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Original Article

Journal of National Institute of Neurosciences Bangladesh, July 2016, Vol. 2, No. 2

oISSN 2518-6612
pISSN 2410-8030

Post-Operative Outcomes of Off-Pump Coronary Artery Bypass Surgery Patients after Topical Use of Tranexamic Acid

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[**Received:** 21 January 2016; **Revised:** 11 March 2016; **Accepted:** 5 May 2016; **Published:** 1 July 2016]

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 OPCAB surgery. **Methodology:** This non-randomized, double blinded, clinical trial was conducted in the Department of Cardiac Surgery at National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh during January 2014 to December 2015 for a period of two (2) years. Patients' undergone CABG after fulfilling the inclusion and exclusion criteria was recruited for this study. 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 (37° 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. **Result:** 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 were 421.67±70.32 vs 593.33±77.38 ml ($p<0.001$). In case of, whole blood transfusion in group 1 and group 2 patients were 0.87±0.0.73 units and 1.77±0.57 units respectively ($p<0.001$). 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. **Conclusion:** In conclusion the efficacy of topical tranexamic acid is helpful for reducing postoperative bleeding after OPCAB surgery. [Journal of National Institute of Neurosciences Bangladesh, 2016;2(2): 79-83]

Keywords: Post-Operative outcomes; topical tranexamic acid; OPCAB surgery

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Conflict of interest: There is no conflict of interest to any of the authors of this article.

Funding agency: The study was not funded by any authority.

Contribution to authors: AH, ABA, RR & SM were involved in protocol preparation, data collection and literature search up to report writing. KAMMH, MU & MKH was involved in manuscript preparation as well as involved in literature search up and manuscript revision and also in statistical analysis.

How to cite this article: Hoque A, Adhikary AB, Hasan KAMM, Rahman R, Uddin M, Hasan MK. Post-Operative Outcomes of Off-Pump Coronary Artery Bypass Surgery Patients after Topical Use of Tranexamic Acid. J Natl Inst Neurosci Bangladesh 2016;2(2): 79-83

Introduction

Antifibrinolytic agents like aprotinin, tranexamic acid, and ε-aminocaproic acid have been shown to inhibit fibrinolysis and, thus, reduce bleeding in cardiac surgery[1]. Systemic administration of antifibrinolytic agents has been commonly employed in the field of

cardiac surgery, and many studies have reported their haemostatic effects[2]. 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[3], renal toxicity[4], anaphylactic reactions, graft vessel occlusion, the risk of myocardial infarction in high-risk cardiac surgery following aprotinin use[5].

Tranexamic acid (TA), structurally a lysine analogue, is a synthetic antifibrinolytic drug, and 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[6]. TA is 7 to 10 times more potent than ε- aminocaproic acid and is far less expensive than aprotinin and a number of studies have shown that both intravenous tranexamic acid[7-8] and topically applied TA[9-11] 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[12].

Several experimental studies have shown that local application of different medications into the pericardial cavity can lead to desirable therapeutic efficacy without significant systemic absorption due to the natural barrier properties of the pericardium, which prevents free diffusion of substances[13]. In light of these findings, topical application of antifibrinolytics may be an effective and safe pharmacological strategy to minimize blood loss in cardiac surgery without any systemic complication[14-15].

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 investigate the topical application of tranexamic acid in the pericardial cavity on post-operative blood loss in off-pump CABG.

Methodology

Study Population and Setting: 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 (2) years. The study was carried out among the patients admitted in NICVD for OPCAB surgery. 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. Patients with ischemic heart disease admitted in NICVD with a plan for OPCAB Surgery with the age of the patients will be within 18 to 60 years in both male and female were include for this study. Renal impairment, hepatic impairment, a 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 patients with known allergy to tranexamic acid were excluded from his study. Study population were divided into two groups named as group 1 which was included 30 patients who received tranexamic acid (TA) topically in the pericardial cavity before closure of the sternum and group 2 which was included 30 patients who 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.

Intervention: Patients admitted for coronary artery bypass grafting that fulfills the selection criteria were enrolled into the study. Cases were selected purposively. Detailed history, clinical examination and relevant investigation reports of all patients were recorded in the data collection sheet preoperatively. All patients were pre-medicated with tablet midazolam 7.5 mg orally the night before surgery. Injection Morphine sulphate 7.5 mg intramuscularly (I.M.) and tablet Metoprolol 25 mg per orally 1 hour before surgery were applied. Standard anesthetic technique including induction, maintenance and recovery were being followed. A median sternotomy was done and at the same time Great saphenous vein was harvested and prepared for graft. Internal mammary artery was prepared for the graft. The distal anastomosis with

reverse saphenous venous graft was done with partial clamp of aorta. The drainage of the chest tubes were measured hourly and were removed when the total drainage volume of < 50 ml over the previous12 hours and of serous color. Uniform transfusion protocol was applied to all patients. Blood and blood components were administered only when the hematocrit level < 24% or the haemoglobin level ≤ 8.0 gm/dL in the postoperative period. In post-operative period all necessary investigations were done routinelyand were being managed accordingly.

Follow up and Outcomes Measures: Post-operatively patients were assessed for amount of bleeding at the end of 4 hour, 12 hour and 24 hour. 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, i.e. CK-MB, Troponin I for ST elevation, Duplex study for DVT, CT Scan of brain for CVA. Pre-operative variables were NYHA (New York Heart Association) functional class and pre-operative use of antiplatelet agent (Aspirin, Clopidegrol) or anticoagulant (warfarin). Per operative variables were total operation times. Post-operative complication i.e. myocardial infarction (MI), deep vein thrombosis (DVT), stroke, thromboembolism and mortality were the post-operative variables.

Data Analysis: Data were collected in a case record form (CRF) from history, physical examination, investigation reports, preoperative and post-operative findings of the individual patient. 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 is 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. Table I shows that the age of the patients undergoing OPCAB surgery ranges from 37 years to 70 years. But most of the patients were in the range of 41 to 60 years (Group 1 90%, Group 76.67%). Moreover there was no statistical significant difference between the groups in terms of age (p>0.05).

Table 1: Distribution of the patients according to age

Age Group (years)	Group		Total	p-value
	Group 1 (n=30)	Group 2 (n=30)		
37 to 40	0(0%)	2(6.67%)	2(3.33%)	
41 to 50	14(46.67%)	12(40.00%)	26(43.33%)	0.867
51 to 60	13(43.33%)	11(36.67%)	24(40.00%)	
61 to 70	3(10%)	5(16.67%)	8(13.33%)	
Total	**30(100.0%)**	**30(100.0%)**	**60(100.0%)**	
Mean±SD	53.5±6.75	52.43±8.18		

Figures in the parenthesis denote corresponding %. Data were analyzed using chi-square Test.

Table 2 compares the peroperative finding between group 1 and group 2 patients. 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 1: Distribution of the patients according to age

Total operation time(Hours)	Group of the Patient		Total	p-value
	Group 1 (n=30)	Group 2 (n=30)		
4.01 to 4.50	6(20%)	8(26.67%)	14(23.33%)	
4.51 to 5.00	20(66.67%)	13(43.33%)	33(0.55%)	0.209
5.01 to 5.50	4(13.33%)	6(20%)	10(16.67%)	
5.51 to 6.00	0(0%)	3(10%)	3(5%)	
Total	**30(100%)**	**30(100%)**	**60(100%)**	
Mean±SD	4.89±0.25	5.01±0.46	4.95±0.37	

Figures in the parenthesis denote corresponding %. Data analyzed using Student's t-Test were presented as mean ± SD; t value=-1.270; df value=58

Table 3 shows that 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: Distribution of the patients according to postoperative complication

Postoperative Complication		Group of the patient		Total
		Group 1 (n=30)	Group 2 (n=30)	
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

National Institute of Cardiovascular Diseases, Dhaka, Bangladesh plays a pivotal role in the field of cardiac surgery in the country. Yearly about one thousand heart surgeries are performed here. Number of OPCAB surgeries is nearly 20% of the total procedures performed.

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[16] reported the mean age of patients undergoing OPCAB surgery to be 53.80±8.57 years which are similar to this study. The mean (±SD) age of group1 and group 2 patients were 53.5±6.75 years and 52.43±8.18 years respectively (p>0.005).

Regarding peroperative variables group 1 and group 2 total operation time was 4.89±0.25 vs 5.01±0.37 hours respectively and have no significant difference between the groups (p>0.05). Total operation time was standard for our country. Mahaffey et al[17] 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).

No post-operative complication like MI, thromboembolism, DVT, CVA or reoperation for bleeding was found in either group in our study. Nouraei et al[17] did not report any complications related to topical tranexamic such as mortality, myocardial infarction, cerebrovascular accident, seizure, or renal failure. Aoki et al[10] reported no side effects of locally administered tranexamic acid. Baric et al[11] reported that local administration of Tranexamic acid is potentially safer than local administration of aprotinin. Tranexamic acid inhibits 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[17].

Conclusion

Topical application of tranexamic acid can significantly and safely reduce postoperative mediastinal bleeding. 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. It has been also recommended for another study on topical administration of tranexamic acid with larger sample size, different dose regimens and also recruitment of patients undergoing OPCAB surgery in other cardiac centers operating in the country as well.

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