INTRODUCTION

In recent times, enormous advances have been made to perfect cardiac surgery, leading to a reduction in the number of complications. Postoperative hemorrhage remains the most common and sinister complication after on-pump cardiac surgery leading to a substantial increase in the morbidity and mortality. With the increase in the number of cardiac surgical procedures, there has been an increasing load on the blood banks and a major proportion of all allogenic blood transfusions in the United Kingdom and the United States occurs in cardiac surgical patients. 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.

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. 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.

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. Aprotinin along with the lysine analogues Epsilon-Aminocaproic Acid (EACA) and Tranexamic Acid (TXA) are the three antifibrinolytic drugs in use in cardiac surgery. Compared to Aprotinin, the lysine analogues (Tranexamic acid and epsilon-Aminocaproic acid) are also effective and are cheaper. 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. Furthermore, Tranexamic acid has been shown to be 10 times more potent than epsilon-Aminocaproic acid. Administration of Tranexamic acid reduces the number of blood transfusions or the return to theatre for bleeding in patients undergoing cardiac surgery. Although antifibrinolytic agents successfully reduce bleeding after open-heart surgery, they may cause a 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.
cardiac surgery but their systemic use has recently become controversial.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 postoperative morbidity and mortality including postoperative bleeding, need for blood transfusions and re-exploration for bleeding.\textsuperscript{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...
Topical application of tranexamic acid reduces postoperative bleeding in open-heart surgery: myth or fact?

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

<table>
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<tr>
<th></th>
<th>Group-A</th>
<th>Group-B</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Mean postoperative bleeding in all patients in ml</td>
<td>340.1 ± 112.4 ml</td>
<td>665 ± 187.2 ml</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean postoperative bleeding in CABG patients in ml</td>
<td>328.8 ± 94.4 ml</td>
<td>657.4 ± 183.4 ml</td>
<td>&lt; 0.001</td>
</tr>
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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.

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
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**


