# EFFICACY OF TOPICAL TRANEXAMIC ACID TO REDUCE BLOOD LOSS AFTER CORONARY ARTERY BYPASS GRAFTING (CABG)

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## ABSTRACT

**Background:** Coronary Artery Bypass Grafting (CABG) with the use of cardiopulmonary bypass technique has a coagulopathy issue. Many factors act on the coagulation process such as heparin level, thrombocytopenia, increased fibrinolysis and acquired platelet dysfunction. The human body responds to stress with dramatic resilience. Bleeding diathesis is one of stress factors. Multiple agents like Tranexamic acid and Aminocaproic acid etc are anti-fibrinolytic agents that can be administered to minimize the bleeding postoperatively.

**Objectives:** To compare the efficacy of topical application of tranexamic acid to reduce blood loss after coronary artery bypass grafting (CABG).

**Methods:** It is randomized controlled trial. This study was carried out at the Unit of Cardiothoracic & Vascular Surgery, Institute of Shaikh Zayed Hospital, Lahore from December 6th, 2017 to December 5th, 2018. First patient evaluated on 11th December 2017. Seventy patients were enrolled, who were eligible for this study, achieving the inclusion criteria. Two groups of the selected population were made by randomization. Group A comprised 35 patients to whom 1 gm of diluted Tranexamic Acid using 100 ml normal saline solution is poured to the pericardial cavity. Group B involved 35 patients as well, whom were given standard of care treatment which in this case is 100 ml normal saline. Since 100ml normal saline did not contain any active ingredient for treatment, therefore it was considered as placebo. Intervention (Placebo or TXA) was considered efficacious if it resulted in blood loss of less than 500ml in 72 hours from immediately post-op to 72 hours post-op. The efficacy of drugs within groups is compared by the use of Chi-square test. Independent sample t-test was applied for data analysis of blood loss with p-value ≤0.05 being taken as significant.

**Results:** In our study, total70patients were enrolled. Group-A (Tranexamic Acid) and Group-B (Placebo) were made. In group-A, there were 30 (85.7%) male and 5(14.3%) female patients. In group-B, 28(80.0%) were male and 7(20.0%) were female. In our study population, mean age of patients were 52.4±9.9 years and 53.6±10.1 years in group A&B respectively. In group-A, there were 22(62.9%) patients in which the intervention showed efficacy (blood loss <500ml), while only 09(25.7%) patients in group-B showed blood loss of <500ml, p-value of 0.002 being statistically significant.

**Conclusion:** Topical application of tranexamic acid reduces blood loss after coronary artery bypass grafting (CABG).

**Key words:** Coronary Artery Bypass Graft, Tranexamic Acid.

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## INTRODUCTION

Coronary Artery Bypass Grafting (CABG) is indicated in patients with ischemic heart disease (IHD) to extend life expectancy and decrease the mortality rate related to cardiac events. The number of deaths caused around the world in the majority of the population is mainly due to ischemic heart disease. The major goals of

CABG are as following; Symptomatic relief, Increased life expectancy, Improve life style.

Coronary Artery Bypass Grafting (CABG) with the use of cardiopulmonary bypass technique has a coagulopathy issue. Many factors act on coagulation process such as heparin level, thrombocytopenia, increased fibrinolysis and acquired platelet dysfunction.[1] Around 2-7% cases of cardiac surgery are re-explored for bleeding. In 50–80% there is medical cause rather than surgical bleeding.[2] In 25-45% cases there is Fibrinolysis which results in significant post-operative bleeding.[3] Aprotinin,[4] Tranexamic acid[5] and Aminocaproic acid[6] are anti-fibrinolytic agents usually administered to rectify consumptive coagulopathy of post-operative period, thereby reducing chances of bleeding and minimizing the requirement of blood components therapy in such patients.

Preventive well-organized actions of Tranexamic acid (TXA) on post-operative bleeding and decreased need of blood transfusions in cardiac surgical procedures is now an established fact.[7,8] TXA acts by competitively occupying lysine binding sites for coagulation pathway factors, especially plasminogen and plasmin. Once the lysine binding sites are saturated the fibrinolysis inhibited by transferring plasminogen from the fibrin surface.[9] It can be administered topically or systemically. However, the threat of thromboembolic complications or early graft closure is very high when used intravenously.[10]

The objective of study was to compare the efficacy of topical application of tranexamic acid to reduce blood loss after coronary artery bypass grafting (CABG). The hypothesis of our study is that the use of topical Tranexamic acid is associated with reduction of post-operative blood loss.

## METHODS

Randomized Controlled Trial was done at the Unit of Cardiac Surgery, Federal Postgraduate Medical Institute, Shaikh Zayed Hospital, Lahore from December 6th, 2017 to December 5th, 2018. Inclusion criteria was adult Patients of both genders undergoing CABG. Exclusion criteria included Off pump & Redo CABG, Bleeding diathesis (Hemophilia or platelet count < 100 × 109 L-1), Clotting factor deficiency, known allergy to TA, Intake of anti-platelets (e.g. Aspirin, Clopidogrel), high-risk medical co-morbidity, Surgical bleed, Renal failure, Not consenting.

After getting permission from ethical review committee and taking informed consent from patients, 70 patients meeting the inclusion criteria were selected and randomized into two separate groups. Group A were given TXA and group B were kept on the placebo treatment. Both the groups contained 35 patients each. Patients in Group A were given Topical TXA before closure of pericardial cavity and in both groups, blood loss measured up to 72hrs in milliliters or until drain out. All the data was analyzed in statistical package for social sciences (SPSS) v23.0. Qualitative data like gender, Diabetes Mellitus, Hypertension & efficacy were analyzed by using frequency and percentages while quantitative data was analyzed by using mean and standard deviation. Chi-square test used while comparing the efficacy with groups. Data analysis for blood loss was done using Mann Whitney U test. Binary logistic regression analysis was used to see the effect of TTA on blood loss in the presence of Age, Gender, Diabetes Mellitus and hypertension. A p-value of $\leq 0.05$ was labeled significant.

## RESULTS

The representation of patients in both groups was similar in gender (A:85.7% males, B: 80%males), age (A: 52.4±9.9yrs, B: 53.6±10.1yrs), diabetes mellitus (A: 62.9%, B:85.7%), Hypertension (A:82.9%, B:85.7%).

TXA was found to be significantly more effective as compared to placebo in reducing post-operative drain output for the observed duration showing Efficacy of 62.9% vs. 25.7% with a p-value 0.002 (table 1) and Mean blood loss 450(390 – 630) ml vs. 660(480 – 870) ml with p-value 0.003(table 2). Binary logistic regression analysis was performed to see the effect of treatment on efficacy in the presence of all other variables. (Table 4)

Table 1: Comparison of efficacy (blood loss <500 ml) between groups

| Efficacy | Group | | | | | |
|---|---|---|---|---|---|---|
| | Gsroup-A (Tranexamic Acid) | | Group-B (Placebo) | | Total | |
| | N | % | N | % | N | % |
| Yes | 22 | 62.9 | 9 | 25.7 | 31 | 44.3 |
| No | 13 | 37.1 | 26 | 74.3 | 39 | 55.7 |
| Total | 35 | 100.0 | 35 | 100.0 | 70 | 100.0 |

Chi-square = 9.79 P-value = 0.002

Table 2: Comparison of blood loss (24-72 hours) between groups

| Group | Blood Loss | | |
|---|---|---|---|
| | Median | $Q_1$ | $Q_3$ |
| Group-A (Tranexamic Acid) | 450.0 | 390.0 | 630.0 |
| Group-B (Placebo) | 660.0 | 480.0 | 870.0 |
| Total | 595.0 | 410.0 | 780.0 |

Table 3: Comparison of blood loss (24-72 hours) between groups by Mann Whitney U testy

| Group | N | Mean Rank | Sum of Ranks | Mann Whitney U | Z | P-value |
|---|---|---|---|---|---|---|
| Group-A (Tranexamic Acid) | 35 | 28.31 | 991.0 | 361.0 | 2.96 | 0.003 |
| Group-B (Placebo) | 35 | 42.69 | 1494.0 | | | |
| Total | 70 | | | | | |

Table 4: Efficacy in relation to treatment by taking gender, age, diabetes and hypertension as confounding variables.

| | P-value | Adj. Odds Ratio | 95% C.I. for Adj. Odds Ratio | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Group A | 0.006 | 5.53 | 1.64 | 18.57 |
| Male | 0.041 | 5.34 | 1.07 | 26.66 |
| Age 25 – 40 | 0.551 | 1.89 | 0.23 | 15.41 |
| Age 41 – 50 | 0.836 | 0.87 | 0.24 | 3.16 |
| Non-Diabetic | 0.094 | 3.25 | 0.82 | 12.91 |
| Non-Hypertensive | 0.398 | 2.14 | 0.37 | 12.60 |
| Constant | 0.001 | 0.16 | | |

## DISCUSSION

In open heart surgery, one of the most known and serious complication is mediastinal hemorrhage. The changes in blood coagulability are due to the contact of blood to the CPB circuit, dilutional effect and residual heparin effect not corrected by protamine. Many anti-fibrinolytic drugs are available to reduce post-operative bleed, Most commonly used include tranexamic acid, aminocaproic acid and most effectively, aprotinin.

After IMAGE (International Multicenter Aprotinin Graft patency Experience) and BART (Blood conservation using Anti-fibrinolytic Randomized Trial) studies showed high graft occlusion mortality with aprotinin and resulted in the discontinuation of the usage of Aprotinin due to its side effects by FDA (Food and Drug Administration) authority.[11-12] Due to this, a new anti-fibrinolytic drug Tranexamic acid has been proved by many studies to decrease the post-operative bleeding in CABG.

This anti-plasmonic agent is analogue of Aminocaproic acid which works by preventing the plasmin activation which converts fibrin to fibrin degradation products (FDP's) to increase fibrinolysis by attaching to lysine binding sites. The affinity of plasmin and plasminogen to the binding site of fibrin is inhibited by TXA.

40 CABG patients were included in a double blinded controlled trial in the year 2000 to see the effect of topical use of TXA in pericardial cavity on post-operative bleeding. The results showed that during the first 3 hours the post-operative bleeding was reduced by around 36%. However, in the next 24 hours the results could not be sustained.[13] Similarly in 2006, a study was carried out with the topical application of TXA in 100 patients that showed a substantial decrease in post-operative bleed and rate of re-exploration of haemostasis.[14] Results of our study compliments the findings of these studies in proving TXA to be efficacious in reducing post-operative blood loss up to 72 hours postoperatively which in turn would also decrease need for re-exploration for complications such as tamponade.

In patient given tranexamic acid, mean blood loss was 450 ml compared to 660ml in control group. This was statistically significant (p=0.003) as was the categorical efficacy of TXA as per our preset criteria that showed 62.9% patients with less than 500ml blood loss after TXA compared to 25.7% after placebo(p=0.002). Irregularity was seen when subsets of groups were compared, for example, it appeared that TXA had better efficacy in men (60% vs. 17.9%) than women (80% vs. 57.1%), in older patients (>50yrs: 65% vs. 20%) than younger patients (21-40yrs: 66.7% vs. 66.7%) and in diabetics (54.5% vs. 20%) than non-diabetics (76.9% vs. 60%). However, this can be attributed to the fact that both groups had a very small number of non-diabetics (13 & 5), females (5 & 7) and younger (3 & 3) patients, due to the small incidence of coronary artery diseases in these demographics. Therefore, results within these subgroups may not be accurate and a larger population size is needed to confirm presence or absence of any such correlation.

There are several limitations for this prospective study:

- Relatively small sample size

- Patients were followed up only for 72 hours after which the drain was removed
- Because HTN, DM and older age are risk factors for disease that indicates CABG, sample size included smaller proportion of patients without these risk factors, hence the results in those subgroups aren't very reliable.

An improved study can be built on this with bigger sample size, that also has a bigger proportion of non-Diabetics, non-Hypertensives and younger patients, and a longer follow up to see longer term benefit and risks of using topical Tranexamic acid in CABG.

## CONCLUSION

Topical use of Tranexamic acid at the end of CABG helps in reducing post-operative blood loss without risk of graft occlusion seen with systemic anti-plasmin, thus reducing complications related to blood product transfusions and tamponade effect.

## ETHICAL APPROVAL

The study was approved by the Institutional Review Board of Shaikh Zayed Postgraduate Medical Institute, SKZ Medical and Dental College, Lahore, vide Reference No. F-39/NHRC/Admin/IRB/373 Dated 06.12.2017

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## AUTHOR'S CONTRIBUTIONS

**AA:** Supervision, Strategic Support
**MM:** Manuscript writing, Data Collection
**YA:** Data Collection