ORIGINAL ARTICLE

Topical Application of Tranexamic Acid Reduces Postoperative Bleeding in Open-Heart Surgery: Myth or Fact?

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ABSTRACT

Objective: To determine the efficacy of topical application of Tranexamic acid in controlling postoperative bleeding in open-heart surgery.

Study Design: Double blind randomized control trial.

Place and Duration of Study: Departments of Cardiac Surgery and Intensive Care of Armed Forces Institute of Cardiology and National Institute of Heart Diseases (AFIC-NIHD), Rawalpindi, Pakistan, from May to October 2011.

Methodology: A total of 100 consecutive adult patients fulfilling the inclusion criteria undergoing elective on-pump cardiac surgeries were randomly divided in groups 'A' and 'B'. A study solution that contained 2.5 g of Tranexamic acid in 250 ml normal saline in group-A and equal amount of normal saline (placebo) in group-B was poured in the pericardial cavity over the mediastinal tissues before sternal closure. Postoperative bleeding was measured in both groups for 24 hours in the cardiac surgical ICU. Efficacy of Topical Tranexamic Acid / Placebo was measured in terms of mean postoperative bleeding in ml.

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Results: There was significant difference in the mean postoperative bleeding within 24 hours among the two groups 340.1 ± 112.4 ml in Tranexamic acid group vs. 665 ± 187.28 ml in placebo group ($p < 0.001$).

Conclusion: Patients who did not have topical Tranexamic acid before chest closure had a significantly higher postoperative bleeding. Topical Tranexamic acid application is an effective and economical way for controlling non-surgical bleeding in patients undergoing cardiac surgery with cardiopulmonary bypass.

Key Words: *Cardiac surgery. Postoperative hemorrhage. Tranexamic acid.*

INTRODUCTION

In recent times, enormous advances have been made to perfect cardiac surgery, leading to a reduction in the number of complications.[1] Postoperative hemorrhage remains the most common and sinister complication after on-pump cardiac surgery leading to a substantial increase in the morbidity and mortality.[2,3] With the increase in the number of cardiac surgical procedures. There has been an increasing load on the blood banks[4] and a major proportion of all allogenic blood transfusions in the United Kingdom and the United States occurs in cardiac surgical patients.[5,6] Blood transfusion in cardiac surgery has been recognized as a strong and independent risk factor for causing post-operative morbidity, early and late mortality, increased hospital stay and cost.[3,6,7]

Re-exploration for postoperative bleeding after cardiac surgery adds to the morbidity and mortality. Non-surgical cause of postoperative bleeding has been found in more than 50% of patients re-explored.[8] Non-surgical postoperative bleeding occurs due to micro-vascular bleeding from pericardial and mediastinal tissues when blood comes in contact with non-endothelial surfaces of the Cardio-Pulmonary Bypass (CPB) machine, compounded by liberal use of heparin and a complex interaction of humoral and cellular pathways.[2]

Of the various blood conservation strategies developed recently, anti-fibrinolytic drugs are being employed in open-heart surgeries to minimize non-surgical blood loss by inhibiting fibrinolysis and consequently the need for blood transfusions.[1,6] Aprotinin along with the lysine analogues Epsilon-Aminocaproic Acid (EACA) and Tranexamic Acid (TXA) are the three antifibrinolytic drugs in use in cardiac surgery.[6] Compared to Aprotinin the lysine analogues (Tranexamic acid and epsilon-Aminocaproic acid) are also effective and are cheaper.[11] Recent studies have shown a statistically significant increase in mortality with Aprotinin, as compared to Tranexamic acid used in cardiac surgery and is no longer being used as of November 2007.[11,12]

Furthermore, Tranexamic acid has been shown to be 10 times more potent than epsilon-Aminocaproic acid.[6] Administration of Tranexamic acid reduces the number of blood transfusions or the return to theatre for bleeding in patients undergoing cardiac surgery.[3] Although antifibrinolytic agents successfully reduce bleeding after

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Received: September 20, 2013; Accepted: December 18, 2014.

cardiac surgery but their systemic use has recently become controversial.[9] Tranexamic acid has been used both systemically and topically, but its intravenous administration increases the risk of thrombo-embolic complications and consequently early graft closure in coronary artery bypass grafting is increased.[10,13] Topical application of antifibrinolytic agents in pericardial cavity after cardiac surgery has been found to avert most of these effects and effectively reduce postoperative bleeding.[9,13]

The authors hypothesized that topical application of Tranexamic acid within the pericardial cavity just before the closure of sternum after open-heart surgery is effective in controlling the amount of postoperative bleeding.

The objective of this study was to determine the efficacy of topical application of Tranexamic acid in controlling postoperative bleeding in open-heart surgery.

METHODOLOGY

This double blind randomized controlled trial was conducted at the Department of Cardiac Surgery, Armed Forces Institute of Cardiology and National Institute of Heart Diseases (AFIC-NIHD), Rawalpindi, Pakistan, from May to October, 2011. After approval of the Hospital Ethics Committee and informed consent 100 consecutive adult patients (age 18 to 70 years) of both genders undergoing first-time elective open-heart surgeries were included in the study. Patients for surgeries for congenital heart diseases and thoracic aorta redo or emergency procedures, patients who were on anti-platelet drugs (Aspirin/ Clopidogrel) within 7 days of surgery, patients with impaired renal functions (creatinine clearance of < 30 ml/minutes), chronic liver disease and bleeding diathesis were excluded from the study. Patients found to have a surgical cause of bleeding on re-exploration, were excluded from the study.

Patients were randomly allocated to one of the two groups of 50 each with the help of random number table. Where patients receiving solution-A containing 2.5 g of Tranexamic acid in 250 ml normal saline were labeled as group-A and the patients receiving solution-B containing equal amount of normal saline (placebo) were labeled as group-B by the hospital pharmacologist. The operator was blinded of the solution and was given either solution-A or solution-B according to the group allotted. On completion of the surgical procedure, thorough surgical hemostasis was ensured before closure of the sternum, study solution at room temperature was poured into the pericardial cavity and over the mediastinal tissues.

After the surgery, patient was transferred to cardiac surgical Intensive Care Unit (ICU) and postoperative bleeding measured with the help of mediastinal and single or bilateral pleural drains which were placed at the end of the operation. The drains were connected to the under-water seal and the amount of blood collected was recorded in milliliters one hourly for the first 24 hours. Drains were removed when there was < 10 ml fluid for three consecutive hours in the drains. Efficacy of topical Tranexamic acid / placebo was determined in terms of mean postoperative bleeding.

Prolonged CPB is an independent predictor of post-operative morbidity and mortality including post-operative bleeding, need for blood transfusions and re-exploration for bleeding.[16] A CPB time of > 120 minutes was taken as a potential effect modifier and noted for each surgery.

Data was analyzed on SPSS version 15.0. Quantitative variables e.g., age, weight, cardiopulmonary bypass time, blood loss after 24 hours were expressed as mean and standard deviation (SD). Frequency and percentages are used to describe gender, disease and surgery. Quantitative variables i.e. mean blood loss between the two groups were compared using independent sample t-test and a p-value < 0.05 was considered as significant.

RESULTS

Results were available for all 100 patients enrolled in this study who underwent various adult cardiac surgical procedures. There was no significant difference in mean age, weight and CPB time in the two groups (Table I). Seventy nine percent of the patients were male and 21% were female. The most common procedure done in the study in both the groups was Coronary Artery Bypass Grafting (CABG) 69% followed by Mitral Valve Replacement (MVR) 15%, Aortic Valve Replacement 7%, Double

Table I: Demographics and mean CPB time in two groups.

	Group-A	Group-B	p-value
Mean age in years (± SD)	51.16 ± 13.32 years	48.84 ± 12.18 years	0.366
Mean weight in kgs (± SD)	76.12 ± 15.33 kg	72.92 ± 13.56 kg	0.272
Mean procedure time in minutes (± SD)	102.12 ± 35.170 minutess	96.44 ± 34.233 minutes	0.415

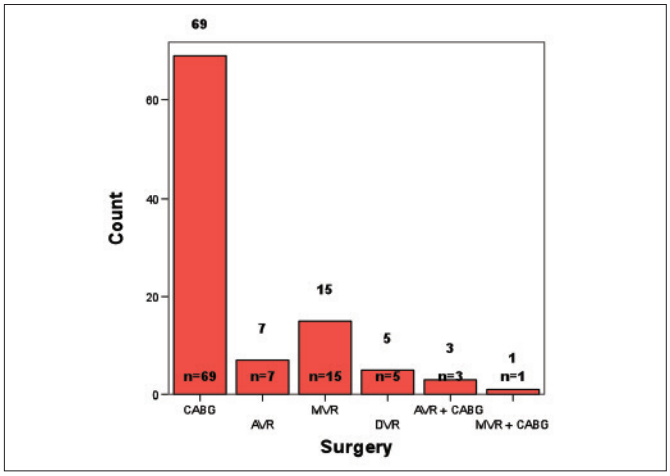

Figure 1: Types of surgeries in the study.

Table II: Mean postoperative bleeding in the two groups in 24 hours.

	Group-A	Group-B	p-value
Mean postoperative bleeding in all patients in ml	340.1 ± 112.4 ml	665 ±187.2 ml	< 0.001
Mean postoperative bleeding in CABG patients in ml	328.8 ± 94.4 ml	657.4 ± 183.4 ml	< 0.001

Valve Replacement (DVR) 3% and combined CABG and Mitral Valve Replacement (CABG + MVR) 1% (Figure 1).

There was significant difference in the mean post-operative bleeding after 24 hours in both the groups. The mean postoperative bleeding was 340.10 ± 112.4 ml in group-A and 665.00 ± 187.28 ml in group-B. This showed that the patients in placebo group had significantly higher ($p < 0.001$) postoperative bleeding as compared to topical Tranexamic acid group (Table II). When comparing only CABG patients, there was a significantly low ($p < 0.001$) mean postoperative bleeding in CABG patients receiving topical Tranexamic acid (328.82 ± 94.4 ml) compared to the placebo group (657.43 ± 183.4 ml).

DISCUSSION

In open-heart surgery with cardiopulmonary bypass, blood comes into contact with extracorporeal or non-endothelial surfaces which activates various cellular and humoral pathways including the coagulation, complement and the fibrinolytic pathways. These interactions lead to hyperfibrinolysis. A direct and very sinister consequence of hyperfibrinolysis is post-operative bleeding.[2,10]

This fibrinolysis after CPB is evident from increased plasmin and Fibrinogen Degradation Product (FDP) levels and the two of these have inhibitory effects on the platelet function, which leads to postoperative bleeding due to the haemostatic dysfunction caused by extracorporeal circulation.[17,18]

Thrombocytopenia, loss of clotting factors and liberal use of heparin leads to significantly enhanced fibrinolysis along with the extracorporeal CPB circuit causing the non-surgical bleeding.[9]

On-pump cardiac surgery leads to diffuse micro-vascular bleeding which is termed as non-surgical bleeding i.e. bleeding which is not correctable *via* surgical means.[17] Upto half of the cardiac surgery patients who require a reoperation due to postoperative bleeding are found to have non-surgical bleeding.[2,8,10]

Topical application of anti-fibrinolytic drugs is a pragmatic strategy employed in open-heart surgeries to minimize non-surgical blood loss by inhibiting fibrinolysis and consequently the need for blood transfusions.[1,18] The lysine analogues; being as effective, safer and economically more viable when compared to Aprotinin, (Tranexamic acid and epsilon- Aminocaproic acid) are now commonly used in cardiac surgery.[11]

Tranexamic acid is the preferred antifibrinolytic as it is more potent than Epsilon-Aminocaproic acid.[6] Topical application of antifibrinolytic agents in pericardial cavity after cardiac surgery reduces postoperative non-surgical bleeding by inhibiting fibrinolysis.[9] The pericardium acts as a natural barrier with no detectable absorption of the topical Tranexamic acid into the blood stream thus not causing any undesirable systemic side effects.[13,15]

The researchers employed topical application of Tranexamic acid solution in this study, which showed a statistically significant reduction in the mean post-operative bleeding after 24 hours in the study group. The mean postoperative bleeding in the study group was 340.10 ml compared to the placebo group where it was 665 ml (Table II). These methods were similar and the results comparable to the study by Baric *et al*.[9] which concluded that the use of topical Tranexamic acid effectively reduces postoperative bleeding after cardiac surgery. Their study showed a lower expected mean bleeding after 24 hours in patients given topical Tranexamic acid 525 ml compared to the placebo group 833 ml. However, their study included approximately 300 patients and along with Tranexamic acid and the placebo group, one group also received topical Aprotinin.[9]

De Bonis *et al*.[15] were the first to conduct a randomized trial, in which they concluded that topical Tranexamic acid reduces mean postoperative bleeding after cardiac surgery. Their study showed mean bleeding after 24 hours in the Tranexamic acid group to be 485 ml and 641 ml in the placebo group. They only enrolled patients undergoing coronary artery bypass grafting with cardiopulmonary bypass and used only one gram in 100 ml Tranexamic acid solution. They also showed that not only topical application of Tranexamic acid in the pericardial cavity is safe but also that after topical application there is no systemic absorption.[15] Another study was carried out by Fawzy *et al*.[10] which showed similar results i.e. statistically significantly lower mean postoperative bleeding after 24 hours in patients receiving topical Tranexamic acid after coronary artery bypass grafting.[10]

In this study, 69 patients out of 100 patients underwent coronary artery bypass grafting i.e. n=34 in Tranexamic acid (TXA) group and n=35 in the placebo group. The mean postoperative bleeding after 24 hours in the TXA group was 328.82 ml whereas in the placebo group it was 657.43 ml (Table II). So, these results in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass receiving topical Tranexamic acid are similar to the results of De Bonis *et al*.[15] and Fawzy *et al*.[10]

A recent meta-analysis by Abrishami *et al*.[13] analyzed various trials regarding topical application of anti-fibrinolytics in the pericardial cavity after cardiac surgery

and only four trials comparing topical Tranexamic acid with placebo were considered. The present study had various similar salient features which included the inclusion of only primary elective surgeries i.e. re-do procedures and emergency cases were ruled out. Patients with pre-operative history or diagnosis of any bleeding diathesis were excluded. All trials poured the study solution into the pericardial cavity on completion of the surgery and thorough surgical hemostasis i.e. before the closure of the sternum and an equal amount of normal saline was used in a similar fashion in the placebo group.[13] Like the trial conducted by Baric *et al*.[9] these patients were also randomized with the help of random-number tables and both the surgeon and the operation theater staff was blinded from the study and the study solution codes were disclosed at the end of the study period by the hospital pharmacologist who was not involved directly in this trial.

It was noted the cardiopulmonary bypass time for each patient, as CPB time is dependent on the complexity of the disease, surgeon and the physiologic response of the patient to the surgery. A CPB time of more than 120 minutes is considered as a prolonged bypass time and is associated with increased postoperative bleeding, along with increased morbidity and mortality for the patient.[16] There was no statistically significant difference between the CPB times of the surgeries in both the groups. The mean CPB time in group-A was 102.12 ± 35.170 minutes and the mean CPB time in group-B was 96.44 ± 34.233 minutes as shown in Table I.

In the study by Baric *et al*.[9] the average cost per patient for Tranexamic acid was 23 (about 2,685 Pakistani Rupees) whereas, the average cost per patient in the study group in this study for Tranexamic acid was Rupees 350. Thus, the topical Tranexamic acid is an economical option for reducing mean postoperative bleeding after cardiac surgery in the Pakistani setup.

Unlike the studies conducted by Fawzy *et al*.[10] and De Bonis *et al*.[15] which included only coronary artery bypass grafting patients or the study by Spegar *et al*.[20] which included heart valve surgeries, this study included all the common elective adult cardiac surgical procedures like coronary artery bypass grafting, valve replacements and combined procedures (Figure 1). The main outcome variable was mean postoperative bleeding after 24 hours. In order to remove any uncertainty about the efficacy of the topical application of Tranexamic acid, a large international randomized controlled trial is underway which will enroll more than 500 cardiac surgical candidates and is expected to be completed by 2014.[21]

To authors' knowledge, this is the only and one of the few randomized control trials conducted in Pakistan, determining the efficacy of topical application of Tranexamic acid in controlling postoperative bleeding in open heart surgery. As discussed earlier, postoperative bleeding after cardiac surgery not only increases the postoperative morbidity, mortality of the patient but also lengthens the hospital stay and thus, adds to the financial burden on the hospital and the patient's family. This specially holds true for a third world country like Pakistan where resources are already limited.

CONCLUSION

Topical application of Tranexamic acid solution in the pericardial cavity after open heart surgery effectively reduced mean postoperative non surgical bleeding and results were comparable to international studies quoted earlier. Topical Tranexamic acid application is an effective and economical way for controlling non-surgical bleeding in patients undergoing cardiac surgery with cardiopulmonary bypass.

Disclosure: This is a dissertation based article.

REFERENCES

1. Shoukat S, Gowani SA, Khimani F, Khan FA, Zaman M, Sharif H. Predictive model of blood transfusion during CABG surgery in Pakistan. *J Pak Med Assoc* 2008; **58**:421-6.
2. Jimenez Rivera JJ, Iribarren JL, Raya JM, Nassar I, Lorente L, Perez R, *et al*. Factors associated with excessive bleeding in cardiopulmonary bypass patients: a nested case-control study. *J Cardiothorac Surg* 2007; **2**:17.
3. Vuylsteke A, Saravanan P, Gerrad C, Cafferty F. The impact of administration of Tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery. *BMC Anesthesiol* 2006; **6**:9.
4. Duara R, Misra M, Bhuyan RR, Sarma PS, Jayakumar K. Does transfusion of residual cardiopulmonary bypass circuit blood increase postoperative bleeding? A prospective randomized study in patients undergoing on pump cardiopulmonary bypass. *Asian J Transfus Sci* 2008; **2**:51-5.
5. Wells AW, Mounter PJ, Chapman CE, Stainsby D, Wallis JP. Where does blood go? Prospective observational study of red cell transfusion in north England. *BMJ* 2002; **325**:803.
6. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011; **(1)**:CD001886.
7. Murphy GJ, Reeves BC, Rogers CA,. Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007; **116**:2544-52.
8. Mataraci I, Polat A, Toker ME, Tezcan O, Erkin A, Kirali K. Postoperative revision surgery for bleeding in a tertiary heart center. *Asian Cardiovasc Thorac Ann* 2010; **18**:266-71.
9. Baric D, Biocina B, Unic D, Sutlic Z, Rudez I, Vrca VB, *et al*. Topical use of antifibrinolytic agents reduces postoperative bleeding: a double-blind, prospective, randomized study. *Eur J Cardiothorac Surg* 2007; **31**:366-71.
10. Fawzy H, Elmistekawy E, Bonneau D, Latter D, Errett L. Can local application of Tranexamic acid reduce postcoronary bypass surgery blood loss? A randomized controlled trial. *J Cardiothorac Surg* 2009; **4**:25.

11. Henry D, Carless P, Fergusson D, Laupacis A. The safety of Aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. *Can Med Assoc J* 2009; **180**:183-93.

12. Takagi H, Manabe H, Kawai N, Goto S, Umemoto T. Aprotinin increases mortality as compared with tranexamic acid in cardiac surgery: a meta-analysis of randomized head-to-head trials. *Interact CardioVasc Thorac Surg* 2009; **9**:98-101.

13. Abrishami A, Chung F, Wong J. Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis. *Can J Anesth* 2009; **56**:202-12.

14. Salis S, Mazzanti VV, Merli G, Salvi L, Tedesco CC, Veglia F, *et al*. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. *J Cardiothorac Vasc Anesth* 2008; **22**:814-22.

15. De Bonis. Topical use of Tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebo-controlled study. *J Thorac Cardiovasc Surg* 2000; **119**: 575-80.

16. Tettey M, Aniteye E, Sereboe L, Edwin F, Kotei D, Tamatey M, *et al*. Predictors of postoperative bleeding and blood transfusion in cardiac surgery. *Ghana Med J* 2009; **43**:71-6.

17. Edmunds LH Jr. Managing fibrinolysis without aprotinin. *Ann Thorac Surg* 2010; **89**:324-31.

18. Jiménez JJ, Iribarren JL, Brouard M, Hernández D, Palmero S, Jiménez A, *et al*. Safety and effectiveness of two treatment regimes with tranexamic acid to minimize inflammatory response in elective cardiopulmonary bypass patients: a randomized double-blind, dose-dependent, phase IV clinical trial. *J Cardiothorac Surg* 2011; **6**:138.

19. Barnard J, Millner R. A review of topical hemostatic agents for use in cardiac surgery. *Ann Thorac Surg* 2009; **88**:1377-83.

20. Spegar J, Vanek T, Snircova J, Fajt R, Straka Z, Pazderkova P, *et al.* Local and systemic application of tranexamic acid in heart valve surgery: a prospective, randomized, double blind LOST study. *J Thromb Thrombolysis* 2011; **32**:303-10.

21. Scohy T. The effect on blood loss of topical and intravenous tranexamic acid in cardiac surgery patients [Internet]. 2013. Available from: http://clinicaltrials.gov/show/NCT01895101