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Efficacy and Safety of Tropical Use of Tranexamic Acid during Off-Pump Coronary Artery Bypass Surgery: A Randomized Control Trial

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Abstract

Background: Postoperative mediastinal bleeding in patients undergoing cardiac surgery is still one of the most common complications. **Objective:** This study was intended to investigate the efficacy of topical tranexamic acid in reducing postoperative bleeding after post-operative cardiovascular surgery. **Methodology:** In this non-randomized, double blinded, clinical trial, patients undergoing Off-Pump Coronary Artery Bypass (OPCAB) surgery in NICVD, Dhaka, Bangladesh during January 2014 to December 2015 and fulfilling inclusion and exclusion criteria were recruited. They were assigned in two groups- 30 patients in tranexamic acid group (Group 1) and 30 patients in placebo group (Group 2). On completion of the grafting, before closure of the sternum tranexamic acid (2.5 g/25 mL) or placebo (25 mL of saline) diluted in 100 mL of warm saline (370 C) was instilled into the pericardial cavity including the mediastinal tissues and left for 5 minutes. Then it was cleared out by wall sucker and sternum was closed. **Results:** There was no significant difference in baseline demographic data, basic clinical characteristics and preoperative coagulation profile between the 2 groups ($P > 0.05$). Total mediastinal bleeding in group 1 and group 2 patients were421.67±70.32 vs 593.33±77.38ml, $p<0.001$. In case of, whole blood transfusion in group 1 and group 2 patients were 0.87±0.0.73 units and1.77±0.57 units respectively, $p<0.001$. **Conclusion:** No patient required reoperation for bleeding and there was no incidence of prolonged ventilation, MI, thromboembolism, DVT or CVA in any of the patients in either group. *[Journal of National Institute of Neurosciences Bangladesh, July 2021;7(2):142-146]*

Keywords: Post-Operative Outcomes; Off-Pump; Coronary Artery Bypass Surgery; Tranexamic Acid

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Introduction

Bleeding is a common complication after coronary artery bypass grafting (CABG)[1]. Excessive bleeding and blood transfusion play an important role in post-CABG mortality and morbidity[2]. Patients undergoing cardiac surgery still receive more blood transfusions than in other surgical procedures, consuming 20.0% of blood bank reserves[3]. Reopening sternotomy to control bleeding has been reported in 2% to 7% of cases. Blood transfusion can cause infection and immunological reactions and increase hospital length stay and cost, which justifies all efforts to reduce bleeding after

CABG[4].

Patients who suffer from excessive postoperative bleeding are vulnerable to increased risk of post-operative complications, re-exploration, ICU stay for longer than 72 hours, mechanical ventilation for longer than 24 hours, receiving any kind of post-operative transfusion and higher mortality rate[5] (Christensen,, et al., 2009). Antifibrinolytic agents (aprotinin, tranexamic acid, and ε-aminocaproic acid) have been shown to inhibit fibrinolysis and, thus, reduce bleeding in cardiac surgery[6]. Systemic administration of antifibrinolytic agents has been commonly employed in the field of cardiac surgery, and many studies have reported their haemostatic effects. However, recent studies on large numbers of patients have raised growing concerns about the serious adverse effects observed following systemic administration of antifibrinolytic agents. These complications include increased mortality, renal toxicity, anaphylactic reactions, graft vessel occlusion, the risk of myocardial infarction in high-risk cardiac surgery following aprotinin use[7-11].

Tranexamic acid is structurally a lysine analogue and is a synthetic antifibrinolytic drug which acts by attaching to the lysine-binding sites of plasmin and plasminogen. Saturation of these sites displaces plasminogen from its fibrin surface, thereby inhibiting fibrinolysis[12] (Longstaff,, et al., 1994). Tranexamic acid is 7 to 10 times more potent than ε- aminocaproic acid and is far less expensive than aprotinin (Verstraete, 1985). A number of studies have shown that both intravenous tranexamic acid[13] (Ferraris,, et al., 2007; Henry,, et al., 2007; Shahidullah, 2012) and topically applied TA (De-Bonis,, et al., 2000; Abul-Azm,, et al., 2006; Baric, 2007; Abrishami,, et al., 2009; Fawzy,, et al., 2009)) are effective in reducing blood loss after cardiac surgery. But intravenous TA administration has been associated with an increased risk of thromboembolic complications and early graft closure in coronary artery bypass grafting (Cosgrove,, et al., 1992; Ovrum,, , et al., 1993). This present study was aimed to quantify the effectiveness and safety of the topical administration of tranexamic acid in reducing bleeding from a variety of causes after OPCAB. The goal of the present study was to assess the efficacy and safety of topical application of tranexamic acid in the pericardial cavity on post-operative blood loss in off-pump CABG.

Methodology

Study Settings and Population: This study was designed as non-randomized, double blinded, clinical trial study. This study was conducted in the department of cardiac surgery at National Institute of Cardiovascular Diseases, Dhaka, Bangladesh from January 2014 to December 2015 for a period of two years. The study was carried out among the patients admitted in NICVD for OPCAB surgery. Patients with ischemic heart disease admitted in NICVD with a plan for OPCAB Surgery with the age of 18 to 60 years and both male and female were included in this study. Patients with renal impairment, hepatic impairment, history of abnormal bleeding, previous history of stroke, previous history of cardiac surgery, any combined cardiac surgical procedure, patient with surgical source of bleeding found on reopening or known allergy to tranexamic acid were excluded from this study.

Allocation: Purposive and convenient sampling technique were used for this study. Study population were divided into two groups named as group 1 who were received tranexamic acid (TA) topically in the pericardial cavity before closure of the sternum and group 2 who were received 0.9% NaCl as placebo in the pericardial cavity before closure of the sternum.

Blinding: The patients, members of the surgical team, and the ICU nurses who measured the post-operative blood loss to record in the ICU chart, were kept blinded. The investigator, after allocating the selected patient in either group supplied the desired solution (tranexamic acid or placebo) to the surgical team for application. The investigator knew which patient was included in which group. The members of operating team, the patients and the assessors did not know which patient was receiving what, tranexamic acid or placebo.

Follow up and Outcomes of the Patients: Pre-operative variables like NYHA (New York Heart Association) functional class and pre-operative use of antiplatelet agent (Aspirin, Clopidegrol) or anticoagulant (warfarin), per operative variables like total operation time and Post-Operative variables like Amount of bleeding, Amount of blood and blood product transfusion, Incidence of reoperation for bleeding, Post-operative complication like myocardial infarction (MI), deep vein thrombosis (DVT), stroke, thromboembolism and Mortality were recorded. Post operatively patients were assessed for amount of bleeding at the end of 4 hours, 12 hours and 24 hours. The total amount of bleeding was also recorded till drain tube were removed. Total amount of transfused unit of blood and blood products, any reoperation for bleeding were noted and, plan to investigate any thrombotic complications, i.e. myocardial infarction (MI), cerebro-vascular accident (CVA), deep vein

thrombosis (DVT), thrombo-embolism etc. according to clinical suspicion was made like CK-MB, Troponin I for ST elevation, Duplex study for DVT, CT Scan of brain for CVA.

Ethical Issues: Approval for this study protocol was taken from the institutional ethical review committee. The purpose of the study was explained to the potential participants. The participants were apprised of the study, about the total plan and its importance. Expected benefit and potential harm of the study was explained to them. The study was conducted with signed informed consent of all the participants with the right to withdraw himself/ herself from the study at any time during the study period. Interests of the study were given the highest priority and confidentiality was maintained with safeguard of the right and health of the participants.

Statistical Analysis: The numerical data obtained from the study were analyzed and significance of difference was estimated by using the statistical methods. Qualitative data are expressed in frequency with corresponding percentage and quantitative data are expressed in mean with standard deviation. Comparison between groups is done by Chi square test and Student's t test. p value less than 0.05 is considered as significant. All data were analyzed by SPSS 20.0 for Windows®.

Results

The present study was intended to assess the local effect of tranexamic acid in reducing postoperative bleeding and subsequent blood transfusion in patients undergoing OPCAB surgery. Among the 60 patients tranexamic acid was topically applied in 30 patients, others received normal saline. The findings of the study obtained from data analyses are presented below. The age of the patients undergoing OPCAB surgery ranges from 37 years to 70 years. However, most of the patients were in the range of 41 to 60 years. Moreover there was no statistical significant difference between the groups in terms of age (p>0.05) (Table 1)

Table 1: Distribution of the patients according to age

Age Group	Group		Total	P value
	Group I	Group II		
37 to 40 Years	0(0%)	2(6.67%)	2(3.33%)	
41 to 50 Years	14(46.67%)	12(40.00%)	26(43.33%)	0.867
51 to 60 Years	13(43.33%)	11(36.67%)	24(40.00%)	
61 to 70 Years	3(10%)	5(16.67%)	8(13.33%)	

Most of the operations (55%) were performed within 4.51 to 5.00 hours. Total operation time in group 1 and 2 is bears no significant difference (4.89±0.25 vs 5.01±0.46, p=0.209) (Table 2).

Table 2: Distribution of the patients according to Total operation time

Total Operation Time (Hours)	Group		Total	P value
	Group I	Group II		
4.01-4.50	6(20%)	8(26.67%)	14(23.33%)	
4.51-5.00	20(66.67%)	13(43.33%)	33(0.55%)	0.209
5.01-5.50	4(13.33%)	6(20%)	10(16.67%)	
5.51-6.00	0(0%)	3(10%)	3(5%)	

No patient required reoperation for bleeding. There was no incidence of MI, thromboembolism, DVT or CVA in none of the patients in either group (Table 3).

Table 3: Distribution of the patients according to postoperative complication

Postoperative complication		Group of the patient		Total
		Group I	Group II	
MI	Yes	0	0	0
	No	30	30	60
Thrombo-embolism	Yes	0	0	0
	No	30	30	60
DVT	Yes	0	0	0
	No	30	30	60
CVA	Yes	0	0	0
	No	30	30	60
Reoperation for bleeding	Yes	0	0	0
	No	30	30	60
Mortality	Yes	0	0	0
	No	30	30	60

Discussion

Topical administration of tranexamic acid is effective and safe in reducing post-operative bleeding[11]. Tranexamic acid when topically applied interferes with local fibrinolytic activity which is one of the major causes of postoperative bleeding. Its efficacy, after local application, has been proven in cardiac surgery, neurosurgery, dental surgery and gynecological surgery. In cardiac surgery tranexamic acid is applied in the pericardial cavity for desired therapeutic effect to reduce post-operative bleeding[13]. When applied locally into the pericardial cavity, it acts by directly attacking the source of bleeding. Moreover it is not absorbed into the systemic circulation due to natural barrier property of the pericardium and low molecular weight, and if at all absorbed it is cleared of from the systemic circulation due to delay in absorption and short half-life[14]. As a result its local application is devoid of any side effects like myocardial infarction, cerebrovascular accidents, deep vein thrombosis, thromboembolism, graft occlusion following CABG which might be associated

with systemic administration of antifibrinolytic agents.

Excessive post-operative haemorrhage in cardiac surgery is a serious clinical complication placing substantial demands on hospital resources[9]. Patients who suffer from excessive postoperative bleeding are vulnerable to increased risk of post-operative complications, re-exploration, ICU stay for longer than 72 hours, mechanical ventilation for longer than 24 hours, receiving any kind of post-operative transfusion and higher mortality rate. This also imposed a service burden on the transfusion department and increased the cost of treatment. Topical application of tranexamic acid has not been studied in patients with OPCAB surgery in Bangladesh. Therefore the study on topical application of tranexamic acid in patients with OPCAB surgery in this institute is quite justified as its result will definitely help the patients with a life of good quality and less morbidity. Mean (±SD) age of the study subjects was 52.97(±7.44) years. Age of the most of the patients was between 41 to 60 years. Hossain, (2013) reported the mean age of patients undergoing OPCAB surgery to be 53.80±8.57 years which is similar to this study. The mean (±SD) age of group1 and group2 patients were 53.5±6.75 years and 52.43±8.18 years respectively (p>.005).

Postoperative mediastinal bleeding at 4 hours, 12 hours in group 1 and group 2 patients were 116.67±44.2 ml vs 190±44.33 ml (p=0.000), 345±74.68 ml vs 511.67±66.54 ml (p=0.000) respectively. Total postoperative mediastinal bleeding was also significantly lower in tranexamic acid group than in placebo group (421.67±70.32 vs 593.33±77.38 ml;p=0.000).

Baric et al[12] reported cumulative blood loss within 24 h 633± 343 ml in tranexamic acid group and 903± 733 ml in placebo group. This study included patients undergoing coronary surgery, valve surgery and other cardiac surgeries. The tranexamic acid group received 2.5 gm TA in 250 ml normal saline and the other group received 250 ml of normal saline in the pericardial cavity and over the mediastinal tissue before median sternotomy closure.

Hossein et al[13] reported to enroll 71 patients in prospective study and grouped patients into two groups. In TA group median of postoperative bleeding at the end of 24 hours was 366 ml in comparison to 788 ml in placebo group bearing significant difference (p<0.001). Though he used lower amount (1g) of tranexamic acid in his study.

Nouraei et al[8] reported total blood loss in Tranexamic acid group to be 313±173ml and 454±268 ml in control group (p<0.01). In the study tranexamic acid (2 g/20 mL) or placebo (20 mL of saline) was diluted in 500 mL of warm saline (37°C), poured into the pericardial cavity, and left for 5 min on completion of CABG (on pump) before sternotomy wound closure. The volume of blood loss were similar to our study.

Masakazu et al[14] reported that the volume of blood loss in 24 h after intensive care unit admission was 492±180 ml in control group and 303±112 ml mL in tranexamic acid group (p<0.0001). They investigated 100 consecutive patients undergoing off-pump coronary artery bypass. In the study group 10 mL of a solution containing 1 g of tranexamic acid was sprayed into the pericardial cavity and mediastinum before the sternum was closed. Our study showed similar volume of blood loss.

Postoperative whole blood transfusion in the study was 0.87±0.73 units in tranexamic acid group and 1.77±0.57 units in placebo group (p<0.001). The volume of each unit of whole blood was about 450 ml. In case of FFP transfusion both groups has no significant difference (p=222). Possibly because no patient undergone cardiopulmonary bypass. Hossein et al[13] noticed significant amount of less packed red cell transfusion in case of tranexamic acid group comparison to placebo group.

Baric et al[12] reported that the total amount of packed red blood cells transfused was 423± 483 ml in tranexamic acid group and 647 ± 1137 ml in placebo group. Although the amount of transfused packed cell almost 250 ml lower in tranexamic acid group compared to placebo, the decrease of transfusion requirements were not statistically significant in the study.

Boris et al[11] found no statistically significant difference between tranexamic acid group and the placebo group regarding packed red cell transfusion when they studied the effect of topical tranexamic acid on postoperative blood loss in patients undergoing conventional CABG. The average number of units transfused in study group and control group were 2.3 units and 2.2 units respectively (1 unit= approximately 360 mL). Masakazu et al[14] found no statistically significant difference in the blood transfusion volumes between tranexamic acid group and the control group in their study on the effect and safety of local administration of tranexamic acid in off-pump coronary artery bypass.

No post-operative complication like MI, thromboembolism, DVT, CVA or reoperation for bleeding was found in either group in our study. Nouraei et al8 did not report any complications related to topical tranexamic such as mortality, myocardial infarction,

cerebrovascular accident, seizure, or renal failure. Masakazu et al[14] reported no side effects of locally administered tranexamic acid. Baric et al[12] reported that local administration of Tranexamic acid is potentially safer than local administration of aprotinin.

Tranexamic acid inhibit the conversion of plasminogen to plasmin. The application of TA into the chest before closure of the median sternotomy could remove plasminogen from the fibrin surface of clots, thereby inhibiting plasmin-induced degradation of fibrin. Thus it might prevent the resolution of formed clots and lead to hemostasis by preserving their integrity.

Conclusion

In conclusion topical use of tranexamic acid has efficacy for the reduction of postoperative mediastinal bleeding during OPCAB surgery. It also reduces whole blood transfusion requirements during immediate postoperative period among patients undergoing OPCAB surgery. It has been recommended that tranexamic acid can be safely used locally to reduce post-operative bleeding and transfusion requirements following OPCAB surgery.

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