INFLUENCE OF DIFFERENT DOSES OF TRANEXAMIC ACID ON EARLY AND TOTAL POSTOPERATIVE BLEEDING IN NON-ANAEMIC PATIENTS UNDERGOING ON-PUMP CARDIAC SURGERY

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Abstract

Introduction: Postoperative bleeding is frequent and clinically significant complication after cardiac surgery due to its invasive nature, cardiopulmonary bypass and perioperative anticoagulation. Excessive bleeding is associated with re-exploration, prolonged intensive care unit stay, increased morbidity and increased mortality. Antifibrinolytic therapy, particularly tranexamic acid (TXA), is strongly recommended to reduce bleeding and transfusion requirements, yet the optimal dosing strategy remains uncertain.

Aim: To assess the influence of three different doses of TXA on early and total postoperative bleeding in non-anaemic patients undergoing on-pump cardiac surgery.

Material and Methods: Prospective, randomized, single-center study of 180 non-anaemic patients, randomized in three TXA dosing groups, low-dose 20mg/kg, medium-dose 35mg/kg and high-dose 50mg/kg. The following outcomes were monitored: postoperative bleeding at 4, 12, 24 hours, total postoperative bleeding, and surgical revision due to bleeding or cardiac tamponade.

Results: Bleeding volumes did not differ significantly between TXA dosing groups at any predefined postoperative interval (0–4 hours, $p = 0.470$; 4–12 hours, $p = 0.853$; 12–24 hours, $p = 0.199$), nor for cumulative bleeding after 24 hours ($p = 0.647$) or total postoperative bleeding ($p = 0.758$). In multivariable models, TXA dose was not an independent predictor of early postoperative bleeding, with no significant differences for low-dose ($B = 0.136$, $p = 0.214$) or medium-dose TXA ($B = 0.182$, $p = 0.087$) compared with the high-dose group. Similarly, TXA dose was not associated with total postoperative bleeding (low-dose: $B = 0.019$, $p = 0.785$; medium-dose: $B = -0.011$, $p = 0.870$). Aortic

valve surgery was associated with significantly lower total postoperative bleeding compared with combined procedures (B = −0.393, 95% CI −0.592 to −0.194; p < 0.001).

Conclusion: These findings do not support routine escalation of tranexamic acid dosing.

Key Words: *Cardiac surgery, Postoperative bleeding, Tranexamic acid.*

Introduction

Because of its invasive nature, usage of cardiopulmonary bypass (CPB) and perioperative anticoagulation, postoperative bleeding still remains a common and clinically relevant complication following cardiac surgery. Excessive bleeding is associated with higher rates of surgical re-exploration, prolonged intensive care unit (ICU) stay, increased morbidity, overall increased healthcare utilization and is an independent risk factor associated with increased mortality (1). Antifibrinolytic therapy, as procoagulant intervention, is recommended to reduce bleeding and transfusion of blood products and reoperation for bleeding in cardiac surgery, Class 1, Level A recommendation (2). Tranexamic acid (TXA), synthesized for the first time in 1962 and added on the WHO essential medicines list from 2011, is a widely used antifibrinolytic agent. While its efficiency in reducing blood loss and transfusion requirements is well established uncertainty still remains regarding the optimal dose and dosing strategies. There is evident heterogenicity in the literature regarding TXA doses, dosing regimens and the optimal dose that maximizes efficiency while avoiding unnecessary drug exposure. Furthermore, postoperative bleeding is the most common cause of postoperative anaemia. The decision for transfusion can generally be influenced by the institutional protocols (3), clinical judgement and patient related factors and may not accurately represent the true extent and dynamics of postoperative haemorrhage. Quantification of postoperative bleeding in non-anaemic patients, especially during the early postoperative period can provide a more objective and physiologically relevant assessment of perioperative haemostasis when fibrinolytic activity is most pronounced. The aim of this study is to evaluate the influence of three different doses of tranexamic acid administered once prophylactically on early and total postoperative bleeding, to analyse the temporal pattern of postoperative bleeding across the different doses of TXA in non-anaemic patients undergoing on-pump cardiac surgery, and to compare the incidence of surgical revision for bleeding and tamponade across the different TXA dosing groups.

Material and Methods

This prospective, randomized, controlled, single-center study was conducted in Acibadem-Sistina Hospital Skopje, at the department of Cardiac Surgery, from 05.2024 till 5.2025. The study protocol was approved by the institutional ethics committee and written consent

was obtained from all participants prior to their enrolment. Adult non-anaemic patients older than 18 years of age with written consent scheduled for elective or urgent Aortocoronary bypass, Aortic valve or combined on-pump cardiac surgery were included. Non-anaemic patients were defined according to the Guideline on haemoglobin cutoffs to define anaemia by the WHO (4), men with Hgb ≥ 130g/L and women with Hgb ≥ 120g/L. Exclusion criteria were: patients with allergy to TXA; anaemic patients, men with Hgb < 130g/L and women with Hgb < 120g/L (4); patients for elective or urgent surgery on the Aorta, Mitral valve, off-pump and Re-Do cardiac surgery; pregnant patients; patients with chronic kidney disease stadium 4 and 5; patients with thrombocytopenia or other coagulation disorders; patients with hypercoagulability syndrome or prior thromboembolic event; patients with positive history of convulsive disorder or prior use of anticonvulsive therapy; patients on vitamin K antagonists ≤5 days prior to surgery or INR >1,5; patients on direct oral anticoagulants (DOAC) ≤2 days prior to surgery; patients on oral P2Y12 inhibitors without the recommended pause time before surgery, Ticagrelor ≤2 days, Clopidogrel ≤4 days and Prasugrel ≤6 days. All of the included patients were analysed with the intention to treat.

Patients were randomly allocated on the day of hospitalisation using a computer-generated list of random numbers. Allocation concealment was ensured with a closed opaque envelope in three equal study groups depending on the dose of TXA administered once prophylactically. High dose group (n=60) TXA 50mg/kg was administered, medium dose group (n=60) TXA 35mg/kg was administered and low dose group (n=60) TXA 20mg/kg was administered. The choice of the studied doses of TXA is within the safety margin doses according to the International Society for Minimally Invasive Cardiothoracic Surgery (5), according to the guidelines for perioperative care in cardiac surgery of Enhanced Recovery After Surgery Society (6) and according to the data of the meta-analysis for optimal dosing of TXA in cardiac surgery by Zufferey et al. (7). The assigned dose of tranexamic acid was administered intravenously 45 minutes prior to skin incision. All patients underwent standardized intraoperative management according to the institutional protocols. Postoperative care was standardized and provided under the supervision of multidisciplinary heart team.

During the study the following data was monitored: postoperative bleeding, thoracic drains output measured in millilitres at 4, 12 and 24 hours; total postoperative bleeding, total postoperative drainage measured in millilitres till removal of thoracic drains; surgical revision for bleeding and surgical revision for tamponade. Continuous data with normal and non-normal distribution is presented as mean with standard deviation and median with interquartile range accordingly. Categorical data is presented as absolute or relative frequencies. Baseline comparability across the randomized groups is analysed with ANOVA or Kruskal-Wallis test as appropriate, and with Chi square or Fischer’s exact test.

The primary analysis of the influence of different TXA dosing groups on bleeding is presented as median with interquartile range, analysed with Kruskal-Wallis test for each bleeding point, and dose dependent response trend is analysed with Jonckheere-Terpstra test for early bleeding, at 4 hours, and total postoperative bleeding. A generalized linear model (gamma distribution with log link) is used to identify weather tranexamic acid is an independent predictor of early and total postoperative bleeding. To evaluate postoperative bleeding trajectories at 4, 12 and 24 hours across TXA groups a linear mixed-effects model is used. The incidence of revision for bleeding and tamponade is presented as absolute and relative frequency, comparison between the groups is analysed with Fisher's exact test. All monitored data was analysed using SPSS statistical software, version 26.0. Statistical significance was defined as p value < 0.05.

Results

A total of 180 non-anaemic patients undergoing on-pump cardiac surgery were enrolled to three TXA dosing groups. No statistically significant differences were observed between the randomized groups at baseline. Demographic data, medical history, and preoperative laboratory parameters are summarized in Table 1.

Table 1. Baseline data across low, medium and high-dose TXA groups

	low-dose TXA (20mg/kg)	medium-dose TXA (35mg/kg)	high-dose TXA (50mg/kg)	p value
Gender Male / Female	32 (53,3%) / 28 (46,7%)	38 (63,3%) / 22 (36,7%)	39 (65%) / 21 (35%)	0,368
Age (year)	66 (62-73)	69,5 (65-73,7)	66,5 (62,2-73,7)	0,295
BMI (kg/m²)	28,8 (25,8-31,2)	27,5 (24,9-31,5)	28,1 (25,5-32,4)	0,805
ASA				0,947
2	10 (16,7%)	12 (20%)	11 (18,3%)	
3	49 (81,7%)	47 (78,3%)	47 (79,5%)	
4	1 (1,6%)	1 (1,7%)	2 (2,2%)	
Hypertension Yes / No	57 (95%) / 3 (5%)	57 (95%) / 3 (5%)	60 (100%) / 0 (0%)	0,212
COPD Yes / No	7 (11,7%) / 53 (88,3%)	11 (18,3%) / 49 (81,7%)	6 (10%) / 54 (90%)	0,364
Chronic kidney disease Yes / No	24 (40%) / 36 (60%)	16 (26,7%) / 44 (73,3%)	16 (26,7%) / 44 (73,3%)	0,190
Diabetes Melitus Yes / No	21 (35%) / 39 (65%)	23 (38,3%) / 37 (61,7%)	23 (38,3%) / 37 (61,7%)	0,909
Peripheral artery disease Yes / No	10 (16,7%) / 50 (83,3%)	17 (28,3%) / 43 (71,7%)	13 (21,7%) / 47 (78,3%)	0,304
Cerebrovascular incident Yes / No	7 (11,7%) / 53 (88,3%)	7 (11,7%) / 53 (88,3%)	2 (3,3%) / 58 (96,7%)	0,180
Myocardial infarction Yes / No	10 (16,7%) / 50 (83,3%)	9 (15%) / 51 (85%)	7 (11,7%) / 53 (88,3%)	0,730
Previous PCI Yes / No	7 (11,7%) / 53 (88,3%)	9 (15%) / 51 (85%)	10 (16,7%) / 50 (83,3%)	0,730
NYHA (1-4)				0,794
1	1 (1,7%)	2 (3,3%)	1 (1,7%)	
2	25 (41,6%)	21 (35%)	24 (40%)	
3	33 (55%)	35 (58,4%)	31 (51,6%)	
4	1 (1,7%)	2 (3,3%)	4 (6,7%)	
Euro SCORE II (%)	2,06 (1,15-2,74)	2 (1,16-3,88)	1,74 (1,04-3,2)	0,481
STS risk score (%)	1,11 (0,73-1,72)	1,26 (0,74-1,83)	1,06 (0,54-2)	0,400
Hemoglobin (g/L)	140 (133-149)	139,5 (131-149)	141 (133,3-153,8)	0,444
Platelet count $x10^9$/L	216,5 (188-268)	232 (191,5-275,5)	216,5 (193,3-250)	0,599
aPTT (s)	24,1 (22-26,1)	24,5 (22,5-25,7)	24,4 (23-25,6)	0,690
INR	1,06 (0,99-1,08)	1,02 (0,97-1,06)	1,03 (0,97-1,09)	0,146
Fibrinogen (g/L)	3,43 (2,83-3,77)	3,06 (2,62-3,89)	3,39 (2,92-3,85)	0,499

No statistically significant differences were observed between the study groups with respect to the urgency of the cardiac procedure (p = 0.639), with elective surgery predominating across all groups. The distribution of surgical procedure types did not differ significantly among groups (p = 0.437), with aortocoronary bypass surgery (CABG) being the most frequently performed procedure.

Table 2. Intra and Postoperative data across low, medium and high-dose TXA groups

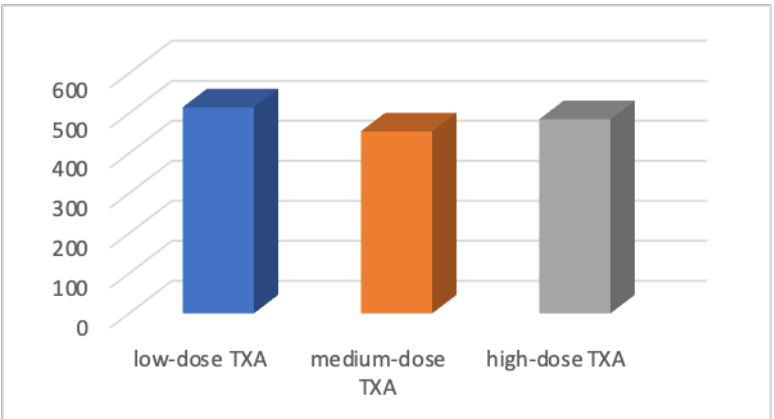
	low-dose TXA (20mg/kg)	medium-dose TXA (35mg/kg)	high-dose TXA (50mg/kg)	p value
Operative urgency Elective / Urgent	53 (88,3%) / 7 (11,7%)	54 (90%) / 6 (10%)	56 (93,3%) / 4 (6,7%)	0,635
Procedure type				0,437
Aortocoronary bypass	37 (61,7%)	27 (45%)	31 (51,6%)	
Aortic valve surgery	17 (28,3%)	23 (38,3%)	19 (31,7%)	
Combined procedure	6 (10%)	10 (16,7%)	10 (16,7%)	
Aotric cross-clamp time (min)	46 (31-60,75)	49 (37,25-65,5)	50 (39,25-64,75)	0,295
Cardiopulmonarybypass time (min)	70,5 (53,5-90,25)	72,5 (61,25-90,75)	74 (59-90,75)	0,549
Lowest temperature (°C)	34,8 (34,8-34,87)	34,8 (34,8-34,9)	34,8 (34,8-35,1)	0,919
Catecholamine support Yes / No	43 (71,7%) / 17 (28,3%)	46 (76,7%) / 14 (23,3%)	45 (75%) / 15 (25%)	0,815
Postoperative temperature (°C)	35,65 (35,32-36)	35,5 (35,1-35,8)	35,5 (35,12-35,8)	0,049
Postoperative ACT (s)	133,5 (125-141)	138 (125,25-144,5)	138 (131-149)	0,121
Postoperative Hemoglobin (g/L)	109,55±12,933	110,87±12,634	114,94±13,918	0,067
Postoperative Platelet count x10^9/L	179 (134-215,5)	186 (151-221)	180,5 (152,25-211,5)	0,800
Postoperative INR	1,21 (1,15-1,28)	1,19 (1,14-1,27)	1,19 (1,13-1,3)	0,780
Postoperative Fibrinogen (g/L)	2,675 (2,29-3,29)	2,51 (2,15-2,94)	2,68 (2,28-3,35)	0,208
Revision for bleeding Yes / No	0 (0%) / 60 (100%)	0 (0%) / 60 (100%)	1 (1,7%) / 59 (98,3%)	0,366
Revision for tamponade Yes / No	1 (1,7%) / 59 (98,3%)	3 (5%) / 57 (95%)	0 (0%) / 60 (100%)	0,167

The use of catecholamines following cardiopulmonary bypass was comparable across the TXA dosing groups. A statistically significant difference was identified in postoperative body temperature among the groups (p = 0.049), driven primarily by a difference between the medium and low dose TXA groups (p = 0.042). Intraoperative and postoperative data are summarized in Table 2.

Figure 1. Graphical presentation of postoperative bleeding at predefined time intervals across different TXA dosing groups

Median bleeding volume for early postoperative bleeding, between 0-4 hours, was 80 (42.5–130) mL in the low-dose, 80 (50–120) mL in the medium-dose and 70 (42.5–110) mL in the high-dose TXA group. No statistically significant difference was observed between TXA dosing groups (p = 0.470). Furthermore, no dose–response relationship was detected (p = 0.385). Bleeding volumes between 4-12 hours were comparable across the three TXA groups (p = 0.853), with median values of 120 (90–150) mL in the low-dose, 110 (62.5–170) mL in the medium-dose and 110 (70–170) mL in the high-dose group. During 12-24 hours interval, median bleeding volumes were 155 (92.5–210) mL in the low-dose, 130 (90–170) mL in the medium-dose and 150 (102.5–197.5) mL in the high-dose group (p = 0.199). Cumulative bleeding after 24 hours remained similar across groups (p = 0.647). Median bleeding volumes were 130 (80–200) mL in the low-dose, 120 (80–195) mL in the medium-dose and 120 (70–190) mL in the high-dose group. Postoperative bleeding volumes at predefined time intervals are presented in Figure 1.

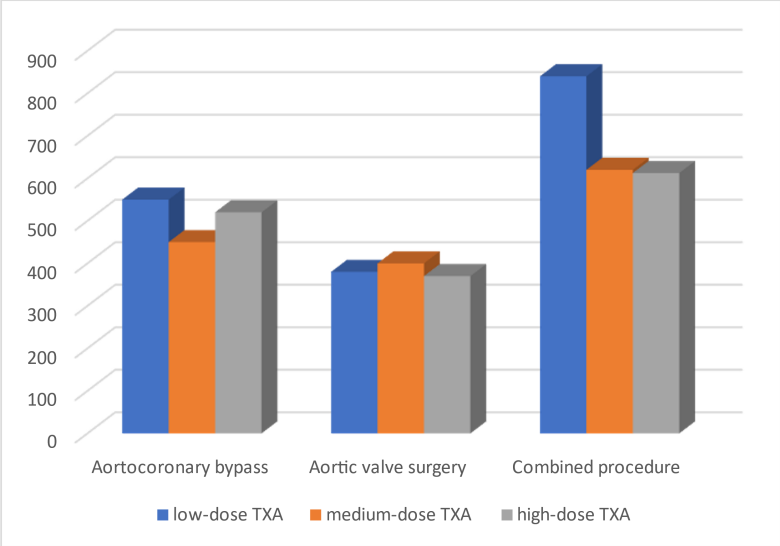
Figure 2. Graphical presentation of total postoperative bleeding across different TXA dosing groups



Total postoperative bleeding volume was 515 (370–675) mL in the low-dose, 455 (345–657.5) mL in the medium-dose and 485 (360–620) mL in the high-dose TXA group (p = 0.758). In addition, no significant dose–response trend was identified (p = 0.510). Total postoperative bleeding volume is presented in Figure 2.

In the adjusted generalized linear model for early postoperative bleeding, compared with the high-dose TXA group, neither low-dose (B = 0.136, p = 0.214) nor medium-dose group (B = 0.182, p = 0.087) demonstrated significant difference in bleeding volume after adjustment for operative urgency, procedure type, cardiopulmonary bypass time, aortic cross-clamp time, lowest intraoperative temperature, and postoperative coagulation parameters. For total postoperative bleeding, compared with the high-dose TXA group, neither low-dose (B = 0.019, p = 0.785) nor medium-dose TXA group (B = −0.011, p = 0.870) demonstrated significant difference after adjustment for operative characteristics and postoperative coagulation parameters.

Figure 3. Graphical presentation of total postoperative bleeding across different TXA dosing groups vs procedure type



In addition, aortic valve surgery was associated with significantly lower total bleeding compared with combined procedures (B = −0.393; 95% CI −0.592 to −0.194; p < 0.001) as shown in Graph 3.

In a linear mixed-effects model used to evaluate postoperative bleeding trajectories at 4, 12 and 24 hours across tranexamic acid dose groups time was treated as a repeated measure and patient identifier was included as a random effect. Bleeding volume was log-transformed to account for non-normal distribution. Postoperative bleeding decreased significantly over time in all groups, however the interaction between time and tranexamic acid dose indicated that bleeding trajectories did not differ between dose groups (p =

0.397). There was no significant difference in the incidence of revision for bleeding (p = 0.366) and tamponade (p = 0.167) across the TXA dosing groups, with only one revision for bleeding and no revision for tamponade in the high-dose TXA group versus one revision for tamponade in low-dose and 3 revisions for tamponade in medium-dose TXA group.

Discussion

In this prospective randomised study of non-anaemic patients undergoing on-pump cardiac surgery, analyses demonstrated no statistically significant differences in postoperative bleeding volumes across low, medium, and high-dose TXA groups at any bleeding interval. These findings suggest that, in a non-anaemic cardiac surgical population, increasing the TXA dose may not confer additional reductions in objectively measured postoperative bleeding beyond a certain threshold. Importantly, the absence of a significant dose–response relationship in early bleeding (p = 0.385) and in total bleeding (p = 0.510) further supports the notion that higher TXA doses may not yield clinically meaningful haemostatic advantages over lower doses in terms of chest drain output alone. Our findings align with randomized and observational studies questioning the incremental benefit of high versus low-dose TXA in routine cardiac surgery. Meta-analyses by Zufferey et al. and Guo et al. demonstrate wide variability in TXA regimens, with both low and high-dose strategies reducing bleeding compared with no TXA, but without consistent superiority of higher doses for transfusion or major clinical outcomes, and with increased adverse effects, including seizures, at higher exposures (7, 8). Likewise, comparative studies by Sigaut et al. and Rangwala et al. report that although high-dose TXA may reduce bleeding in selected high-risk patients, overall benefits over lower doses are modest and frequently not statistically significant (9, 10). The OPTIMAL multicenter randomized trial by Shi et al. comparing high versus low-dose TXA infusions in cardiac surgery showed a modest reduction in red blood cell transfusion with high-dose TXA but no significant difference in postoperative chest tube output (11). This finding highlights the imperfect correlation between measured bleeding and transfusion, which is influenced by transfusion thresholds, haemodynamic management, and institutional practices. Other randomized studies assessing dose-effects report heterogeneous results; in coronary artery bypass surgery trail by Armellin et al. no significant differences were found in bleeding or transfusion between low and high-dose regimens, suggesting a plateau of antifibrinolytic efficacy beyond a certain dose (12). Meta-analytic data by Rangwala et al. similarly indicate that although high-dose TXA may reduce 24-hour blood loss or chest tube drainage in some cohorts, the effect size is small and must be weighed against potential dose-related risks (10).

Additionally, escalation of tranexamic acid (TXA) dosing was not independently associated with either early or total postoperative bleeding after adjustment for operative

characteristics and postoperative coagulation parameters. This finding aligns with the evidence from the ATACAS trial by Myles et al. and with the meta-analyses by Zufferey et al. and Guo et al. demonstrating that standard TXA dosing effectively attenuates fibrinolysis, while higher doses do not necessarily yield further reductions in bleeding and may increase the risk of adverse events (13, 7, 8). The absence of a dose–response relationship across both early and cumulative bleeding endpoints in the present analysis reinforces the concept of a therapeutic ceiling effect for TXA in adult cardiac surgery confirmed by the meta-analyses by Zufferey et al. and Guo et al. (7, 8). Our results support the concept that, beyond a certain threshold, antifibrinolytic efficacy plateaus, and bleeding risk becomes predominantly driven by patient-specific and procedure-related haemostatic factors rather than antifibrinolytic dose alone. Early postoperative bleeding is largely driven by cardiopulmonary bypass–induced haemostatic derangements, including platelet dysfunction and consumption.

Our study's strength, by the opinion of the authors, is the assessment of clinically relevant bleeding time intervals combined with advanced statistical approaches that allow adjustment for confounders and comprehensive evaluation of dose–response relationships in this group of patients. Additionally, the investigated TXA dosing regimens are grounded on contemporary evidence thus supporting clinical applicability. However, the single-center design and the exclusion of higher-risk populations restrict extrapolation to broader surgical cohorts.

Conclusion

Escalation of tranexamic acid dosing was not associated with a reduction in either early or total postoperative bleeding after cardiac surgery when adjusted for operative characteristics and postoperative coagulation parameters. These findings support the use of lower tranexamic acid doses in non-anaemic patients undergoing on-pump cardiac surgery, potentially minimizing drug exposure without compromising haemostatic efficacy.

Ethical approval: The study was approved by the institutional ethics committee of Acibadem Sistina prior to patient enrolment, approval reference 02-15663/02.

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