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Effect of Topical Tranexamic Acid on Postoperative Bleeding in Cardiac Surgery

MOHAMED A.M. ISMAIL, M.Sc.; MOHSEN M. ABDULKARIM, M.D.; ASHRAF A. EL MIDANY, M.D. and MOHAMMED ABDEL-GAYED IBRAHIM, M.D.

The Department of Cardiothoracic Surgery, Faculty of Medicine, Ain Shams University

Abstract

Background: One of the major cardiac surgery problems is post-operative bleeding which may lead to blood transfusion. Blood loss is due to many causes one of them is fibrinolysis. Many antifibrinolytic drugs have been used to decrease the post-operative bleeding for cardiac surgery including e-aminocaproic acid, aprotinin and tranexamic acid. Tranexamic acids are synthetic derivatives of the amino acid lysine. It binds with the lysine on binding site of plasminogen and plasmin due to that the plasminogen dislodge from the surface of the fibrin so demoralizing the fibrinolysis process.

Aim of Study: To study the effect of application of topical tranexamic acid in reducing the postoperative bleeding in patients undergoing cardiac surgery by median sternotomy.

Patients and Methods: A Randomized Controlled Clinical Trialwas carried out one 50 subjects was programmed for elective open cardiac surgery, enrolled by computer program and divided randomly in two group, group A (n=25) received TxA 2g in 100ml NSS in the pericardial cavity and mediastinum before the sternal closure While group B (n=25) 100ml of NSS alone. The drains will be monitored in the next 24 hours with calculation of blood loss. Blood products will be calculated when given for patient. Re exploration is done if there urgency.

Results: The result of the study revealed statistically significant difference between TxA group and the placebo group regarding the postoperative blood loss and the need for packed RBC transfusion. This means the topical application of TxA decreasing the postoperative bleeding, blood transfusion and the need for reopration, but there was no statistically significant difference in plasma and platelet transfusions between the two groups.

Conclusion: The use of topical TXA have a significant effect on the reduction of bleeding after Cardiac Surgery, also was able to decrease the blood transfusions. Moreover, show better results in reducing the return to the operating room due to bleeding.

Key Words: *Cardiac surgery – Topical tranexamic acid – Postoperative bleeding.*

Correspondence to: Dr. Mohamed Ahmed Mohamed Ismail, E-Mail: aajourneyzzz@gmail.com

Introduction

CARDIOVASCULAR diseases (CVD) are the most common cause of death in patient. CVD covers a number of disorders e.g. coronary heart disease. World Health Organization reported about 17.9 million people died worldwide from these diseases, they represented 32% of all deaths. In Egypt, cardiovascular disease (CVD) has been the leading cause of death since the 1990 **[1]**. CVD accounted for 46.2% of the overall mortality in Egypt by 2017 **[2]**.

Most CVD can be prevented by decreased risk factors such as tobacco use, unhealthy life style. There are also causes of CVDs. These social, economic and cultural change-globalization, population ageing, poverty, stress and hereditary factors **[1]**.

In addition, drug treatment of hypertension, diabetes and high blood lipids are necessary to reduce cardiovascular risk and prevent heart attacks and strokes among people with these conditions **[3]**.

There are various ways for management of cardiovascular diseases, one of which is surgery, which leads to a reduction in mortality from this disease **[3]**. About 60% of patients suffering from coronary artery disease undergo surgery **[4]** all surgical methods have complications, but bleeding post-operative is an important issue in s surgery **[5]**. The risk associated with blood transfusion has increased the need for safer and alternative ways to preserve the blood of patients undergoing heart surgery like use of drugs such as aminocaproic acid, aprotinin and tranexamic acid **[6-8]**.

Bleeding in patients can be due to different factors, including surgery, trauma and gynecology, and impaired blood clotting. Meantime, bleeding

in cardiovascular surgery is a major complication that prolongs hospital stay, increases the need for blood transfusions, and leads to overall mortality from complications such as thrombotic events and stroke [9]. Administration of blood for several time associated with major complications [10]. Coronary artery bypass grafting (CABG) surgery requires different amounts of blood [11]. The rate of blood transfusion in a study in 13 CABG centers in 2020 has been reported from 10.9 to 59.9% [12]. It seems that the main cause of bleeding is impaired platelet function and coagulation actors [13,14].

Blood preservation during heart surgery is very important. Because increased bleeding from surgery is associated with an increased risk of cardiac tamponade, the need for blood transfusions. Therefore, due to the variety of causes of bleeding, it is necessary to use antifibrinolytic drugs, which are often used for this purpose. The use of antifibrinolytic drugs can reduce blood loss in heart surgery and non-surgical diseases. Effectiveness of drugs has been increasing for years [15,16]. Tranexamic acid is one of these drugs use in patients undergoing heart surgery [8]. Many studies have reported that tranexamic acid significantly reduces blood loss and need for blood transfusions [17].

Preoperative use of tranexamic acid in patients at risk for bleeding under coronary artery bypass grafting was associated with a reduction in bleeding [18]. Topical application of tranexamic acid has the advantage of inducing partial microvascular hemostasis by stopping fibrin clot dissolution in the affected area [19-21]. Once tranexamic acid topically applied is rapidly absorbed and achieves the effect of hemostasis. One study report use of topical tranexamic acid has significant effect on decrease bleeding post Coronary artery bypass graft and blood transfusion [22].

A randomize control trial (RCT) done on 2006 showed that applying of tranexamic acid before wound closure, significantly reduced postoperative blood loss and need for blood transfusions [23]. Other RCT demonstrated Patients who did not have topical Tranexamic acid had a significantly higher postoperative bleeding comparing to the other group [24]. Hassam et al., reported topical application of tranexamic acid in patients undergoing coronary artery bypass grafting led to a significant reduction in postoperative blood loss [25]. Otherhand similar result has been showed on this study [26].

Aim of the work:

To study the effect of application of topical tranexamic acid in reducing the postoperative bleeding in patients undergoing cardiac surgery by median sternotomy. In way we will compare two groups of patients, one group will receive topical tranexamic acid before sternal closure but the other group undergo the same surgeries and conditions without the use of topical tranexamic acid.

Patients and Methods

A Randomized Controlled Clinical Trial was carried out one 50 subjects at Cardiothoracic Department in Ain Shams University Hospitals were programmed for elective open cardiac surgery during 2022, enrolled by computer program and divided randomly in two group, group A (n=25) received TxA 2g in 100ml NSS in the pericardial cavity and mediastinum before the sternal closure While group B (n=25) 100ml of NSS alone.

All patients undergoing elective open cardiac surgery by median sternotomy, adult patients, both males and females and patients with elective intervention classification were enrolled in the study. While patients with bleeding disorder, Coagulopathy diseases, allergy to tranexamic acid, use of antiplatelet before surgery, coexisting comorbidities which includes ischemic stroke, hemorrhage stroke, systemic thromboembolism, heart failure, liver failure, renal failure were excluded from the study.

Patients will be randomly allocated by computer generated randomization into two groups A and B, each group includes 25 patients.

The study is approved by the ethical committee of cardiothoracic surgery department and Faculty of Medicine in Ain-Shams University. An informed consent is taken from to the patients. The operations is be performed under general anesthesia.

Each patient in both groups would be subjected to full history taking, general examination, cardiac examination, 12 lead ECG and Chest X-ray, transthoracic Echocardiogram (TTE), angiography for the patients undergoing CABG and laboratory investigations: Hb, HCT, Platelet, PT, PTT, INR, Urea, Creatinine, Liver enzymes.

Induction of anasethia:

In the operation theatre and induction room, the aneshesiologist secured a 18 gauge cannula and gave midazolam 0.05mg/kg i.v, and an infusion of Ringer acetate was started. Standard monitoring was used in the form of 5 lead electrocardiogram with ST segment monitoring, pulse oximetry, end tidal CO_2, invasive arterial blood pressure. Prior to induction of anaesthesia, a baseline laboratory

evaluation was done including prothrombin time, hemoglobin, hematocrit and renal function tests and liver function tests. Induction of anaesthesia was done using thiopental (3-5mg/kg), fentanyl (5mic/kg), Atracurium (0.5mg/kg) for patient intubation. Anaesthesia was maintained with isoflurane, fentanyl (5mic/kg), and Atracurium 0.1mg/kg.

Study interventions:

Both groups had the same conditions, and the operations were by median sternotomy. After sternotomy, Cardiopulmonary bypass was started with 1000-1500ml crystalloid priming volume and mild hypothermia (32ºC) with a sarns CPB machine perfusion rate of 2.2 to 2.4 L/min/m^2 and a mean arterial pressure of 70 to 75mmHg. A systemic hypothermia of 28 to 30° C and hematocrit level of 20 to 26% was provided during perfusion. Myocardial protection was achieved by cold blood cardioplegia. During CPB, homologous donor packed RBCs were transfused if HB is below 6 g.dl. An activated clotting time (ACT) more than 400 was considered adequate for commencing CPB. CPB was conducted with non occlusive roller pumps, membrane oxygenators, arterial line filtration and cold blood enriched hyperkalemic arrest. Systemic hypothermia to an oesophageal temperature of 28-30 c was maintained during aortic cross clamping. After completion of CPB and removal of the arterial cannula, heparin was neutralised by 1mg of protamine sulphate for every 100U of heparin administrated, the anesthesiologist administrated the protamine into the central line by continuous infusion over a period of 15-20 minutes. Then a second dose of protamine 50mg was administered if ACT remained above baseline ACT. Core body temperature, urine output, arterial blood gases, total amount of blood loss and transfusion requirements were monitored.

Before sternal closure and after insertion of chest tubes: The group A (TxA) (n=25) will receive 2g of TxA in 100ml of normal saline in the mediastinum and around the heart with the chest tubes clamped, but the other group B (no TxA) (n=25) will receive 100ml of normal saline alone. After sternal closure and tubes declamping, the drains will be monitored in the next 24 hours in the ICU. After surgery all patients were transferred to the ICU. The drains will be monitored in the next 24 hours with calculation of blood loss. Blood products will be calculated when given for the patient. The patient Hb, HCT, PT, PTT, INR are done for control. Re exploration is done if there is urgency.

Statistical analysis: Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20 and the following were done: Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges. The comparison between two groups with qualitative data were done by using Chi-square test. The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent *t*-test. The comparison between two paired groups with quantitative data and parametric distribution were done by using paired *t*-test. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

Results

Table (1): Comparison between group A and group B regarding mean age and operation.

	Group A No.=25	Group B No.=25	Test value	*p*-value	Sig.
Age:					
Mean ± SD	52.72±13.01	53.96±13.47	–0.331•	0.742	NS
Range	25-78	19-75			
Gender:					
Female	5 (20.0%)	6 (24.0%)	0.117*	0.733	NS
Male	20 (80.0%)	19 (76.0%)			
Operation:					
CABG	13 (52.0%)	16 (64.0%)	0.739*	0.390	NS
DVR	1 (4.0%)	3 (12.0%)	1.087*	0.297	NS
MVR	10 (40.0%)	4 (16.0%)	3.571*	0.059	NS
AVR	0 (0.0%)	1 (4.0%)	1.020*	0.313	NS
MV redo	1 (4.0%)	1 (4.0%)	0.000*	1.000	NS

p-value >0.05: Non significant. *: Chi-square test.
p-value <0.05: Significant. •: Independent *t*-test.
p-value <0.01: Highly significant.

The previous table shows that there was no statistically significant difference between group A and group B regarding mean age and type of operation with *p*-value 0.742 and 0.207 respectively.

Table (2): Comparison between group A and group B regarding mean preoperative HB, HCT and platelets.

	Group A No.=25	Group B No.=25	Test value	*p*-value	Sig.
Platelets (Pre):					
Mean ± SD	230.24±57.68	239.12±60.51	–0.531•	0.598	NS
Range	137-402	55-352			
HB (gm%) (Pre):					
Mean ± SD	13.33±1.50	13.61±1.70	–0.618•	0.540	NS
Range	10.9-17	11.3-17			
HCT (%) (Pre):					
Mean ± SD	39.61±4.66	40.86±6.81	–0.756•	0.453	NS
Range	30.5-49.7	25.5-59.8			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Independent *t*-test.

The previous table shows that there was no statistically significant difference between group A and group B regarding mean preoperative HB, HCT and Platelets with *p*-value 0.540, 0.453 and 0.598 respectively.

Table (3): Comparison between group A and group B regarding mean preoperative PT, PTT and INR.

	Group A No.=25	Group B No.=25	Test value	*p*-value	Sig.
PT (Pre):					
Mean ± SD	14.66±1.66	15.59±5.66	–0.790•	0.433	NS
Range	12.6-19.7	13-41.4			
PTT (Pre):					
Mean ± SD	36.72±4.86	35.84±8.80	0.438•	0.663	NS
Range	28-48	13.5-59.5			
INR (Pre):					
Mean ± SD	1.13±0.15	1.10±0.19	0.543•	0.590	NS
Range	0.93-1.46	0.96-1.8			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Independent *t*-test.

The previous table shows that there was no statistically significant difference between group A and group B regarding mean preoperative PT, PTT and INR with *p*-value 0.790, 0.663 and 0.590 respectively.

Table (4): Comparison between group A and group B regarding mean blood, plasma in and platelet transfusion.

	Group A No.=25	Group B No.=25	Test value	*p*-value	Sig.
Blood (given):					
Mean ± SD	1.20±0.58	1.84±1.21	–2.381•	0.021	S
Range	0-2	0-5			
Plasma (given):					
Mean ± SD	3.96±0.61	4.56±2.42	–1.204•	0.235	NS
Range	2-5	0-12			
Platelet (U) (given):					
Mean ± SD	15.00±12.73	15.00±6.41	0.000•	1.000	NS
Range	6-24	6-24			
Albumin:					
Mean ± SD	1.04±0.61	1.46±0.78	–2.096•	0.041	S
Range	0-2	0-3			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Independent *t*-test.

The previous table shows that there was statistically significant difference between group A and group B regarding mean blood transfusion (1.20 ±0.58 vs 1.84±1.21) with *p*-value 0.021. There was no statistically significant difference between group A and group B regarding mean plasma in and platelet transfusion with *p*-value 0.0.235 and 1.0 respectively.

Table (5): Comparison between group A and group B regarding mean postoperative platelets, HB and HCT.

	Group A No.=25	Group B No.=25	Test value	*p*-value	Sig.
Platelets (post):					
Mean ± SD	169.68±39.56	187.72±64.88	–1.187•	0.241	NS
Range	58-231	109-403			
HB (gm%) (post):					
Mean ± SD	11.23±1.39	10.94±1.73	0.658•	0.514	NS
Range	8.9-13.8	7.9-15.3			
HCT (%) (post):					
Mean ± SD	33.18±4.74	31.90±5.66	0.873•	0.387	NS
Range	23.7-42.8	21.9-43.9			

p-value >0.05: Non significant. *p*-value <0.01: Highly significant.
p-value <0.05: Significant. •: Independent *t*-test.

The previous table shows that there was no statistically significant difference between group A and group B regarding mean postoperative PT, PTT and INR with *p*-value 0.552, 0.885 and 0.965 respectively.

Table (6): Comparison between group A and group B regarding mean postoperative PT, PTT and INR.

	Group A No.=25	Group B No.=25	Test value	*p*-value	Sig.
PT (post):					
Mean ± SD	15.77±2.11	16.13±2.19	–0.599•	0.552	NS
Range	13-23.4	13.1-23.1			
PTT (post):					
Mean ± SD	44.12±9.09	44.52±10.74	–0.145•	0.885	NS
Range	31-65.4	31.2-79.5			
INR (post):					
Mean ± SD	1.18±0.15	1.19±0.17	–0.044•	0.965	NS
Range	1-1.73	0.9-1.71			

p-value >0.05: Non significant. *p*-value <0.01: Highly significant.
p-value <0.05: Significant. •: Independent *t*-test.

The previous table shows that there was no statistically significant difference between group A and group B regarding mean postoperative PT, PTT and INR with *p*-value 0.552, 0.885 and 0.965 respectively.

Table (7): Comparison between group A and group B regarding mean drain blood loss.

	Group A No.=25	Group B No.=25	Test value	*p*-value	Sig.
Drains in ml (24h):					
Mean ± SD	110.00±62.92	366.00±166.28	–7.200•	<0.001	HS
Range	50-300	100-800			
CABG:					
Mean ± SD	134.62±74.68	384.38±143.43	5.672•	<0.001	HS
Valves:					
Mean ± SD	83.33±32.57	333.33±206.16	4.167•	0.001	HS
Re exploartion	0 (0.0%)	2 (8.0%)	2.083 *	0.149	NS

p-value >0.05: Non significant. •: Independent *t*-test.
p-value <0.05: Significant. *: Chi-square test.
p-value <0.01: Highly significant.

The previous table shows that there was statistically significant difference between group A and group B regarding mean drain blood loss in ml found higher in group B than group A (366 ± 166.28 Vs 110±62.92) with p-value <0.001. Two patients were re-explored in group B with non significant different p-value 0.149.

Table (8): Comparison between group A pre and post regarding mean preoperative platelets, HB and HCT.

Group A	Pre No.=25	Post No.=25	Test value	p-value	Sig.
Platelets:					
Mean ± SD	230.24±57.68	169.68±39.56	5.932•	0.000	HS
Range	137-402	58-231			
HB (gm%):					
Mean ± SD	13.33±1.50	11.23±1.39	6.781•	0.000	HS
Range	10.9-17	8.9-13.8			
HCT (%):					
Mean ± SD	39.61±4.66	33.18±4.74	6.126•	0.000	HS
Range	30.5-49.7	23.7-42.8			

p-value >0.05: Non significant. p-value <0.01: Highly significant.
p-value <0.05: Significant. •: Paired t-test.

The previous table shows that there was highly statistically significant difference between group A pre and post regarding mean preoperative mean preoperative platelets, HB and HCT with p-value 0.000.

Table (9): Comparison between group A pre and post regarding mean preoperative PT, PTT and INR.

Group A	Pre No.=25	Post No.=25	Test value	p-value	Sig.
PT:					
Mean ± SD	14.66±1.66	15.77±2.11	–2.299•	0.031	S
Range	12.6-19.7	13-23.4			
PTT:					
Mean ± SD	36.72±4.86	44.12±9.09	–4.343•	0.000	HS
Range	28-48	31-65.4			
INR:					
Mean ± SD	1.13±0.15	1.18±0.15	–2.040•	0.053	NS
Range	0.93-1.46	1-1.73			

p-value >0.05: Non significant. p-value <0.01: Highly significant.
p-value <0.05: Significant. •: Paired t-test.

The previous table shows that there was statistically significant difference between group A pre and post regarding mean preoperative PT and PTT with p-value 0.031 and 0.000 respectively.

Table (10): Comparison between group B pre and post regarding mean preoperative platelets, HB and HCT.

Group B	Pre No.=25	Post No.=25	Test value	p-value	Sig.
Platelets:					
Mean ± SD	239.12±60.51	187.72±64.88	3.745•	0.001	HS
Range	55-352	109-403			
HB (gm%):					
Mean ± SD	13.61±1.70	10.94±1.73	6.576•	0.000	HS
Range	11.3-17	7.9-15.3			
HCT (%):					
Mean ± SD	40.86±6.81	31.90±5.66	5.338•	0.000	HS
Range	25.5-59.8	21.9-43.9			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Paired t-test.

The previous table shows that there was highly statistically significant difference between group B pre and post regarding mean preoperative mean preoperative platelets, HB and HCT with p-value 0.000.

Table (11): Comparison between group B pre and post regarding mean preoperative PT, PTT and INR.

Group B	Pre No.=25	Post No.=25	Test value	p-value	Sig.
PT:					
Mean ± SD	15.59±5.66	16.13±2.19	–0.438•	0.665	NS
Range	13-41.4	13.1-23.1			
PTT:					
Mean ± SD	35.84±8.80	44.52±10.74	–3.449•	0.002	HS
Range	13.5-59.5	31.2-79.5			
INR:					
Mean ± SD	1.10±0.19	1.19±0.17	–3.607•	0.001	HS
Range	0.96-1.8	0.9-1.71			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Paired t-test.

The previous table shows that there was statistically significant difference between group A pre and post regarding mean preoperative PTT and INR with p-value 0.002 and 0.001 respectively.

Table (12): Comparison between group A and group B regarding the amount of change regarding platelets, HB, HCT, PT, PTT and INR.

	Group A No.=25	Group B No.=25	Test value	*p*-value	Sig.
Platelets: Mean± SD	–60.56±51.05	–51.40±68.63	0.535•	0.595	NS
HB (gm%): Mean ± SD	–2.10±1.55	–2.68±2.03	1.135•	0.262	NS
HCT (%): Mean ± SD	–6.42±5.24	–8.96±8.39	1.284•	0.205	NS
PT: Mean ± SD	1.11±2.42	0.54±6.20	0.428•	0.670	NS
PTT: Mean ± SD	7.40±8.52	8.68±12.59	0.421•	0.676	NS
INR: Mean ± SD	0.06±0.14	0.08±0.12	0.542•	0.590	NS

p-value >0.05: Non significant. *p*-value <0.01: Highly significant.
p-value <0.05: Significant. •: Independent *t*-test.

The previous table shows that there was no statistically significant difference between group A and group B regarding platelets, HB, HCT, PT, PTT and INR with *p*-value >0.05.

Discussion

In our Randomized Controlled Clinical Trial we studies the effect of application of topical TxA in reducing the postoperative mediastinal bleeding in cardiac surgery.

A 50 subjects was programmed for elective open cardiac surgery, enrolled by computer program and divided randomly in two group, group A (n=25) received TxA 2g in 100ml NSS in the pericardial cavity and mediastinum before the sternal closure While group B (n=25) 100ml of NSS alone.

The result of the study revealed statistically significant difference between TxA group and the placebo group regarding the postoperative blood loss and the need for packed RBC transfusion. This means the topical application of TxA decreasing the postoperative bleeding, blood transfusion and the need for reopration, but there was no statistically significant difference in plasma and platelet transfusions between the two groups.

In our experiment two patients were for redo cardiac surgery, the patent who had topical TxA show less blood loss than the placebo group one, but we need more subjects sample to study clearly these redo operation patients. A total of two patents went to re-exploration surgery for excessive mediastinal bleeding in the few hours postopreativley to control the hemorrhage.

Rostami et al., **[20]** evaluate the effect of TxA in reducing postoperative hemorrhage in patients undergoing coronary artery bypass graft. In this study 62 patients were randomly divided into two groups of TxA and control. After surgery and removal from the CPB, in the first group TxA 2g at NSS 100cc was injected locally into the mediastinum and the second group control the same amount of NSS 100cc was given. A significant difference was found between the 2 groups in terms of postoperative hemorrhage, packed cell volume, platelet transfusion, duration of surgery, and received FFP, were found to be lower in the TxA group than in the placebo group. Which is consistent with our study, but contrary to our results, that platelet and FFP transfusions levels were not significantly different between the two groups.

Rostami et al., **[20]** study indicate that the use of topical TxA not only has a significant effect on the reduction of bleeding after CABG but also was able to reduce the blood product transfusions, however, no significant effect was seen for mortality reduction and return to the operating room due to bleeding.

In a previous study by Fawzy et al., **[23]** investigated the effect of application of TxA on the mediastinal cavity if can decrease blood loss after the on-pump CABG procedure. A total of 38 patients participated in the study. The TxA group received 1g of TxA and the control subjects received 100mL of NSS. The findings of this study showed that the mean of blood loss during the first 24h after the surgery was 626mL in the TxA and 1040mL in the control groups. Hence, the amount of blood loss in the experimental group was less than the controls and was significantly different. There was no significant difference in the post-op Packed RBCs transfusion between both groups. On other hand, the rate of platelet transfusion in the experimental group was less than that of the control group. Finally, Fawzy et al., **[23]** concluded that the topical application of TxA for the patients undergoing CABG surgery induced a decrease in post-operative blood loss without imposing extra risks on the patients. These findings are consistent with those of our study.

In other study by Abul-Azm and Abdullah **[21]**, evaluated the effect of topical application of TxA to the mediastinal cavity on post-operative blood loss in patients undergoing open heart surgery. A 100 patients undergoing elective open heart surgery divided into two groups, the first group received 2g of TxA and the control group received just NSS. The findings showed that blood loss in the exper-

imental group was less than control groups, which was statistically significant. These findings are consistent with those of our study. The rate of blood transfusion in the TxA was less than that in the control group.

The bypass of coronary artery in Abul-Azm and Abdullah **[21]** study was with CPB in which the rate of blood loss and transfusion was greater compared with the off-pump CABG surgery. In this study, eight cases was reoperated to control the bleeding were observed, while in our study two case was re-expolrated in the control group. This can be also due to the use of cardiopulmonary pump in which the inflammatory system and complement are affected by the procedure, this is differ in contrast to the off-pump procedure which have less affection. Of course, the fibrinolysis system is moderately activated by factors as cardiac manipulation, sternotomy and pericardiotomy.

Baric et al., **[25]** investigated the application of antifibrinolytic drugs on decreasing the post-operative bleeding after cardiac surgery in a clinical trial. In this study, 300 adult cardiac patients who underwent cardiac surgery were divided into three groups. In the first group aprotinin, in the second group TxA and in the third group (control group) NSS was used. The findings demonstrated a decrease in post-operative blood loss as a result of the topical application of aprotinin and tranexamic acid. Furthermore, the rate of blood loss in the aprotinin group was the least among groups, but it was not significantly different from the TxA. This study showed that the most amount of effect of TxA and aprotinin was during the first 12h after the surgery, which is due to the 3-4h half-life of the antifibrinolytic drugs. Another finding of this study was the lack of significant differences among the three groups with respect to blood transfusion. In our study, the need for blood transfusion was significantly different among the two groups, though it was less in the tranexamic acid.

In a study by Hosseini et al., **[26]** evaluated the topical application of TxA on post-operative blood loss in off-pump coronary artery bypass surgery on 71 patients assigned in 2 equal groups, the first group received 1g of TxA in 100 NSS which applied to the pericardium and mediastinal cavity while in the other group only 100ml NSS was applied. The result of the study after 24h of chest drain monitor show the average volume of blood loss was 366mL for the TxA group and 788mL for the control group. There was a statistically significant difference between the two groups (p<0.001). These findings are consistent with those of our study. The amount of packed red blood cells transfusion in the first group was less than that of the control group, which was not statistically significant. There was no statistically significant difference between the amount of HB, HCT, Platelets, PT and PTT in the post-operative stage in the two groups. The difference in our study that we used 2g of tranexamic acid in on-pump cardiac surgery. Ultimately, Hosseini et al., **[26]** concluded that the topical application of TxA in off-pump CABG patients leads to a decreased post-operative blood loss.

Moreover, Kurt study in **[27]** aimed to evaluate the effects of topical and systemic application of TxA and aprotinin on the rate of patient's blood loss after the on-pump CABG procedure. A total of 100 patients were divided in to five groups. In the first group, topical TxA was sprayed to the pericardial cavity. In the second group, TxA was injected systemically. In the third group, aprotinin was applied topically. In the fourth group, aprotinin was applied systemically and the fifth group is the control. The findings demonstrated that the rate of blood loss was less in the groups that received TxA and aprotinin compared to the controls. This study suggests the topical application of antifibrinolytic drugs to the mediastinal cavity has no systemic complication also there were no specific complications observed here. The findings of this study are consistent with our findings on lack of complications in patients who used topical antifibrinolytic drugs.

In a first pilot RCT study by Habbab et al., **[28]** investigate the role of TxA route of administration (IP vs IV) in cardiac surgery (CABG and/or aortic valve replacement), where the effects of applied topically were comparable with IV TxA with a tendency for decreased bleeding, transfusion requirements, reoperations, and postoperative seizures. A 97 adult patients undergoing nonemergent on-pump cardiac operations were enrolled and randomized to IP or IV TxA groups. The intervention (IP) group included 49 patients who received 5g TxA diluted in 50mL NSS poured into the pericardial cavity in two equal doses, 25mL after protamine and 25mL before sternotomy is closed and IV placebo 50mL NSS administered alone. The control group included 48 patients who received IV TxA 5g diluted in 50mL NSS administered alone and IP placebo 50mL NSS, 25 given when the patients come off-pump and 25mL before sternotomy is closed.

The outcome of topical TxA (IP) group shows decreased blood loss, transfusion requirements, reoperations, and postoperative seizures. The find-

ings indicate that the topical application of TxA is at least as effective and as safe as IV TxA in cardiac surgery. In our study we use 2g of TxA and our findings are consistent with the primary out come in first 24h as Habbab et al., [28] study.

In another study by Spegar et al., [29] a prospective, randomized, double blind to examine a possible augmentation of systemic administration of TxA by the additional topical application during heart valve surgery in the post-aprotinin era. A 100 patients were enrolled and randomized into two groups, all the patients were given TxA intravenously, and before the sternal closure, the group A received 250ml of NSS + TxA 2.5g poured into the pericardial cavity, but the placebo group B received 250ml of NSS. Twenty-four hours postoperatively the blood loss was 504.2 (436.0, 583.0) ml in group A, 569.7 (476.0, 681.7) ml in group B, p=0.293 and p=0.014, respectively.

There were a significant difference in the intergroup variance of blood loss and the proportion of patients requiring fresh frozen plasma; however evident differences in mean postoperative blood loss were not statistically significant. Our study has the same result of decreasing postoperative mediastinal bleeding in TxA group without the use of additional IV TxA but there was no significant difference in plasma transfusion between the two groups.

However, In a comparison with Taman et al., [30] study that evaluate topical administration of TxA if can be a good adjuvant to the I.V route for decreasing postoperative seizure incidence?, both studies show that the addition of topical application to IV TxA vs IV TxA alone did not add benefit in reducing postoperative 24h blood loss compared with IV drug alone but significantly less products were used, or significantly less seizures were observed with IV TxA plus topical TxA as in Taman HI, Amer GF, Amera SA study due to the lower dose of IV TxA used.

Between 2000 to 2016, seven small RCTs comparing the inter pericardial application of TxA vs placebo were reported in cardiac surgery [22,25,31-36] . In all these trials, except one using a small dose, topical application of TxA significantly reduced the 24-hour postoperative blood loss. A performed meta-analysis of these trials was done and confirmed the substantial reduction in 24-hour blood loss with topical application of TxA [36]. The range of mediastinal drainage following Topical TxA in our study was less than that reported in these studies (50-300 vs 303-730mL, respectively) [36].

Conclusion:

The results of our study indicate that the use of topical TXA have a significant effect on the reduction of bleeding after Cardiac Surgery, also was able to decrease the blood transfusions. Moreover, show better results in reducing the return to the operating room due to bleeding.

References

1- Global Burden of Diseases (2010): Egypt. Instituite of Health Metrics; 2010. https:// www.healthdata.org/sites/default/files/files/country_profiles/GBD/ihme_gbd_country_report_egypt.pdf. Accessed 4 Mar 2020.

2- Global health estimates 2014 summary tables (2014): Estimated deaths by cause, sex and WHO Member State 2012. Geneva: World Health Organization, 2014. http://www.who.int/healthinfo/global_burden_disease/estimates/en/ index1.html. Accessed 4 Mar 2020.

3- BABAEE G., KESHAVARZ M. and SHAYEGAN A.H.M.: Effect of a health education program on quality of life in patients undergoing coronary artery bypass surgery. Acta. Medica Iranica, 69-75, 2007.

4- GHAEM H.M., ASAR O. and SAFAEI N.: Assessing patient's quality of life after open hart surgery in Bandar Abbass, Iran. Hormozgan Univercity of Medical Science Journal, 15: 254-59, 2011.

5- FAS SIN W., HIMPE D., ALEXANDER J.P., BORMS S., THEUNISSEN W., MUYLAERT P. and VAN CAUWELAERT P.: Predictive value of coagulation testing in cardiopulmonary bypass surgery. Acta. Anaesthesiologica Belgica, 42 (4): 191-198, 1991.

6- CASATI V., GUZZON D., OPPIZZI M., COSSOLINI M., TORRI G., CALORI, G. and ALFIERI O.: Hemostatic effects of aprotinin, tranexamic acid and e-aminocaproic acid in primary cardiac surgery. The Annals of thoracic surgery, 68 (6): 2252-2256, 1999.

7- HEKMAT K., ZIMMERMANN T., KAMPE S., KASPER S.M., WEBER S.M., GEISSLER H.J. and MEHLHORN U.: Impact of tranexamic acid vs. aprotinin on blood loss and transfusion requirements after cardiopulmonary bypass: A prospective, randomised, double-blind trial. Current medical research and opinion, 20 (1): 121-126, 2004.

8- CASATI V., DELLA VALLE P., BENUSSI S., FRANCO A., GERLI C., BAILI P. and D'ANGELO A.: Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: Comparison between on-pump and off-pump techniques. The Journal of thoracic and cardiovascular surgery, 128 (1): 83-91, 2004.

9- CAI J., RIBKOFF J., OLSON S., RAGHUNATHAN V., AL-SAMKARI H., DELOUGHERY T.G. and SHATZEL J.J.: The many roles of tranexamic acid: An overview of the clinical indications for TXA in medical and surgical patients. European journal of haematology, 104 (2): 79-87, 2020.

10- KARKOUTI K., BEATTIE W.S., DATTILO K.M., MCCLUSKEY S.A., GHANNAM M., HAMDY A. and YAU T.M.: A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion, 46 (3): 327-338.

11- KAPPETEIN A.P., FELDMAN, T.E., MACK M.J., MORICE M.C., HOLMES D.R., STÅHLE E. and COLOMBO A.: Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of the SYNTAX trial. European heart journal, 32 (17): 2125-2134, 2011.

12- FITZGERALD D.C., SIMPSON A.N., BAKER R.A., WU X., ZHANG M., THOMPSON M.P. and REGISTRY P.: Determinants of hospital variability in perioperative red blood cell transfusions during coronary artery bypass graft surgery. The Journal of thoracic and cardiovascular surgery, 2020.

13- CRAMER E.M., LU H., CAEN J.P., SORIA C., BERNDT M.C. and TENZA D.: Differential redistribution of platelet glycoproteins Ib and IIb-IIIa after plasmin stimulation [published erratum appears in Blood, Jul 15; 78 (2): 545], 1991.

14- HENRY D.A., CARLESS P.A., MOXEY A.J., O'CONNELL D., STOKES B.J., FERGUSSON D.A. and KER K.: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane database of systematic reviews, (3), 2011.

15- BROWN J.R., BIRKMEYER N.J. and O'CONNOR G.T.: Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. Circulation, 115 (22): 2801-2813, 2007.

16- MYLES P.S., SMITH J.A., FORBES A., SILBERT B., JAYARAJAH M., PAINTER T. and WALLACE S.: Tranexamic acid in patients undergoing coronary-artery surgery. New England Journal of Medicine, 376 (2): 136-148, 2017.

17- WONG J., ABRISHAMI A., EL BEHEIRY H., MAHOMED N.N., DAVEY J.R., GANDHI R. and CHUNG F.:Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: A randomized, controlled trial. JBJS, 92 (15): 2503-2513, 2010.

18- MAY J.H., RIESER G.R., WILLIAMS C.G., MARKERT R.J., BAUMAN R.D. and LAWLESS M.W.: The assessment of blood loss during total knee arthroplasty when comparing intravenous vs intracapsular administration of tranexamic acid. The Journal of arthroplasty, 31 (11): 2452-2457, 2016.

19- WANG H., SHEN B. and ZENG Y.: Comparison of topical versus intravenous tranexamic acid in primary total knee arthroplasty: A meta-analysis of randomized controlled and prospective cohort trials. The Knee, 21 (6): 987-993, 2014.

20- ROSTAMI A., HOSEINI A.H. and KAMALI A.: The effect of tranexamic acid in reducing postoperative hemorrhage in patients undergoing coronary artery bypass graft. Saudi Journal of Anaesthesia, 14 (4): 431, 2020.

21- ABUL-AZM A. and ABDULLAH K.M.: Effect of topical tranexamic acid in open heart surgery. European journal of anaesthesiology, 23 (5): 380-384, 2006.

22- SHAH M.A., ASGHAR M.I., SIDDIQI R., CHAUDHRI M.S., JANJUA A.M. and IQBAL A.: Topical application of tranexamic acid reduces postoperative bleeding in open-heart surgery: myth or fact?. J. Coll Physicians Surg. Pak, 25 (3): 161-165, 2015.

23- FAWZY H., ELMISTEKAWY E., BONNEAU D., LATTER D. and ERRETT L.: Can local application of Tranexamic acid reduce post-coronary bypass surgery blood loss? A randomized controlled trial. Journal of cardiothoracic surgery, 4 (1): 1-6, 2009.

24- HATAMI F., VALIZADEH N., SALEHI F. and HOSSEINZADEH MALEKI M.: Topical versus low-dose systemic tranexamic acid in pediatric cardiac surgery: A randomized clinical study. Journal of Cardiac Surgery, 35 (12): 3368-3373, 2020.

25- BARIC D., BIOCINA B., UNIC D., SUTLIC Z., RUDEZ I., VRCA V.B. and IVKOVIC M.: Topical use of antifibrinolytic agents reduces postoperative bleeding: A double-blind, prospective, randomized study. European journal of cardio-thoracic surgery, 31 (3): 366-371, 2007.

26- HOSSEINI H., RAHIMIANFAR A.A., ABDOLLAHI M.H., MOSHTAGHIYOON M.H., HADDADZADEH M., FEKRI A. and RAHIMIANFAR F.: Evaluations of topical application of tranexamic acid on post-operative blood loss in off-pump coronary artery bypass surgery. Saudi journal of anaesthesia, 8 (2): 224, 2014.

27- KURT T.: Evaluation of the effects of systematic or topical use of tranexamic acid and aprotinin on the blood loss and the used amount of blood products following cardiopulmonary bypass surgery. AJCI, 5: 116-21, 2011.

28- HABBAB L.M., HUSSAIN S., POWER P., BASHIR S., GAO P., SEMELHAGO L. and LAMY A.: Decreasing postoperative blood loss by topical vs. intravenous tranexamic acid in open cardiac surgery (DEPOSITION) study: Results of a pilot study. Journal of Cardiac Surgery, 34 (5): 305-311, 2019.

29- SPEGAR J., VANEK T., SNIRCOVA J., FAJT R., STRAKA Z., PAZDERKOVA P. and MALY M.: Local and systemic application of tranexamic acid in heart valve surgery: A prospective, randomized, double blind LOST study. Journal of thrombosis and thrombolysis, 32 (3): 303-310, 2011.

30- TAMAN H.I., AMER G.F. and AMER S.A.: Can topical administration of tranexamic acid be a good adjuvant to the intravenous route for decreasing postoperative seizure incidence? A double blinded randomized study. Ain-Shams Journal of Anaesthesiology, 8 (1): 36, 2015.

31- DE BONIS M., CAVALIERE F., ALES SANDRINI F., LAPENNA E., SANTARELLI F., MOSCATO U. and POSSATI G.F.: Topical use of tranexamic acid in coronary artery bypass operations: A double-blind, prospective, randomized, placebo-controlled study. The Journal of thoracic and cardiovascular surgery, 119 (3): 575-580, 2000.

32- AOKI M., OKAWA Y., GOTO Y., OGAWA S. and BABA H.: Local administration of tranexamic acid in off-pump coronary artery bypass. Asian Cardiovascular and Thoracic Annals, 20 (6): 658-662, 2012.

33- PATEL J., PRAJAPATI M., PATEL H., GANDHI H., DEODHAR S. and PANDYA H.: Topical and low-dose intravenous tranexamic acid in cyanotic cardiac surgery. Asian Cardiovascular and Thoracic Annals, 25 (2): 118-122, 2017.

34- CHAUDHARY F.A., PERVAZ Z., ILYAS S. and NIAZ M.N.: Topical use of tranexamic acid in open heart surgery. J. Pak. Med. Assoc., 68 (4): 538-542, 2018.

35- MIRMOHAMMADSADEGHI A., MIRMOHAMMADSADEGHI M. and KHEIRI M.: Does topical tranexamic

acid reduce postcoronary artery bypass graft bleeding?. Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences, 23, 2018.

36- HABBAB L.M., SEMELHAGO L. and LAMY A.: Topical use of tranexamic acid in cardiac surgery: A meta-analysis. The Thoracic and Cardiovascular Surgeon, 4 (03): 212-218, 2020.

تأثير حمض الترانيكساميك الموضعى على نزيف ما بعد الجراحة فى جراحة القلب

الخلفية : واحدة من أكبر مشاكل جراحة القلب هى النزيف ما بعد الجراحة الذى قد يؤدى إلى نقل الدم. ويعود فقدان الدم والنزيف إلى أسباب عديدة، أحدهما هو انحلال الفيبرين. لقد تم استخدام العديد من الأدوية المضادة للفيبرين لتقليل النزيف ما بعد الجراحة فى جراحة القلب بما فى ذلك حمض الأمينو كابرويك والأبروتينين وحمض الترانيكساميك. وأحماض الترانيكساميك هى مشتقات تركيبية من الحمض الأمينى ليسين. حيث أنه يرتبط مع الايسين على مواقع مستقبلات الليسين على سطح البلازمين والبلازمينوجين مما يؤدى إلى فك ارتباط البلازمينوجين من سطح الفايبرين وبالتالى ايقاف عملية انحلال الفايبرين.

الهدف من البحث : دراسة تأثير تطبيق حمض الترانيكسا ميك الموضعى على تقليل النزيف ما بعد الجراحة فى المرضى الذين يخضعون لعمليات جراحة القلب عبر الشق القصى المنصف ومقارنتهم مع مجموعة مرضى آخرين تجرى لهم عمليات مماثلة بنفس الظروف من دون استخدام حمض الترانيكساميك الموضعى.

المرضى وطرق العلاج : فى تجربتنا السريرية ذات الشواهد فى العينات العشوائية فى قسم جراحة القلب والصدر فى مستشفيات جامعة عين شمس، حيث تم اختيار ٥٠ شخصاً لإجراء عمليات جراحة القلب المفتوح المحددة مسبقاً، وتم تسجيلهم بواسطة برنامج كمبيوتر وقسموا عشوائياً إلى مجموعتين، المجموعة أ (ع=٢٥) تلقت حمض الترانيكساميك ٢ جم فى ١٠٠ مل محلول الملح المتعادل ووضعت حول القلب والحيز المنصف قبل اغلاق عظمة القص بينما المجموعة ب (ع=٢٥) تلقت ١٠٠ مل من محلول الملح المتعدل فقط. وبعد اغلاق عظمة القص وفتح الأنابيب الصدرية، تمت مراقبة الأنابيب لمدة ٢٤ ساعة تالية فى العناية المركزة، مع حساب كمية الدم المفقودة فى الأنابيب بالإضافة لكمية الدم والبلازما والصفائح الدموية التى أعطيت للمريض ، وكذلك تم احتساب عدد الحالات التى احتاجت للعودة للعمليات للاستكشاف فى حالة النزيف المتزايد.

النتائج : كشفت نتيجة الدراسة عن فرق معتد به إحصائياً بين مجموعة حمض الترانيكساميك ومجموعة الدواء الوهمى فيما يتعلق بفقدان الدم بعد الجراحة والحاجة إلى نقل الدم. هذا يعنى أن التطبيق الموضعى لحمض الترانيكساميك يقلل من النزيف بعد عمليات القلب المفتوح، ونقل الدم والحاجة إلى إعادة الجراحة، ولكن لم يكن هناك فرق ذو دلالة إحصائية فى عمليات نقل البلازما والصفائح الدموية بين المجموعتين.

الخلاصة : وتشير نتائج دراستنا إلى أن استخدام حمض الترانيكساميك الموضعى له تأثير كبير على تقليل النزيف بعد جراحة القلب، كما أنه كان قادراً على تقليل عمليات نقل الدم. وإضافة إلى ذلك، أظهر نتائج جيدة فى تقليل الحوجة للعودة إلى غرفة العمليات بسبب النزيف.