors helped do the work of patient recruitment and data collecting. All authors have read the manuscriptand and approved the final paper submitted.

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Tables

Table 1:

Perioperative Fibrinogen, D-Dimers and TEG test at different time points between the three groups.

	placebo group (n = 10)	low dose group (n = 10)	high dose group (n = 10)	P-value
Fibrinogen [mean(SD); g/L]				
Preoperative	3.2 ± 0.9	3.0 ± 0.4	3.5 ± 1.1	0.408
Intra-operative period				0.786
T_1	3.1 ± 0.8	3.1 ± 0.4	3.4 ± 0.8	
T_2	3.0 ± 0.9	2.9 ± 0.4	3.2 ± 0.8	
T_3	1.43 ± 0.30	1.55 ± 0.25	1.50 ± 0.35	
T_4	1.7 ± 0.4	1.8 ± 0.4	1.7 ± 0.5	
T_5	1.7 ± 0.5	1.9 ± 0.4	1.8 ± 0.5	
when arriving at ICU	2.0 ± 0.5	2.1 ± 0.4	2.1 ± 0.5	0.875
in the first post-operative morning	2.9 ± 1.1	3.1 ± 1.2	4.3 ± 0.8*	0.027
D-Dimer [median(IQR); ug/L]				
Preoperative	290(213–705)	235(188–518)	280(210–665)	0.715
Intra-operative period				0.465
T_1	305(255–470)	305(228–445)	295(220–500)	
T_2	330(270–490)	315(270–443)	295(220–545)	
T_3	305(248–370)	220(220–270)	235(220–308)	
T_4	750(415–1133)	420(318–555)	280(220–393)	
T_5	745(430–1343)	480(235–605)	255(220–373)	
when arriving at ICU	1540(1078–1900)	555(483–770)*	260(220–440)#	< 0.001
in the first post-operative morning	1530(1030–2155)	710(520–1070)*	540(405–880)#	0.008

*: Low-dose group compared with placebo group; #: High-dose group compared with placebo group; §: High-dose group compared with Low-dose group. T_1 = per-operatively before TXA injection (baseline); T_2 = 5 min after TXA bolus administration (bolus); T_3 = 5 min after the onset of CPB (CPB); T_4 = 5 min before the end of CPB (End of CPB); T_5 = 5 min after protamine injection (protamine).

Continue Table 1: Perioperative Fibrinogen, D-Dimers and TEG test at different time points between the three groups.

	placebo group (n = 10)	low dose group (n = 10)	high dose group (n = 10)	P-value
TEG-R [mean(SD); min]				0.439
T_1	6.8 ± 1.7	5.9 ± 1.1	5.7 ± 1.0	
T_2	6.3 ± 1.9	6.4 ± 1.4	5.5 ± 0.8	
T_5	5.9 ± 1.5	7.9 ± 2.7	6.7 ± 3.2	
TEG-K [median(IQR); min]				0.551
T_1	1.75(1.68–2.50)	1.60(1.40–1.85)	1.35(1.15–1.63)	
T_2	2.00(1.30–2.45)	1.85(1.55–1.93)	1.65(1.20–2.05)	
T_5	2.40(1.85–3.05)	2.30(2.00-3.10)	2.60(1.85–3.20)	
TEG-Angle[mean(SD); °]				0.420
T_1	68.8 ± 7.0	72.1 ± 3.3	74.3 ± 2.3	
T_2	70 ± 5	68 ± 9	73 ± 4	
T_5	68 ± 5	65 ± 8	66 ± 7	
TEG-MA [mean(SD); mm]				0.618
T_1	63 ± 6	64 ± 3	66 ± 4	
T_2	62 ± 5	63 ± 4	66 ± 4	
T_5	52 ± 6	52 ± 5	51 ± 9	
TEG-EPL [median(IQR); %]				0.779
T_1	0.20(0-0.90)	0(0-0.18)	0(0-0.38)	
T_2	0(0-0.20)	0(0-0.03)	0(0-0.10)	
T_5	0(0-0.80)	0(0-0.45)	0(0-0.85)	
TEG-A[mean(SD); mm]				0.600
T_1	62 ± 6	63 ± 4	65 ± 6	
T_2	62 ± 5	62 ± 5	65 ± 6	
T_5	50 ± 6	51 ± 7	51 ± 10	
TEG-LY30[median(IQR); %]				0.427

T_1	0(0-0.25)	0(0-0.13)	0(0-0.23)	
T_2	0(0-0.05)	0(0-0.03)	0(0-0.10)	
T_5	0(0-0.8)	0(0-0.45)	0(0-0.85)	
TEG-CI[median(IQR)]				0.433
T_1	0.8(-1.2-1.2)	1.0(0.5–1.7)	1.8(1.3–2.6)	
T_2	-0.2[(-1.0)-2.2]	0.9[(-0.6)-1.7]	1.4(0.6–2.4)	
T_5	-0.9[(-2.5)-(-0.2)]	-2.1[(-5.2)-(-0.4)]	-1.5[(-2.9)-0.7]	

T_1 = per-operatively before TXA injection (baseline); T_2 = 5 min after TXA bolus administration (bolus); T_3 = 5 min after the onset of CPB (CPB); T_4 = 5 min before the end of CPB (End of CPB); T_5 = 5 min after protamine injection (protamine). R = Reaction time; MA = maximum amplitude; A = amplitude of clot firmness after clotting time; CI = coagulation index.

Table 2:

Coagulation proteins at different time points between the three groups.

	placebo group (n = 10)	low dose group (n = 10)	high dose group (n = 10)	P-value
PAI-1 [mean(SD); ng/mL]				0.032
T_1	23.7 ± 2.5	22.9 ± 2.5	24.1 ± 2.2	
T_2	28.2 ± 1.9	27.6 ± 2.8	28.4 ± 1.9	
T_3	56 ± 5	50 ± 7*	57 ± 6	
T_4	52 ± 6	45 ± 8*	51 ± 6	
T_5	43.0 ± 2.2	39.6 ± 7.9	43.2 ± 4.5	
TAFI [mean(SD); ng/mL]				0.046
T_1	17.5 ± 1.6	18.1 ± 1.1	16.4 ± 0.7	
T_2	20.9 ± 1.7	21.8 ± 2.0	21.5 ± 1.6	
T_3	43.0 ± 2.9	37.1 ± 4.4*	40.5 ± 5.2	
T_4	37 ± 5	32 ± 6*	37 ± 5	
T_5	33.5 ± 2.2	29.4 ± 4.1*	32.5 ± 3.6	
PAP [mean(SD); ng/mL]				0.176
T_1	14.2 ± 2.0	15.8 ± 1.5	13.3 ± 2.1	
T_2	19.7 ± 2.4	20.2 ± 2.3	19.7 ± 2.5	
T_3	42 ± 4	39 ± 6	45 ± 8	
T_4	37 ± 7	34 ± 7	39 ± 6	
T_5	31 ± 6	28 ± 3	33 ± 5	
tPA [mean(SD); ng/mL]				0.113
T_1	3.0 ± 0.3	3.5 ± 0.4	3.3 ± 0.6	
T_2	3.67 ± 0.37	4.24 ± 0.55	4.17 ± 0.24	
T_3	7.9 ± 1.2	7.5 ± 1.6	8.3 ± 1.1	
T_4	6.6 ± 1.1	6.3 ± 1.0	7.2 ± 1.1	

T_5	5.7 ± 1.1	5.6 ± 0.7	6.3 ± 0.9	
TM [mean(SD); ng/mL]				0.019
T_1	1.37 ± 0.14	1.55 ± 0.15	1.57 ± 0.14	
T_2	1.69 ± 0.16	1.65 ± 0.15	1.72 ± 0.18	
T_3	3.5 ± 0.5	3.2 ± 0.5	3.7 ± 0.6	
T_4	2.9 ± 0.4	2.6 ± 0.5	3.3 ± 0.7§	
T_5	2.66 ± 0.48	2.24 ± 0.32	2.57 ± 0.28	

*: Low-dose group compared with placebo group;§: High-dose group compared with Low-dose group. PAI-1: plasminogen activator inhibitor-1, TAFI: thrombin activatable fibrinolysis inhibitor, PAP: plasmin-antiplasmin complex, tPA: tissue plasminogen activator, TM: thrombomodulin. T_1: per-operatively before TXA injection (baseline); T_2: 5 min after TXA bolus administration (bolus); T_3: 5 min after the onset of CPB (CPB); T_4: 5 min before the end of CPB (End of CPB); T_5: 5 min after protamine injection (protamine).

Figures

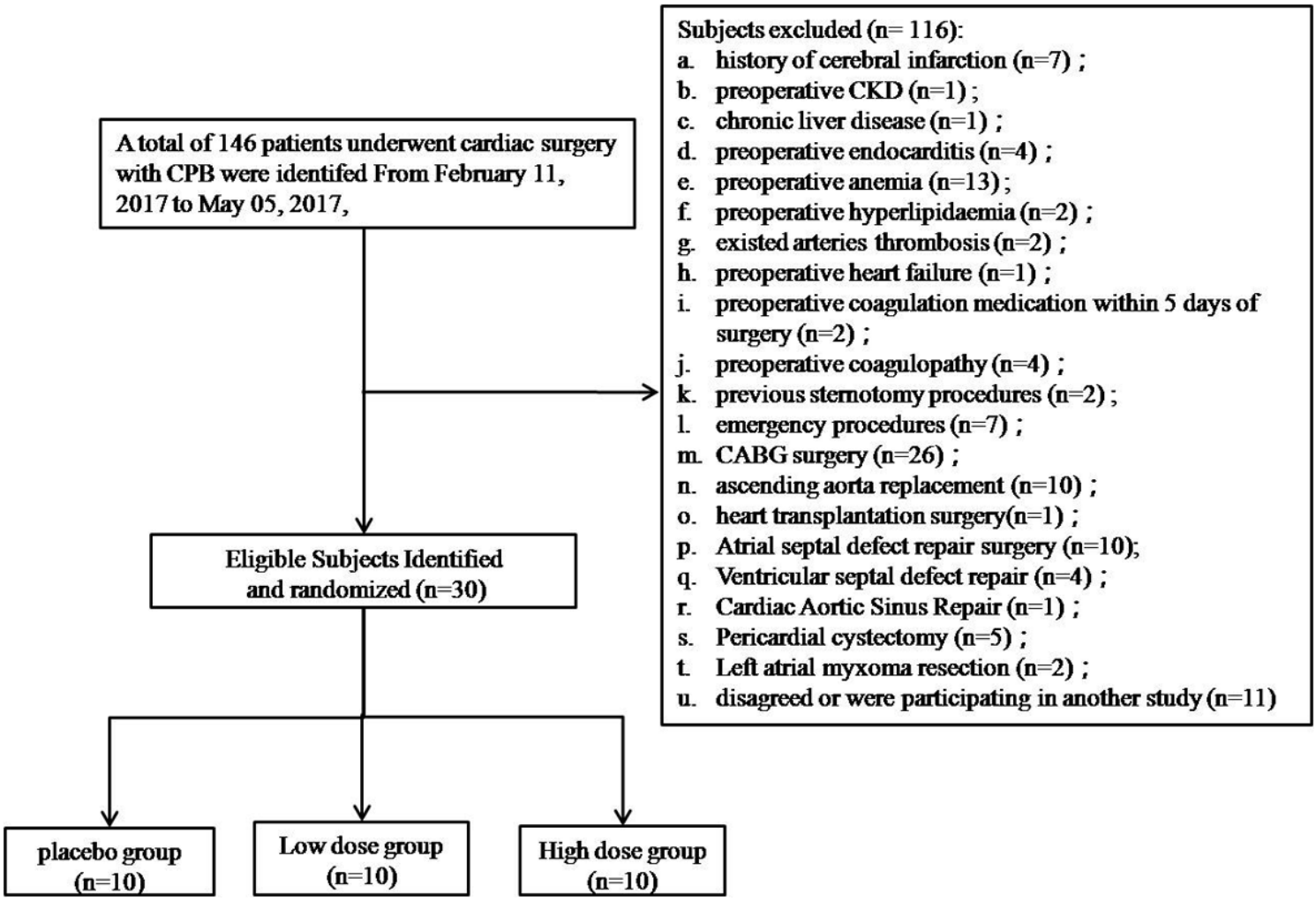

Figure 1

Study flowchart Study population recruitment summary.

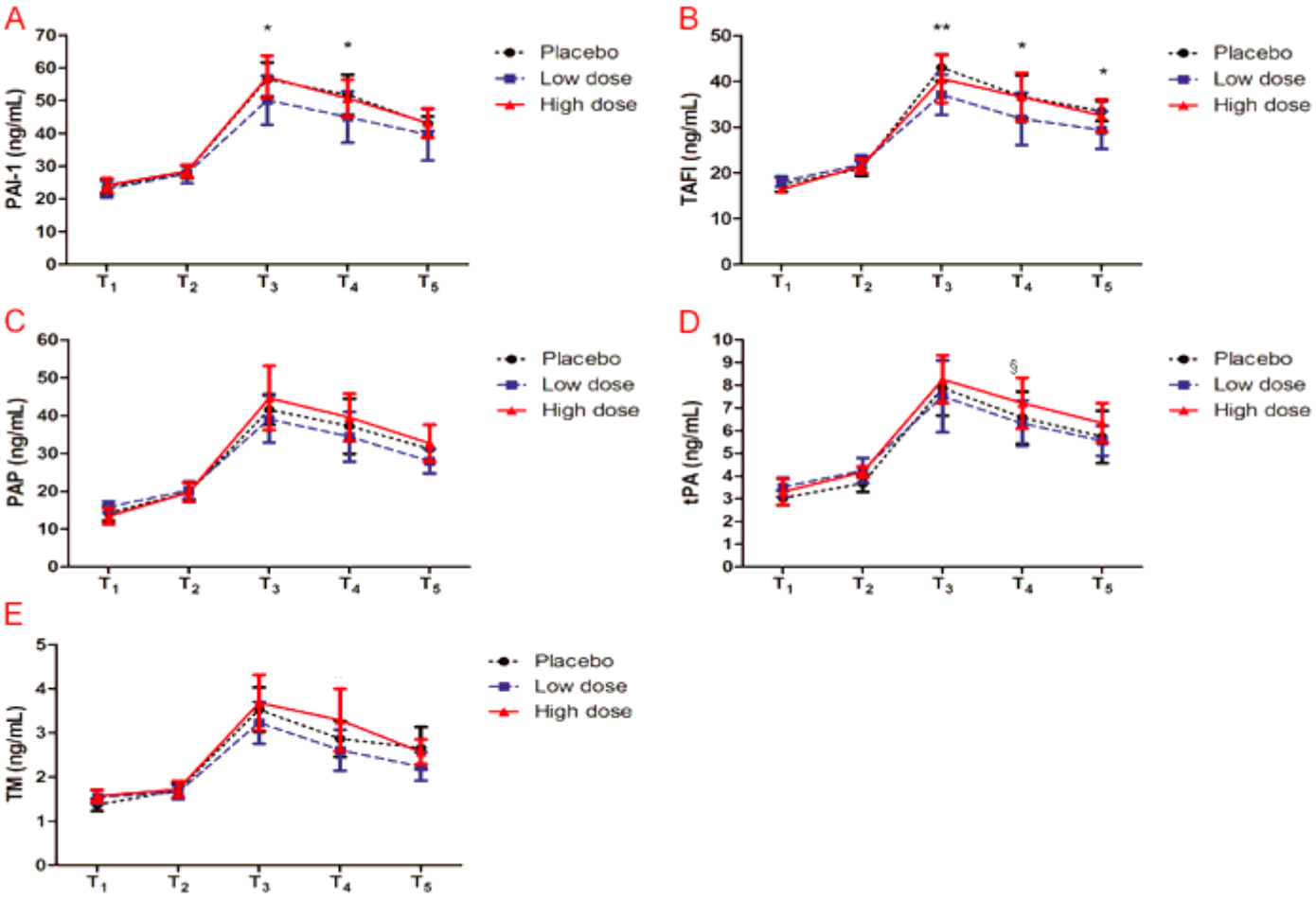

Figure 2

Concentration curves of Coagulation proteins at different sample points between the three groups. PAI-1: plasminogen activator inhibitor-1, TAFI: thrombin activatable fibrinolysis inhibitor, PAP: plasmin-antiplasmin complex, tPA: tissue plasminogen activator, TM: thrombomodulin. T1: per-operatively before TXA injection (baseline); T2: 5 min after TXA bolus administration (bolus); T3: 5 min after the onset of CPB (CPB); T4: 5 min before the end of CPB (End of CPB); T5: 5 min after protamine injection (protamine). *: Low-dose group compared with placebo group; §: High-dose group compared with Low-dose group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- S6CONSORTChecklist.doc
- S7Studydata.xlsx
- S5Studyprotocol.doc
- S4SupplementalTable4.doc
- S3SupplementalTable3.doc

- S2SupplementalTable2.doc
- S1SupplementalTable1.doc