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# Evaluating Perioperative Blood Loss in Cardiac Surgery Patients Receiving High and Low Dose Tranexamic Acid

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## Abstract

**Background:** Excessive perioperative blood loss is a concern for patients undergoing high risk procedures; thus, tranexamic acid (TXA) is administered at the beginning of surgery to minimize blood loss. Previous studies have had mixed results. The aim of this retrospective chart review is to determine whether low or high dose TXA minimizes blood transfusions and post-operative adverse events.

**Methods:** Retrospective data was obtained on patients undergoing elective, major cardiovascular surgery performed by the same surgeon. Participants were separated into low and high dose TXA groups based on total amount given intra-operatively. Negative binomial regression and t-tests were used to compare primary outcomes, including total blood components transfused and their individual components. Secondary post-operative events (stroke, mortality, MI, seizure, PE, renal failure, and DVT) were rare and compared observationally.

**Results:** The high TXA group received more units of RBCs (2.05 vs. 1.21, $p < 0.05$), FFP (1.06 vs. 0.66, $p < 0.05$) and total units transfused (4.40 vs. 2.81, $p < 0.05$), compared to the low group. There was no significant difference between groups regarding platelet (0.69 vs. 0.46, $p = 0.11$), cryoprecipitate (0.38 vs. 0.31, $p = 0.50$) and factor concentrate administration. Secondary events were rare, though 6 patients (7.1%) in the high TXA group had post-operative seizures compared to 2 (2.4%) in the low dose.

**Conclusion:** Higher doses of TXA were associated with increased transfusions among cardiac surgery patients and increased seizures post-operatively. This suggests using a lower dose of TXA could minimize blood transfusion in the perioperative setting and minimize post-operative seizures.

## Introduction

Excessive perioperative blood loss is a concern for patients undergoing high risk cardiovascular surgeries. Cardiopulmonary bypass (CBP) can alter the hemostatic balance, leading to an increased risk of coagulopathy and excessive perioperative bleeding [1]. This can ultimately lead to an increased risk for postoperative morbidity in those patients requiring blood components post CBP [2]. As a prophylactic treatment, tranexamic acid is administered at the beginning of surgery to help minimize blood loss. Tranexamic acid is a synthetic anti-fibrinolytic drug, which controls fibrinolysis through blocking of attachment of plasminogen to fibrin [3,4].

A systematic review done by Ker, et al. [5] studied 129 randomized controlled trials comparing patients receiving tranexamic with a control of either no tranexamic acid or a placebo, concluding that evidence exists for tranexamic acid reducing blood transfusion requirements in surgery patients. Initially, bolus dosing compared to continuous infusions of tranexamic acid showed both led to similar reductions in perioperative bleeding, [6] demonstrating the need to explore different dosing to determine optimal concentration to maximize patient care and resources associated with blood transfusions.

Studies evaluating the effects of high dose and low dose tranexamic acid have had mixed results. While a double-blinded, randomized study done by Sigaut, et al. [7] showed a high dose of tranexamic acid to be more effective than a low dose to decrease transfusion needs, blood loss and repeat surgery, low dose tranexamic acid was deemed to be as

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effective as a higher-dose regimen by Waldow, et al. [8] and again by Du, et al. [9] However, confounding factors including the extended study period of 7 days may have affected results due to the short half-life of tranexamic acid being in appropriate for a 7 day evaluation [10].

In this retrospective chart review, the aim of the study is to determine whether a high total dose or low total dose leads to minimal perioperative blood loss. Determining whether a low dose or high dose of tranexamic acid results in improved post-op outcomes can help improve cardiovascular surgery patient safety. If a lower dose is shown to be as effective as a high dose, it could lead to a more cost-efficient and resourceful practice. If found that a high dose of tranexamic acid is shown to be more effective for minimizing blood loss and transfusion rates, then it will lead to better cost and resource management of blood products.

## Materials and Methods

Research ethics board approval at the QEII Health Science Centre, Halifax, Nova Scotia, Canada (Chairperson Dr. Richard Hall), was obtained for this study (ROMEO file #1020017) on August 20, 2015. Retrospective data was obtained for 217 patients undergoing cardiovascular surgery from 2007 to 2014 at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia from their electronic health records (HPF clinical portal) and Maritime Heart Centre (MHC) database of Cardiac Surgery. The database captures all intra- and postoperative blood transfusions up to 48 hours after the surgery. All patients underwent elective, complex surgery performed by the same surgeon. Complex procedures are defined as any double procedure (coronary artery bypass grafting (CABG) + aortic valve repair (AVR), CABG + mitral valve repair (MVR), AVR + MVR), aortic root repair, valve sparing root repair, or AVR + ascending aortic repair. Procedures involving the descending aorta were excluded. Eighteen patients had incomplete data in their charts, and were excluded, leaving 199 totals.

Preoperative patient characteristics, intraoperative data and postoperative outcomes were manually collected. Total doses of TXA given intraoperatively were calculated from the bolus loading dose, and the continuous infusion throughout the surgery. Two groups were formed based on the median dose of 4.5 grams: The 95 patients above 4.5 grams being the high dose TXA group, and the 104 below and including 4.5 grams were the low dose TXA group.

The two groups were matched based on age, sex, and procedure type and anemia status using World Health Organization criteria for non-anemic, mild anemia or moderate anemia. Matching was done using propensity score matching using the 1:1 nearest neighbor matching method with a caliper of 0.20. After matching, the sample size was reduced from 199 to a matched sample of N = 170, with 85 in each of the high and low dose TXA groups.

Negative binomial regression was performed to predict the primary outcomes of blood components transfused with a p-value less than 0.05 indicating significant difference between the two groups. Independent t-tests were used to compare secondary outcomes of post-operative blood laboratory values including hemoglobin, platelets, hematocrit, PTT, INR, along with intra-operative cardiopulmonary bypass time and aortic clamp time. Frequencies of dichotomous secondary outcomes including stroke, death, myocardial infarction, seizure, pulmonary embolism, new renal failure, and deep vein thrombosis were reported as percentage of occurrence and no inferential statistics were conducted.

## Results

Table 1 shows patient characteristics after the high and low groups were matched. Our two sample groups had similar

**Table 1:** Descriptive statistics for matched sample.

| Patient and Procedure Characteristics | Low Group (n = 85) | High Group (n = 85) | p-value |
|---|---|---|---|
| Age, mean (SD) | 62.38 (14.05) | 64.18 (14.03) | 0.41 |
| Sex, male (%) | 75.3% | 76.5% | 1.00 |
| Anemia | | | 0.93 |
| none (%) | 76.5% | 77.6% | |
| mild (%) | 14.1% | 11.8% | |
| severe (%) | 9.4% | 10.6% | |
| Procedure Type | | | 0.57 |
| 1. iAVR + iCABG | 24.7% | 25.9% | |
| 2. AVR + another valve +/- CABG | 4.7% | 3.5% | |
| 3. valve-AVR +/- CABG | 3.5% | 3.5% | |
| 4. AVR + any Aortic | 31.8% | 23.5% | |
| 5. valve-AVR + Aortic | 3.5% | 11.8% | |
| 6. Aortic only | 17.6% | 20.0% | |
| 7. CABG + Valve + Aortic | 9.4% | 9.4% | |
| 8. all other cases | 4.7% | 2.4% | |

P-values for age calculated using an independent t-test. P-values for sex, anemia, and procedure type calculated using Fisher's Exact Test.

**Table 2:** Primary outcomes.

| | High Group | | Low Group | | |
|---|---|---|---|---|---|
| **Outcome** | **M** | **95% CI** | **M** | **95% CI** | **p** |
| RBC | 2.05 | [1.58, 2.65] | 1.21 | [0.91, 1.62] | 0.01* |
| Platelets | 0.69 | [0.50, 0.97] | 0.46 | [0.31, 0.67] | 0.11 |
| FFP | 1.06 | [0.79, 1.42] | 0.66 | [0.47, 0.92] | 0.04* |
| Cryo | 0.38 | [0.25, 0.57] | 0.31 | [0.20, 0.48] | 0.50 |
| FVII | 0.19 | [0.11, 0.32] | 0.14 | [0.08, 0.26] | 0.49 |
| Prothrombin | 0.35 | [0.01, 0.11] | 0.35 | [0.01, 0.11] | 1.00 |
| Total Units | 4.40 | [3.48, 5.57] | 2.81 | [2.20, 3.60] | 0.01* |

**Table 3:** Secondary outcomes blood lab values.

| | High Group | | Low Group | | 95% Confidence Interval of the Mean Difference | | |
|---|---|---|---|---|---|---|---|
| **Outcome** | **M** | **SD** | **M** | **SD** | **Lower** | **Upper** | **p** |
| Post-op haemoglobin (g/L) | 93.58 | 19.69 | 93.72 | 13.11 | -5.21 | 4.93 | 0.96 |
| Post-op platelet ($10^9$/L) | 133.02 | 46.46 | 119.73 | 41.34 | -0.02 | 26.61 | 0.05 |
| Post-op hematocrit | 0.28 | 0.05 | 0.27 | 0.04 | -0.01 | 0.02 | 0.69 |
| Post-op PTT (sec) | 29.85 | 5.04 | 29.78 | 7.07 | -1.79 | 1.93 | 0.94 |
| Post-op INR | 1.31 | 0.25 | 1.34 | 0.21 | -0.1 | 0.04 | 0.37 |
| Time CP bypass (min) | 195.86 | 59.38 | 180.26 | 65.68 | -3.36 | 34.56 | 0.11 |
| Aorta clamp time (min) | 135.4 | 53.2 | 130.16 | 48.72 | -10.21 | 20.68 | 0.5 |

M = Mean; SD = Standard Deviation; CI = Confidence Interval.

values for age (mean values of 62 in the low group and 64 in the high group, p = 0.41) and the same proportion of male to female participants (75.3% low, 76.5% high p = 1.00). The two groups had similar incidences of mild, moderate, and severe anemia statuses pre-operatively and no significant statistical difference in the various procedure types was observed.

Our primary outcomes show on average the patients receiving a higher dose of TXA received 4.4 units of blood components compared to 2.8 in the low dose group (p < 0.01). Similarly for individual components the high dose TXA group received significantly more units of RBCs (2.05 and 1.21, p < 0.01) and FFP (1.06 and 0.66, p = 0.04). No statistical significance was seen for transfusion rates of platelets, cryoprecipitate, or factor VII concentrate though there were higher numbers transfused in the high dose TXA group for each (Table 2).

Secondary outcomes including post-operative laboratory values showed no significant difference, specifically for hemoglobin (p = 0.96), platelets (p = 0.05), hematocrit (p = 0.69), PTT (p = 0.94), and INR (p = 0.37). There was also no observable difference in cardiopulmonary bypass time (p = 0.11) or aortic clamp time (p = 0.50) (Table 3).

Post-operative adverse events were rare and, therefore, inferential statistics were not conducted. However, the frequencies of each varied between groups. While there were a higher number of post operative stroke seen in the low dose TXA group (5 compared to 4), death (3 compared to 2) and new renal failure (7 compared to 4), a higher number was observed in the high dose TXA group for seizure (6 compared to 2), pulmonary embolism (1 compared to 0) and deep vein thrombosis (1 compared to 0) (Table 4).

**Table 4:** Frequencies of dichotomous secondary outcomes.

| | (High Group) # Yes (%) | (Low Group) # Yes (%) |
|---|---|---|
| Stroke | 4 (4.7%) | 5 (5.9%) |
| Patient death | 2 (2.4%) | 3 (3.5%) |
| Myocardial Infarction | 0 (0%) | 0 (0%) |
| Seizure | 6 (7.1%) | 2 (2.4%) |
| Pulmonary Embolism | 1 (1.2%) | 0 (0%) |
| Renal Failure | 5 (5.9%) | 7 (8.2%) |
| Deep Vein Thrombosis | 1 (1.2%) | 0 (0%) |

## Discussion

The results of this retrospective review demonstrate a higher number of blood components transfused in patients receiving a higher dose of TXA than those who received a lower dose. This could be indicative of a lower dose TXA being as effective at reducing perioperative blood loss in cardiovascular surgery as a higher dose and thus decreasing the need for allogeneic blood product transfusion in the perioperative setting.

These results are noteworthy given the 2014 prospective study [7] comparing high and low dose regimes (30 mg/kg

loading dose and 16 mg/kg/hr infusion vs. 10 mg/kg loading dose and 1 mg/kg/hr infusion) in which the higher TXA dose was more effective at reducing transfusion needs, blood loss and repeat surgery. Similarly, a randomized trial done by Bokesch, et al. [11] comparing low and high dose TXA with ecallantide found both groups reduced blood transfusion requirement more so than ecallantide. However, interestingly, the higher dose TXA group received 0 intraoperative transfusions while the lower dose required 400 mL of packed red cells on average. The high dose used in this trial originated from the recommendations in the BART study where it was found this dose of TXA to be better suited for cardiovascular surgery patients than other anti-fibrinolytics at the time.

A more recent retrospective study by McHugh, et al. [12] evaluated low dose vs. high dose TXA in CABG patients. Their results determined a low dose regime (15 mg/kg loading dose, 6 mg/kg/hr infusion) was as effective in reducing perioperative blood loss than the higher dose recommended in the BART study. The low dose used in this study is a median dose between the high and low doses used in the Sigaut study. Our study reiterates these results, and could help prevent over dosing leading to the increase in seizures documented in the literature.

The post-operative adverse events were rarely observed, possibly due to the smaller sample size compared to other studies. Despite this, there is a larger observable discrepancy in the number of seizures post-operatively in this retrospective review. Previous studies have demonstrated increasing doses of TXA are associated with higher risk of post-operative seizures, specifically those undergoing cardiac surgery [13,14]. A recent prospective, multi-centre study published in the New England Journal of Medicine [15] showed this by comparing TXA and placebo administration and obtaining a significantly higher number of seizures in the TXA group. They also calculated an increased relative risk for patients to have a stroke or die if they suffer a post-operative seizure.

The results from our study demonstrate similar incidence of seizures as a review done by Lecker, et al. [16] where they found 6.4-7.3% of patients were experiencing seizures from high dose TXA following cardiovascular surgery. This is important, as increased incidence of seizures could possibly extend hospital length of stay and have profound impact on neurological outcomes, including stroke and death.

As the study was retrospective in nature, certain confounding variables need to be considered with the data analysis. While we controlled to the best of our ability for surgical procedure (same surgeon, excluded all urgent and emergent cases that would predispose patients to higher blood loss) some irregularities with anesthesiologist TXA dosing were noted. Not all anesthetists were using a high loading dose and a high infusion dose, or vice versa, but there was significant interchangeable dosing (i.e. 30 mg/kg bolus and 6 mg/kg/hr infusion), which led us to use the total calculated TXA dose over the entire procedure. This may have an effect such that a patient who bleeds more may remain in the OR longer and therefore receives a larger dose of total TXA. Should this be the case, it would be reasonable to infer that increasing the TXA dose because of bleeding does not in fact reduce bleeding and lends itself to more perioperative adverse events such as seizures. There may also be inconsistencies with anesthetist dosing for individual patients. For example an anticoagulated patient preoperatively may gain favour and receive a higher dose of TXA in anticipation of perioperative bleeding than a patient with similar baseline characteristics. It is difficult to control for patient characteristics which may affect blood transfusion due to the retrospective nature of the study. However, our secondary outcomes of post op laboratory values along with CPB and aorta clamp time show no significant difference leading us to believe their influence on blood loss and transfusion was minimal. Similarly, different transfusion triggers among anesthetists could lead to a higher number of transfusions in different patient populations. Some initiate transfusion when hemoglobin drops below 80 g/L while others wait until it drops below 70 g/L.

## Conclusion

Our study demonstrates a lower dose tranexamic acid to be at least as effective as to a higher dose regime for patients undergoing complex cardiovascular surgery. Further, the findings reinforce previous data regarding negative outcomes associated with higher TXA dosing, specifically post-operative seizures.

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## References

1. Magovern JA, Sakert T, Benckart DH, et al. (1996) A model for predicting transfusion after coronary artery bypass grafting. Ann Thorac Surg 61: 27-32.

2. Soliman R, Hassan Y, Alghadam F, et al. (2013) Prospective, Randomized, comparative study between aprotinin and tranexamic acid in cardiac surgery. J Anaes Clin Sci 2: 13.

3. Adler Ma SC, Brindle W, Burton G, et al. (2011) Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: A systematic review and meta-analysis. J Cardiothorac Vasc Anesth 25: 26-35.

4. Hosseini H, Rahimianfar AA, Abdollahi MH, et al. (2014) Evaluations of topical application of tranexamic acid on post-operative blood loss in off-pump coronary artery bypass surgery. Saudi J Anaesth 8: 224-228.

5. Ker K, Edwards P, Perel P, et al. (2012) Effect of Tranexamic Acid on Surgical Bleeding: Systematic review and cumulative meta-analysis. BMJ 344.

6. Imtiaz A, Mujahid-ul-Islam, Ansa I, et al. (2014) Effects of Bolus Dose and Continuous Infusion of Tranexamic Acid on Blood Loss after Coronary Artery Bypass Grafting. J Ayub Med Coll Abbottabad 26: 371-375.

7. Sigaut S, Tremey B, Ouattara A, et al. (2014) Comparison of two doses of tranexamic acid in adults undergoing cardiac surgery with cardiopulmonary bypass. Anesthesiology 120: 590-600.

8. Waldow T, Szlapka M, Haferkorn M, et al. (2013) Prospective Clinical Trial on Dosage Optimizing of Tranexamic Acid in Non-Emergency Cardiac Surgery Procedures. Clin Hemorheol Microcirc 55: 457-468.

9. Du Y, Xu J, Wang G, et al. (2014) Comparison of Two Tranexamic Acid Dose Regimens in Patients Undergoing Cardiac Valve Surgery. J Cardiothorac Vasc Anesth 28: 1233-1237.

10. Sanfilippo F, Astuto M, Maybauer M (2014) Effects and Timing of Tranexamic Acid on Transfusion Requirements in Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass. Anesthesiology 121: 902.

11. Bokesh P, Gabor S, Ryszard W, et al. (2012) A Phase 2 Prospective, Randomized, Double-Blind Trial Comparing the Effects of Tranexamic Acid with Ecallantide on Blood Loss from High-Risk Cardiac Surgery with Cardiopulmonary Bypass. J Thoracic and Cardiovascular Surgery 143: 1022-1029.

12. McHugh S, Kolarczyk L, Lang R, et al. (2016) A Comparison of High Dose and Low Dose Tranexamic Acid Antifibrinolytic Protocols for Primary Coronary Artery Bypass Surgery. Indian J Anaesth 60: 94-101.

13. Kalavrouziotis D, Voisine P, Mohammadi S, et al. (2012) High-Dose Tranexamic Acid is an Independent Predictor of Early Seizure After Cardiopulmonary Bypass. Ann Thorac Surg 93: 148-154.

14. Manji RA, Grocott HP, Leake J, et al. (2012) Seizures Following Cardiac Surgery: The Impact of Tranexamic Acid and Other Risk Factors. Can J Anaesth 59: 6-13.

15. Myles P, Smith JA, Forbes A, et al. (2017) Tranexamic-Acid in Patients Undergoing Coronary-Artery Surgery. NEJM 376: 136-148.

16. Lecker I, Wang DA, Whissell P, et al. (2016) Tranexamic Acid Associated Seizures: Causes and Treatment. Ann Neurol 79: 18-26.

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