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Original study

A comparative study to evaluate the effect of two different doses of tranexamic acid in reducing intraoperative blood loss during pancreaticobiliary surgeries

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Abstract

Background: **Studies comparing the effect of different doses of tranexamic acid (TXA) in pancreaticobiliary surgeries are lacking. We conducted this randomized controlled trial to compare the effect of two different doses of TXA on intraoperative blood loss during pancreaticobiliary surgeries.**
Methods: **62 adult patients undergoing pancreaticobiliary surgeries were randomized to receive either 15mg/kg bolus of TXA before incision (group A) or 15 mg/kg TXA bolus before incision followed by 1/mg/kg/hr TXA infusion for the length of surgery (group B). The primary objective was to compare intraoperative blood loss between the two groups. Secondary objectives were to compare intraoperative blood transfusion, change in hematocrit, length of hospital stay (LOS), incidence of deep vein thrombosis (DVT) and 28-day mortality.**
Results: **There was no significant difference in blood loss between the two groups {553.0 ml (257.5-728.0) in group A and 423.0 ml (313.5-499.0) in group B, p=0.17}. The change in hematocrit (2.2% and 0.4% in groups A and B respectively, p=0.35) and LOS (25 ± 8 days in group A vs. 20 ± 6 days in group B, p =0.80) were comparable between the groups. Both groups had a 0% 28-day mortality and no DVT was observed in any patient.**
Conclusion: **We found that there was no difference in intraoperative blood loss in pancreaticobiliary surgeries when a bolus only or a bolus plus infusion regimen of TXA was used. No patient in either group had thrombotic complications.**

Key words: **Tranexamic acid, blood loss, pancreaticobiliary surgery, abdominal surgery, hemorrhage, blood transfusion.**

Introduction

Blood loss during abdominal surgeries increases the requirement of intravenous fluids which in-turn increases the risk of gut oedema, ileus, and anastomotic leaks. In addition, blood transfusion carries the risk of transfusion associated complications[1]. Nakanishi K. et al reported that reducing intraoperative blood loss avoids acute anemia and decreases transfusion rate and is of fundamental significance to improve prognosis[2].

The benefit of intraoperative tranexamic acid (TXA) in orthopedic and trauma surgeries is established. NICE guidelines recommend the use of TXA intraoperatively when the blood loss is expected to be greater than 500 ml[3]. Data on the benefit of TXA in abdominal surgeries are largely derived from studies conducted in gynecological surgeries[4]. There is a paucity of studies evaluating effect of TXA in patients undergoing pancreaticobiliary surgeries. While in spine surgeries, a bolus plus infusion regimen has been found to reduce intraoperative blood loss more than when used as a bolus alone, to the best of our knowledge, studies comparing a single bolus vs bolus plus infusion regimen in pancreaticobiliary surgeries are lacking. Thus, we conducted this randomized controlled trial to compare the effect of two different doses i.e., single bolus vs bolus plus infusion of TXA on intraoperative blood

loss in patients undergoing pancreatico-biliary surgeries with an estimated blood loss of more than 500 ml.

Materials and Methods

We conducted this randomized controlled double blinded trial on 62 adult patients undergoing open pancreaticobiliary surgeries in a tertiary hospital after Institutional Ethical Committee approval (IECPG-163/24.03.2022;27.04.2022, chairperson Dr. S.C.Tiwari) and clinical trial registration (CTRI/2022/10/046692) from 31/10/2022 to 05/11/2023. Informed written consent was obtained from all participants and this study was conducted in accordance with the principles in the Helsinki Declaration.

The primary objective was to compare intraoperative blood loss between the two groups. Secondary objectives were to compare intraoperative blood transfusion, change in hematocrit, length of hospital stay (LOS), incidence of deep vein thrombosis (DVT) and 28-day mortality.

Patients who were posted for open pancreaticobiliary surgeries (including surgeries for tumors, obstruction, injuries of the pancreas and bile ducts e.g., Whipple surgery, pancreatectomy, extended cholecystectomy) were included in this study if they were more than 18 years of age and belonged to American Society of Anesthesiology Physical Status (ASA-PS) grade 1 and 2. Patients undergoing emergency surgeries, or those with coagulopathy or thrombocytopenia, history of stroke, coronary artery disease or peripheral vascular disease, chronic kidney disease (CKD) or Chronic liver disease, history of DVT or thromboembolism, pregnant and lactating women, patients with preoperative hemoglobin less that 10g/dl, patients undergoing major hepatic surgeries, and patients having indwelling catheters (e.g., chemoports) were excluded from the study.

Patients were randomly assigned into two groups based on a computer-generated sheet in 1:1 allocation. Allocation concealment was achieved using sequentially numbered opaque sealed envelopes. Patients in group A received 15mg/kg TXA iv over 10 minutes prior to surgical incision followed by normal saline infusion, for the duration of surgery. Patients in group B received 15mg/kg TXA iv over 10 minutes prior to surgical incision followed by an infusion of TXA at 1mg/kg/hr for the duration of surgery. Bolus dose of TXA was diluted in 100 ml of saline and administered over 10 minutes. Infusion of TXA/saline was prepared in a 50 ml syringe and infused at the desired rate. The envelopes were opened and drug infusions were prepared according to the random number by an anesthesia colleague not involved in patient care and data collection. The investigators, clinicians involved in patient care as well as the patients themselves were blinded to the intervention till the conclusion of the study.

All patients received a thoracic epidural with general anesthesia for the surgery. Patients were induced with fentanyl (2 µg/kg) and propofol (2 mg/kg). Atracurium (0.5 mg/kg) was administered to facilitate tracheal intubation. Anesthesia was maintained with isoflurane (MAC of 0.8 to 1.0) in an oxygen - air mixture (FiO2= 0.5). Intraoperative analgesia was provided with a combination of epidural infusion (0.1% ropivacaine with 2 µg/ml fentanyl @ 4-6 ml/hour) and iv morphine (50 µg/kg boluses). Patients received ringer's lactate as maintenance fluid at 4-6 ml/kg/hr. Blood loss was replaced by crystalloids or Hydroxy Ethyl Starch as per the treating anesthetist. Transfusion trigger was hemoglobin level of 8 g/dl. Muscle relaxant was reversed and trachea was extubated if patients were hemodynamically stable. All patients received multimodal postoperative pain management (morphine via epidural catheter, 1 gram paracetamol thrice daily intravenous and 30 mg ketorolac intravenous twice daily if there was no contraindication). Patients who could not be extubated were not included in the final analysis.

Intraoperative blood loss

The volume of blood in the suction bottle was noted after subtracting the volume of ascites drained, if present. The volume of intraoperative saline used and the weight of mops and gauzes was noted. Mops and gauzes were weighed at 2-hour intervals to reduce the effect of evaporation. A sample of the mops and gauzes to be used intraoperatively were weighed prior to surgery (dry weight of mops and gauzes respectively). This was then multiplied by the total number of mops and gauzes used intraoperatively to estimate the dry weight. The total intraoperative blood loss was then calculated using the formula below:

Total amount of blood loss= (total volume in suction bottle- volume of ascites - amount of saline used) + (weight of mops and gauze used intraoperatively- dry weight of the mops and gauzes).

Postoperative management and monitoring

Patients were monitored 2 hourly for the first 24 hours and then daily during their hospital stay for any symptoms or signs of DVT/coronary artery disease/stroke. Lower limb ultrasound (3 point)

was performed on postoperative day (POD) 1 to look for DVT.

Study data

Hemoglobin, hematocrit, platelet count, serum fibrinogen, D-dimer and International normalized ratio (INR) were measured preoperatively and on POD 0. Intraoperative blood loss, intravenous fluids and blood products administered, duration of surgery and anesthesia were recorded. Hospital LOS, 28-days mortality and the incidence of postoperative complications (defined as Clavien-Dindo grade III, IV and V) or thrombosis were noted.

Statistical analysis

Categorical variables are represented in the form of number and percentage (%). Data was checked for normality by using Kolmogorov-Smirnov test. Quantitative data is represented as mean with standard deviation or median with interquartile range. Non parametric data was analyzed using Mann-Whitney Test and parametric data was analyzed using independent t test. Qualitative data was analyzed using Chi Square test or Fisher's exact test. Statistical Package for Social Sciences (SPSS)TM, IBM Corp., V.25.0 was used for statistical analysis. P-value ≤0.05 was considered significant.

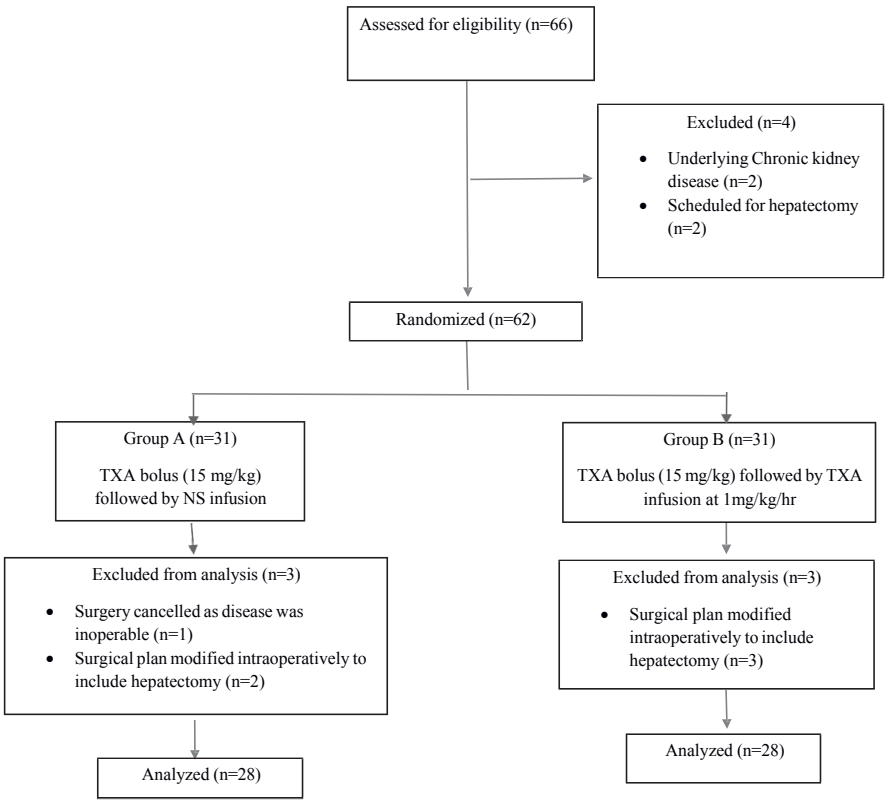
Sample size

Assuming a mean intraoperative blood loss of 500 ± 200 ml, we calculated that to detect a 30% decrease in blood loss with alpha error as 0.05 % and power of 80%, 28 patients will be required in each group i.e., a total of 56 patients5. Assuming a drop out of 10%, a total of 62 patients were recruited with 31 patients in each group.

Results

Sixty-six patients were assessed for eligibility, of whom 4 were excluded (2 participants had underlying chronic kidney disease and 2 participants were scheduled for hepatectomy). A total of 62 participants were randomized of whom, 6 patients were excluded from final analysis (surgery was abandoned in 1 patient as the disease was inoperable and 5 patients were excluded due to change in the surgical plan to include major hepatectomy, Fig 1). Data for twenty eight patients each in groups A and B were analyzed.

The two groups were similar in terms of age, gender distribution and Body Mass Index (BMI). There were more patients belonging to ASA-PS 2 category in group B as compared to group A (60.7% vs 32.1% respectively, Table I). Preoperative hemoglobin, platelet count, serum



Abbreviations: n: number of participants, TXA: Tranexamic Acid, NS: Normal Saline.

Fig. 1 — Consort diagram.

Table I. — Patient Characteristics.

Variables	Group A*	Group B*	P- value
Age (years)	49.9 ± 15.2	51.8 ± 11.3	0.60
Gender (Male: Female)	14:14	16:12	0.59
BMI (kg/m^2)	28.9 ± 3.6	31.2 ± 5.4	0.06
ASA grade (1:2)	19:9	11:17	0.03
Diagnosis, n (%)			
Periampullary Carcinoma	14 (50)	16 (57.1)	0.79
Benign Biliary Stricture	8 (28.6)	7 (25)	
Carcinoma Gall Bladder	5 (17.8)	3 (10.7)	
Carcinoma head of pancreas	1 (3.6)	1(3.6)	
Cholangiocarcinoma	0 (0)	2 (7.2)	
Type of surgery n (%)			
Extended cholecystectomy	5 (17.2)	3 (11.1)	0.52
Roux-en-Y Hepaticojejunostomy	9 (31)	6 (22.5)	
Whipple's surgery	15(51.7)	18 (66.7)	
Preoperative laboratory values			
Hemoglobin(g/dl)	12.3 ± 1.6	11.4 ± 1.3	0.02
Hematocrit (%)	38.1 ± 5.2	35.3 ± 5.7	0.07
Platelet count (10^3/µl)	278 ± 99	275 ± 100	0.88
INR	1.01 ± 0.17	1.07 ± 0.17	0.20
D-dimer (ng/ml)	350.8 ± 147.4	374.6 ± 174.5	0.58
Fibrinogen(mg/dl)	333 ± 109	352 ± 81	0.45

*Group A : 15mg/kg TXA followed by normal saline infusion; Group B: 15mg/kg TXA followed by TXA infusion at 1mg/kg/hour.
Data is represented as mean±Standard Deviation or n (%). BMI: Body Mass Index, ASA: American Society of Anesthesiologists, INR: International Normalized Ratio.

fibrinogen and D-dimer levels were also similar between the groups (Table I). Most of the patients were diagnosed with periampullary carcinoma (50% and 57.14% in group A and B respectively) followed by Benign Biliary Stricture, Carcinoma Gall Bladder, carcinoma head of pancreas and cholangiocarcinoma. Patients in both groups underwent similar surgeries (Table I). All patients were extubated at the end of surgery.

There was no difference in intraoperative blood loss between the two groups {553 ml (257.5-728.0) in group A and 423ml (313.5-499.0) in group B, p=0.17}. In group A, 3 patients received 1 unit of PRBC and 3 patients received 2 units of PRBC while in group B 3 patients received 1 unit of PRBC and 4 patients received 2 units of PRBC. The change in hematocrit between postoperative and preoperative levels was 2.24% and 0.41% in groups A and B respectively and was not significantly different between the two groups (p=0.35). All patients had a platelet count, fibrinogen and D-dimer levels within the normal range postoperatively (Table II). The LOS in hospital (25 ± 8 days in group A Vs. 20 ± 6 days in group B, p =0.80) was comparable. All patients were alive at 28-days and no patient in either group developed thrombotic complications. The incidence of postoperative complications was similar in both groups.

Discussion

We conducted a randomized controlled trial to compare the effect of two different regimens of TXA (bolus vs a bolus-plus-infusion of TXA) on reducing intraoperative blood loss in patients undergoing pancreaticobiliary surgeries and found that there was no difference in the intraoperative blood loss between the two groups. We recruited patients posted for surgeries with an estimated blood loss of more than 500 ml (including Whipple's surgery, pancreatectomy, and extended cholecystectomy).

Surgical bleeding during abdominal surgeries can be broadly divided into vascular or non-vascular causes. Reducing the former predominantly depends on the surgical skill and techniques used. Non vascular causes of bleeding can be reduced by using hemostatic agents like Surgicel™ in the operative field or antifibrinolytic agents like TXA and aprotinin. The Crash 2 study and WOMAN trial established the importance of TXA in trauma patients and in postpartum hemorrhage respectively[6,7]. NICE guidelines recommend the administration of TXA intraoperatively for all surgeries with an expected blood loss of greater than 500 ml in adults[3]. Thus, a placebo group was not used in the present study. In a recent metanalysis conducted on 19 studies, Koh et al found that TXA reduced intraoperative blood loss by a mean of 188.35 ml (95 % CI 254.98 ml

Table II. — Outcome parameters.

	Group A*	Group B*	P- value
Intraoperative Blood loss (ml)	553.0 (257.5,728.0)	423.0(313.5-499.0)	0.17
Intraoperative fluids			
PRBCs[#]	0(0-0)	0(0-0.25)	0.73
Intravenous Fluids (litres)	2.55 ± 0.77	2.6 ± 0.85	0.80
Duration of surgery(minutes)	399 ± 108	396 ± 111	0.92
LOS-hospital (days)	25 ± 8	20 ± 6	0.80
Clavien-Dindo n (%)			
Grade 1	21 (75.0)	22(78.6)	0.75
Grade 2	7 (25.0)	6 (21.4)	
Postoperative laboratory values			
Hematocrit (%)	36.6 ± 4.8	35.5 ± 4.1	0.29
Change in haematocrit (%)	2.2 (3.0, 9.3)	0.4 (5.9, 6.3)	0.35
Fibrinogen (mg/dl)	413 ± 109	396 ± 98	0.52
D-dimer (ng/dl)	309.5 ± 113.5	316.5 ± 145.4	0.84
Platelet count (10^3/µl)	262 ± 77	271 ± 83	0.68

*Group A: 15mg/kg TXA followed by normal saline infusion; Group B: 15mg/kg TXA followed by TXA infusion at 1mg/kg/hour.
Data is represented as mean ±Standard Deviation, median (Q1, Q3) or n (%).
#Number of units,1 unit of PRBC is approximately 350 ml, PRBC: Packed Red Blood Cells LOS: Length of Stay.

to 121.72 ml) in patients undergoing extrahepatic abdominal surgery[8]. Most studies have compared the effect of TXA to a placebo. Sallam et al conducted a study in abdominal hysterectomies comparing TXA bolus(1g), normal saline and intra-abdominal topical TXA (2g) after hysterectomy and found reduction in blood loss in intravenous and topical TXA group as compared to normal saline group[9]. Alhomoud et al compared TXA bolus (10 mg/kg) with placebo in lap sleeve gastrectomy surgeries and found that TXA significantly reduced intraoperative blood loss during surgery[10]. While most of the studies on TXA in non-orthopedic surgeries have been conducted on trauma and gynecological surgeries, to the best of our knowledge, studies on pancreaticobiliary surgeries are lacking.

Most literature on bolus-plus-infusion regimen of TXA has been derived from orthopedic surgeries like scoliosis surgeries. However, even in spine surgeries there is a wide variation in the dose administered. Bolus doses range from 10mg/kg to 20mg/kg in low dose regimens to as high as 100mg/kg in high dose regimens. The infusion rate also is not standardized with rates ranging from 1mg/kg/hour (low dose regimens) to 10-30 mg/kg/hr (high dose regimens). Hasan et al compared a low and high dose regimen in scoliosis surgeries and reported that there was no significant difference in blood loss between the two regimens[12]. Based on the above studies, we chose a dose of 15 mg/kg bolus followed by an infusion of 1mg/kg/hour.

Few studies have explored the effect of a bolus-plus-infusion regimen in non-orthopedic surgeries. In 2020, Monaco et al compared 500 mg of TXA bolus with a continuous infusion of TXA at 250 mg/hr in patients undergoing repair for abdominal aortic aneurysm. They found that a continuous infusion did not reduce intraoperative blood loss as compared to a bolus dose[12]. The results from the present study are in concordance with this study. We found that in the current RCT, the administration of a continuous infusion of TXA following a bolus did not decrease blood loss when compared to a bolus alone. In abdominal surgeries most of the non-vascular bleeding occurs during tumour dissection and adhesiolysis. In orthopaedic surgeries unlike abdominal surgeries a major cause of blood loss is bleeding from cut surfaces of muscles which continues until closure. This could possibly explain the difference in the effect of an infusion of TXA between the two types of surgeries.

Our secondary objectives were to compare the change in hematocrit and the number of PRBCs transfused intraoperatively. We found no difference in the change in hematocrit or number of patients who received transfusions. This result is expected as there was no difference in blood loss (primary objective) and the baseline hematocrit levels between the two groups. The amount of intravenous fluids received in the two groups was comparable.

We also followed patients for possible thromboembolic complications using USG, and clinical signs and symptoms. No patient in any group had any incidence of DVT during our study period. This is in concordance with findings of meta- analysis of 19 studies on 2205 patients who underwent abdominal, pelvic, gynecological and urological surgeries[13]. The authors found that TXA reduced blood loss without increasing the risk of

thromboembolism. This meta-analysis included studies where TXA was used in either bolus or infusion doses. A recently published HALT IT trial on 12009 patients of gastrointestinal bleed concluded that TXA did not reduce blood loss after an acute upper gastrointestinal bleed, but was associated with a significant risk of venous thromboembolism[14]. However, in this study most of the causes of upper gastrointestinal bleed were due to variceal bleeding and this result cannot be extrapolated to surgical bleeding.

We hypothesized that an increase in blood loss would increase postoperative morbidity. We found that there was no difference in the incidence of complications, duration of hospital stays or 28-day mortality. This could be explained by the fact that in our study, there was no difference in the amount of intravenous fluids and blood transfusions administered between the two groups.

Our study has the following strengths. Firstly, this study was conducted in patients operated by the same lead surgeon thus reducing bias which can arise due to different surgical skill levels. Secondly, the mops were weighed every 2 hourly to decrease the effect of evaporation. However, this study was a single-centre study. The study was powered to detect a 30% decrease in blood loss and a larger sample size would be required to detect smaller differences in blood loss. Furthermore, we did not measure markers of platelet function or plasma levels of TXA, which could have provided deeper insight into the effect of TXA. Nevertheless, this study is, to the best of our knowledge, the only study on different doses of TXA conducted in pancreaticobiliary surgeries.

To conclude, we found that there was no difference in intraoperative blood loss in pancreaticobiliary surgeries when a bolus only or a bolus plus infusion regimen of TXA was used. No patient in either group had thrombotic complications.

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