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ORIGINAL ARTICLE

Postoperative thrombotic effects of tranexamic acid in open heart surgery

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Abstract

Background Following the administration of tranexamic acid, the occurrence of thromboembolic events is a controversial issue.
Aims In this retrospective cohort study, we aimed to determine the possible thromboembolic complications due to tranexamic acid as a prophylactic method in patients undergoing open heart surgery.
Methods The data of 172 adult patients undergoing open heart surgery were analyzed. All patients received tranexamic acid at a dose of 50 mg/kg. The patients were divided into 3 groups as multiple-valve surgery (group 1), coronary bypass alone (group 2), and coronary bypass with valve surgery (group 3). The amount of blood transfusion, bleeding in intra- and postoperative period, and the presence of thromboembolic events including myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis were investigated.
Results Patient demographics and duration of surgery were not significantly different in groups ($p > 0.05$). Hb, Htc, INR, and platelet levels of all groups did not differ significantly ($p > 0.05$). In total, 7 patients underwent reexploration. Postoperative DVT, stroke, and seizure were not seen at all. There was no statistically significant difference between groups in terms of the amount of blood transfusion, drainage, or peritoneal hematoma. The length of hospital stay and the mortality rate did not differ ($p > 0.05$).
Conclusions In patients receiving tranexamic acid infusion at 50 mg/kg dose, reexploration rates remained at 4.1% even after major cardiac surgeries. No thrombosis, stroke, or seizure were reported. Our findings support that tranexamic acid is a safe drug which has positive effect on reducing perioperative bleeding.

Keywords Cardiac surgery · Thrombosis · Tranexamic acid

Introduction

Tranexamic acid (TXA), a lysine analogue, was added in the list of essential medicines by the World Health Organization [1]. TXA is protective against simplified fibrinolysis and can increase clot stability by 13 times, and fibrinolytic resistance continues for up to 6 h after cardiac surgery [2]. TXA has been discovered in 1962 [3, 4]. Systemic use has been proven to be safe and effective in reducing blood loss in patients undergoing cardiac surgery [5]. Due to the mechanism of action of lysine analogues, a theoretical increased risk of developing venous thromboembolic complications, such as deep vein thrombosis (DVT) or pulmonary embolism, is introduced [6]. It has been reported that there may be a rise in the incidence of myocardial infarction (MI), stroke, or other thrombotic complications after cardiac surgery. The issue whether TXA is thrombogenic is widely discussed. In a recently published meta-analysis involving 67 studies, in which the data of 6034 patients were analyzed, topical and iv administration of TXA were compared and the amount of blood transfusion or blood loss was found to be significantly lower as compared to placebo groups [7]. In that meta-analysis, which assessed the data mainly from orthopedic surgeries, TXA administration was reported to be not associated with increased incidence of venous thromboembolism; underlining that, there was a

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need for analyses related to other branches, such as cardiac surgery. Recently published large-scale, multi-center studies, such as the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS), emphasize the fact that TXA is not associated with thrombotic complications [8]. The present retrospective cross-sectional cohort study aimed to evaluate perioperative thrombotic complications caused by prophylactical use of TXA in patients undergoing open heart surgery.

Methods

Following the approval of the ethics committee, we analyzed the data of 172 adult patients undergoing open heart surgery with cardiopulmonary bypass between 2013 and 2016. All patients received tranexamic acid at a dose of 50 mg/kg. The patients were divided into 3 groups as multiple-valve surgery (group 1), coronary bypass alone (group 2), and coronary bypass with valve surgery (group 3). The amount of blood transfusion, bleeding in intra- and postoperative period, and the presence of thromboembolic events including myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis were investigated. The length of hospital stay, the amount of drainage in ICU, and mortality rates were also evaluated. For the diagnosis of DVT, we used venous compression USG or bedside doppler USG.

Statistical analysis

The SPSS 22.0 program was used for the analysis of the study data. The descriptive statistics employed in the study were mean, standard deviation, median, minimum, maximum, frequency, and ratio. The Kolmogorov-Smirnov test was used to measure the distribution of variables. The Mann-Whitney *U* test was used to analyze

Table 1 Patient demographics, perioperative transfusion rate, and postoperative complications

		Min–max	Median	Mean±sd	
Age (years)		23.0–87.0	66.0	64.1 ± 12.8	
Gender	Female			78	45.3%
	Male			94	54.7%
BMI		22.5–31.6	26.0	26.7 ± 1.8	
Length of surgery (h)		25.0–300.0	205.0	208.4 ± 35.3	
CPB time (min)		60.0–330.0	110.0	123.3 ± 46.8	
CX time (min)		30.0–220.0	90.0	94.4 ± 32.0	
EF (%)		40.0–60.0	50.0	49.6 ± 4.6	
Perioperative bleeding (mL)		100–9200	700	1070 ± 1332	
Drainage in ICU (mL)		150.0–2200.0	450.0	462.3 ± 241.1	
Hospital stay (days)	7 days			126	73.3%
	8 days			41	23.8%
	9 days			4	2.3%
Mortality rate				0	0.0%
RBC		4.8–6.7	3.0	1.0 ± 54.0	
	RBC transfused			11	6.4%
	RBC not transfused			161	93.6%
FFP		5.9–12.4	3.0	1.0 ± 95.0	
	FFP transfused			40	23.3%
	FFP not transfused			132	76.7%
Platelet		40.8–45.8	18.0	1.0 ± 200.0	
	Platelet transfused			139	80.8%
	Platelet not transfused			33	19.2%
Cryopresipitate	Not transfused			165	95.9%
	Transfused			7	4.1%
Postoperative DVT				0	0.0%
Postoperative stroke or seizure				0	0.0%
Reexploration	(−)			165	95.9%
	(+)			7	4.1%
Extubation time in ICU (h)		6.6–1.4	6.0	4.0 ± 12.0	

quantitative independent data while the chi-square test was used to assess the qualitative independent data. In cases where the chi-square conditions were not met, the Fisher test was used for the qualitative data. A value of $P < 0.05$ was considered statistically significant.

Results

Data belonging to a total of 172 patients was analyzed. No significant difference was observed between the groups regarding their demographics ($p > 0.05$, Table 1). While the total duration of surgery did not differ between groups, the coronary bypass alone group (group 2) was found to have the shortest CPB time and Cx time ($p < 0.05$). The CPB and Cx time did not differ between the groups 1 and 3. There was no significant difference between the groups regarding drainage amount at the intensive care unit as well as duration of hospital stay, mortality rate, perioperative bleeding, and extubation time ($p > 0.05$). Also, the RBC, FFP, platelet, and cryo-transfusion volumes did not differ significantly between the groups ($p > 0.05$). No significant difference was detected between the groups regarding postoperative complication rates including re-exploration, DVT, or stroke ($p > 0.05$, Table 2)

In all groups, there was a significant decrease in the Hb, Htc, platelet, and INR levels in the postoperative period as compared to the preoperative period ($p < 0.05$, Table 3).

Table 2 The comparison of groups in terms to patient demographics, surgical features, transfusion rate, and postoperative complications

		Group 1		Group 2		Group 3		*p*	
		Mean±sd/*n* (%)	med	mean±sd/*n* (%)	Med	Mean±sd/*n* (%)	Med		
Age (years)		63.7 ± 12.4	63.0	61.8 ± 14.0	64.0	66.8 ± 10.6	69.0	0.121	K
Gender	Female	26 44.8%		36 50.7%		16 37.2%		0.372	X^2
	Male	32 55.2%		35 49.3%		27 62.8%			
BMI		26.8 ± 1.8	26.6	26.8 ± 1.9	26.6	26.4 ± 1.8	26.0	0.282	K
Length of surgery (h)		208.9 ± 45.9	205.0	203.9 ± 26.6	200.0	215.1 ± 30.8	210.0	0.139	K
CPB time (min)		132.4 ± 40.8	120.0	106.1 ± 37.7	90.0	139.5 ± 58.5	120.0	0.000	K
CX time (min)		100.7 ± 27.9	92.5	81.9 ± 30.1	70.0	106.6 ± 33.8	100.0	0.000	K
EF (%)		50.4 ± 4.5	50.0	49.1 ± 4.6	50.0	49.5 ± 4.8	50.0	0.218	K
Perioperative bleeding (mL)		1172 ± 1685	700	1080 ± 1203	650	916 ± 961	600	0.551	K
Drainage in ICU (mL)		456.6 ± 216.2	450.0	463.2 ± 208.9	450.0	468.4 ± 316.8	450.0	0.766	K
Hospital stay (days)	7 days	42 72.4%		51 71.8%		33 76.7%		0.780	X^2
	8 days	14 24.1%		20 28.2%		7 16.3%			
	9 days	2 3.4%		0 0.0%		2 4.7%			
Mortality rate		0 0.0%		0 0.0%		0 0.0%		–	
RBC		4.7 ± 5.6	3.0	5.5 ± 8.3	3.0	3.8 ± 4.4	2.0	0.298	K
Not transfused		2 3.4%		4 5.6%		5 11.6%		0.237	X^2
Transfused		56 96.6%		67 94.4%		38 88.4%			
FFP		6.1 ± 13.7	2.0	5.5 ± 12.9	3.0	6.2 ± 9.0	3.0	0.994	K
Not transfused		14 24.1%		12 16.9%		14 32.6%		0.156	X^2
Transfused		44 75.9%		59 83.1%		29 67.4%			
Platelet		42.4 ± 53.2	16.0	45.0 ± 46.0	23.0	30.4 ± 32.1	18.0	0.851	K
Not transfused		44 75.9%		59 83.1%		36 83.7%		0.499	X^2
Transfused		14 24.1%		12 16.9%		7 16.3%			
CRYO	Not transfused	56 96.6%		69 97.2%		40 93.0%		0.529	X^2
	Transfused	2 3.4%		2 2.8%		3 7.0%			
Postoperative DVT		0 0.0%		0 0.0%		0 0.0%		–	
Postoperative stroke or seizure		0 0.0%		0 0.0%		0 0.0%		–	
Reexploration	(−)	55 94.8%		69 97.2%		41 95.3%		0.778	X^2
	(+)	3 5.2%		2 2.8%		2 4.7%			
Extubation time in ICU (h)		6.8 ± 1.6	7.0	6.4 ± 1.3	6.0	6.7 ± 1.5	6.0	0.295	K

[K] Kruskal–Wallis (Mann–Whitney *U* test)

[X2] Chi-square test

Table 3 Comparison of groups in regard to Hb, Htc, platelet, and INR levels

	Group 1		Group 2		Group 3		*p*	
	Mean±sd/*n*-%	Med	Mean±sd/*n*-%	Med	Mean±sd/*n*-%	Med		
Hb								
Preoperative	12.8 ± 1.8	12.9	12.7 ± 1.7	12.7	13.4 ± 1.4	13.6	0.086	K
Postoperative	10.1 ± 0.9	10.1	10.3 ± 1.1	10.1	10.4 ± 1.2	10.5	0.364	K
Change p	0.000	*w*	0.000	*w*	0.000	*w*		
HTC								
Preoperative	37.7 ± 4.8	37.7	37.4 ± 4.2	37.6	39.0 ± 3.9	39.1	0.134	K
Postoperative	29.5 ± 2.8	29.3	30.3 ± 3.1	29.6	30.5 ± 3.0	30.8	0.238	K
Change p	0.000	*w*	0.000	*w*	0.000	*w*		
INR								
Preoperative	1.3 ± 1.7	1.1	1.5 ± 2.2	1.1	1.1 ± 0.1	1.0	0.780	K
Postoperative	1.6 ± 3.1	1.2	1.3 ± 0.3	1.2	1.2 ± 0.1	1.2	0.318	K
Change p	0.000	*w*	0.000	*w*	0.000	*w*		
PLT								
Preoperative	220.8 ± 65.3	224.5	219.8 ± 84.0	205.0	217.0 ± 51.7	206.0	0.845	K
Postoperative	151.6 ± 55.0	138.0	153.7 ± 59.4	146. .0	160.1 ± 48.8	153.0	0.594	K
Change *p*	0.000	*w*	0.000	*w*	0.000	*w*		

Discussion

In this study, the prophylactic use of 50 mg/kg TXA did not cause an increase in the incidence of thrombotic complications, such as myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis, in patients, who had cardiac surgery.

The use of heparin in cardiac surgery leads to hemostatic defects, such as hemodilution associated with priming, activation of clotting due to non-endothelial CPB surface, hypothermia, tissue trauma, and acidosis of the stomach [9–11]. Blood transfusion has been reported to be the most commonly performed procedure across US hospitals [12]. Although there are differences in practice among hospitals, TXA-an antifibrinolytic agent has routinely been used in at many cardiac surgery centers.

The CRASH-2 trial (Clinical Randomization of An Antifibrinolytic in Significant Hemorrhage), the largest study investigating the efficacy of TXA with 20,000 patients, was published in 2010 [13]. The CRASH-2 demonstrated that the incidence of death and all causes of mortality were reduced when TXA was administered within the first 3 h after trauma in adult patients with severe bleeding. Considering the incidence of fatal or non-fatal vascular occlusive events, there was no significant difference in the placebo group.

In ATACAS, researchers evaluated 4631 patients, who had an increased risk of developing major complications and underwent on- or off-pump coronary artery surgery [8]. Of all 4631 patients, 2311 were given TXA while 2320 were given placebo. In that study, TXA was found to be related with lower perioperative bleeding and higher seizure rate, but it was not associated with a significant increase in the incidence of death or thrombotic complications within 30 days after surgery. Kagoma et al. [14] reported in their systemic review including 29 randomized controlled trials (RCT) that antifibrinolytic agents were associated with reduced blood transfusion, but did not increase the risk for thromboembolic events. Similarly, another Cochrane systematic review including 33 RCTs revealed that TXA was associated with neither mortality nor thromboembolic episodes [15]. Nevertheless, for tranexamic acid, a meta-analysis of 8 RCTs calculated reduced risks for overall allogeneic blood component transfusion (RR 0.47, 95% CI 0.33–0.66) and for red cell transfusion (RR 0.51, 95% CI 0.36–0.71). No association was found between tranexamic acid and thromboembolic events [16]. Our results support the results reported by this meta-analysis and systemic reviews. However, the size of the samples and low incidence of events prevent making a definitive decision. As suggested in Ortmann et al.'s review [17], there is a need for studies evaluating the safety of TXA.

Coagulopathy developing after prolonged CPB can lead to consumptive coagulopathy, resulting in clinically significant bleeding and/or thrombosis with factor consumption [18]. Excessive generation of thrombin and activation of tissue factors lead to endothelial dysfunction [19]. Strong activation of fibrinolysis can produce concomitant coagulopathy. For this reason, we evaluated longer lasting complex surgeries, in which valve repair and coronary artery bypass surgery are performed simultaneously, as a separate group. The CPB time and Cx time were found to be longer in complex surgeries.

However, there was no increase in the need for blood transfusion or in the incidence of thromboembolic complications in these groups. Our records also included postoperative follow-up, without any significant increase in in-hospital mortality or amount of drainage at the ICU.

TXA appears to be the most useful one among the antifibrinolytic agents recommended for use in cardiac surgery. TXA is ten times more potent than epsilon aminocaproic acid (EACA) and 100 times cheaper than aprotinin [20]. Studies making comparison between TXA and EACA or aprotinin are mostly retrospective studies and bring the reliability of TXA to the forefront. Thus, we think that TXA can be routinely preferred during the perioperative period in patients undergoing cardiac surgery. Our study suggests that the risk of thromboembolic complications is limited to this agent, consistent with available data obtained from increasing number of studies.

Intra-cardiac clot formation after cardiac procedures is rare, but has been described following atrial septal defect repairs with autologous pericardium in the absence of coagulation factors [21]. This study included adult patients undergoing cardiac surgery, but no case of intra-cardiac complication was observed.

Limitations

One of the major limitations of this study is that it was designed as a retrospective study. Limited sample group forms another limitation. There is a need for further prospective studies with larger series. In this way, we believe that reliable steps can be taken regarding the reliability and effectiveness of TXA. Another limitation is that we did not include coagulation monitoring techniques, such as thromboelastometry, into our analyses.

Conclusion

In conclusion, as TXA is considered as a cheap, easy to apply, effective and reliable agent in cardiac surgery, it has come into routine use at many centers for cardiac surgery. Our study data revealed that no thromboembolic complication was observed in 172 patients during 3 years of the study. We have concluded that TXA can be safely used not only in coronary artery bypass surgery, but also in multi-valve surgery and in combined and complex procedures.

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Compliance with ethical standards

Conflict of interest Author A.S. declares that she has no conflict of interest. Author M.E. declares that he has no conflict of interest. Author K.T.S. declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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