Major Liver Resection, Systemic Fibrinolytic Activity, and the Impact of Tranexamic Acid

Running head: Fibrinolysis during Liver Resection

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Abstract

Background

Hyperfibrinolysis may occur due to systemic inflammation or hepatic injury that occurs during liver resection. Tranexamic Acid (TXA) is an antifibrinolytic agent that decreases bleeding in various settings, but has not been well studied in patients undergoing liver resection.

Methods

In this prospective, phase II trial, 18 patients undergoing major liver resection were sequentially assigned to one of three cohorts: (1) Control (no TXA); (2) TXA Dose I- 1 g bolus followed by 1 g infusion over 8 hours; (3) TXA Dose II- 1 g bolus followed by 10 mg/kg/hr until the end of surgery. Serial blood samples were collected for thromboelastography (TEG), coagulation components and TXA concentration.

Results

No abnormalities in hemostatic function were identified on TEG. PAP complex levels increased to peak at 1106 ug/L (normal 0-512 ug/L) following parenchymal transection, then decreased to baseline by the morning following surgery. TXA reached stable, therapeutic concentrations early in both dosing regimens. There were no differences between patients based on TXA.

Conclusions

There is no thromboelastographic evidence of hyperfibrinolysis in patients undergoing major liver resection. TXA does not influence the change in systemic fibrinolysis; it may reduce bleeding through a different mechanism of action.

Keywords: Blood Transfusion, Fibrinolysis, Hemostasis, Hepatectomy, Tranexamic Acid

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INTRODUCTION

Liver resection is the optimal treatment for patients with primary or metastatic liver malignancies, benign liver tumors, and some biliary diseases.[1-5] Despite many technical advances, intraoperative bleeding remains a problem during liver resection with 30-40% of patients receiving perioperative blood transfusions.[6-8] Blood transfusion carries several risks, including transfusion-transmitted viruses, transfusion-related acute lung injury, transfusion-associated circulatory overload, acute hemolytic transfusion reactions, bacterial contamination and severe allergic reactions.[9] In addition, bleeding and blood transfusion are risk factors for postoperative morbidity and in some reports, long-term cancer recurrence.[6,10-22] Furthermore, blood products are sometimes scarce and associated with appreciable expense. Thus, there is compelling rationale to reduce blood loss and blood transfusion as much as possible in patients undergoing liver resection.

Hemostatic function is determined by the interaction of the vascular wall, platelets, coagulation factors, and fibrinolytic function.[7,23,24] The hemostatic system may be abnormal in patients who have compromised liver function and this may contribute to excessive bleeding during liver surgery. In particular, primary hyperfibrinolysis may occur as a result of the systemic inflammatory effect of surgery or due to hepatic injury that occurs during liver surgery. Hyperfibrinolysis may be inhibited by the administration of antifibrinolytic agents including plasmin inhibitors (aprotinin) and plasminogen inhibitors (lysine analogues - tranexamic acid (TXA) and episilon aminocaproic acid (EACA)). Although aprotinin appears to be effective at reducing bleeding, its use has been associated with an increased risk of death and renal compromise when compared to the lysine analogs.[25,26]

TXA decreases bleeding in various settings including multisystem trauma, orthopedic surgery, spine surgery, cardiopulmonary bypass, and liver transplantation.[7,27-31] It has not been well studied in patients undergoing liver resection, and it is rarely used in that setting.[32,33] Our objectives were to characterize the impact of liver resection on systemic fibrinolysis, and to define the impact of TXA at two different doses on fibrinolysis.

METHODS

We conducted a prospective, open label, phase II trial examining the impact of TXA at two doses on fibrinolysis during major liver resection. The protocol was approved by the Sunnybrook Health Sciences Centre Research Ethics Board and registered with ClinicalTrials.gov (NCT01651182).

Patient Eligibility

Patients over the age of 18 undergoing anticipated open or laparoscopic major liver resection (greater than two segments) were approached and invited to participate in the trial. Patients were excluded if they were scheduled for hepatectomy associated with vascular or biliary reconstruction, had a platelet count less than 100,000 x 10^9/L, severe anemia (hemoglobin level less than 90 g/L), documented arterial or venous thrombosis in the past three months, known disseminated intravascular coagulation, severe renal insufficiency (CrCl < 30 mL/min), history of seizure disorder, hypersensitivity to TXA or any of the ingredients, were pregnant or lactating, unable to receive blood products, had received chemotherapy within 4 weeks of scheduled operation, were taking anticoagulants, direct thrombin inhibitors or thrombolytic therapy within the last week, or were previously enrolled in this study. Patients

were screened in the surgical clinic at the time of surgical consent and provided a separate consent to participate in this trial.

Interventions

Cohorts of 6 subjects were enrolled sequentially to one of the three regimens: (1) Control (no TXA); (2) TXA Dose I - 1 g bolus followed by 1 g infusion over 8 hours initiated 15 minutes after the bolus dose; and (3) TXA Dose II: -1 g bolus followed by 10 mg/kg/hr initiated 15 minutes after the bolus dose until the end of surgery. Dose I was selected based on the CRASH-2 trial, in which 20,000 trauma patients worldwide were randomly assigned to TXA or placebo.[27] This dose was effective at reducing death due to bleeding and was not associated with increased adverse events. The higher dose, Dose II, is more frequently used in liver transplant surgery, with no increase in thrombosis, reoperation or mortality in this setting.[34]

General anaesthesia and liver resection proceeded according to standard institutional practices with no other modifications for the purposes of this trial. Clinicians were not permitted to utilize other systemically administered antifibrinolytic agents. All patients had a central line with the central venous pressure (CVP) maintained as low as possible during anaesthesia.[35-37] Liver transection was accomplished using the Kelly-crush technique with portal inflow clamping (the Pringle maneuver) at the surgeons' discretion. Transfusion of blood products (red blood cells, fresh frozen plasma, platelets, or cryoprecipitate) was guided by a standardized restrictive protocol. Red blood cells were transfused for Hgb < 70 g/L; or Hgb 70-90 g/L based on medical judgment with an indication provided by the transfusing clinician (coronary ischemia, hemodynamic instability, ongoing blood loss, etc). Red blood cells were transfused one unit a time in non-bleeding patients. Fresh frozen plasma was transfused for INR

> 1.5 with clinically active bleeding. Platelets were transfused only if the patient was clinically bleeding with platelet count < 50 x 10^9/L and cryoprecipitate only if patient was bleeding with fibrinogen < 1.0 g/L.

Outcomes

Routine clinical data were collected including patient demographics, extent of liver resection, intraoperative blood loss, transfusions, and postoperative complications until discharge.

Blood samples were collected at four time points to determine the extent of fibrinolysis: (1) baseline – immediately after induction; (2) after liver mobilization, prior to transection; (3) after liver transection; and (4) post-operatively, 24 hours following induction. At each of these times two 5 ml samples of arterial blood were collected into standard citrated blood tubes. The following laboratory parameters were measured: INR, PTT, fibrinogen, and plasmin-antiplasmin (PAP) complex. PAP is a relatively stable complex of plasmin (the key enzyme of the fibrinolytic system) and its inhibitor α2-antiplasmin. The plasma PAP concentration is thus a measure of the current activity of the fibrinolytic system. Expected normal values for PAP complex levels are 0–514 ug/L (2.5–97.5% percentiles).

A 2 mL sample was collected from each patient for thromboelastography (TEG) assessment, which assesses the viscoelastic properties of whole blood clotting under low shear conditions. TEG samples were processed within 1 h of blood draw at 37 °C using a Rotational Thromboelastometry (TEG) delta instrument (TEM International, Munich, Germany). The methodology and the parameters of TEG have been described previously in detail[38]. Two separate TEG assays were performed for each patient: (1) the EXTEM assay activates

haemostasis via the physiological activator tissue factor and is a screening test for extrinsic haemostatic function; (2) the FIBTEM assay eliminates the platelet contribution of clot formation by inhibiting the platelets irreversibly with cytochalasin D. A comparison of EXTEM and FIBTEM allows for the detection of fibrinogen deficiency or fibrin polymerization disorders.

Blood samples were collected in all patients for pharmacokinetic analysis at the following times: baseline (immediately prior to drug bolus), during drug infusion at time 0, 30, 60, and every 120 min after initiation of the infusion, and during the drug elimination phase after discontinuation of drug infusion at time 0, 4, and 24 hours. Blood samples were collected in standard 2.5 ml citrated tubes (Vacutainer, Becton Dickson, Franklin Lakes, NJ, USA), centrifuged and the plasma supernatant stored at -70°C within 6 hours of sampling. TXA concentration was measured using solid phase microextraction techniques and Tandem liquid chromatography-mass spectrometry as previously described[39,40].

Statistical Analysis

Descriptive statistics were used to summarize patient demographics and clinical outcomes. Categorical variables were reported as absolute values (N) and frequencies (%) and compared between groups using Fisher's exact test (F-E). Continuous variables were reported as medians and interquartile ranges (IQRs) and Kruskal-Wallis (K-W) testing was used to detect statistically significant differences between the three groups. Non-linear mixed effects modeling explored the extent of fibrinolysis that occurs during liver resection, the impact of TXA on fibrinolysis, and the impact of TXA dosing regimen on TXA plasma concentration.

The analytical plan was to select the most appropriate dose of TXA for future study based on the inhibition of hyperfibrinolysis using TEG or PAP complexes. In the absence of

differences in either of these measures, the dose was selected as the minimum required to achieve a stable plasma TXA concentration of 10 mcg/ml; the concentration demonstrated in vitro to be required to completely inhibit fibrinolysis. The sample size calculation was based on the pharmacokinetic modeling; with six patients in each group the pharmacokinetic profile of both regimens could be confidently differentiated using pharmacokinetic computer modeling (NONEM, GloboMax LLC, Hanover, MD).

RESULTS

The majority of patients (16 of 18) underwent liver resection for colorectal cancer liver metastases, with only one patient diagnosed with hepatocellular carcinoma and one with cholangiocarcinoma (Table 1). Operations were extensive; including extended right hepatectomy (5), right hepatectomy (4), left hepatectomy (1), and a variety of non-anatomic resections encompassing greater than two segments. Median operative time was 291 minutes, including 67 minutes of parenchymal transection time. Surgeons used intermittent inflow occlusion (Pringle maneuver) in the majority of cases (15).

Clinical outcomes were favorable, with no mortalities and only one patient receiving red blood transfusion, while no patients received other blood products (Table 2). There were no major complications. Notably, there were no thromboembolic events or seizures noted during the study period. Median length of stay was 5 days with a range of 3-18 days. Two patients were readmitted after discharge, neither with bleeding or thromboembolic events.

TEG analysis revealed normal whole blood clotting parameters with no evidence of hyperfibrinolysis, and no differences between control and TXA treatment groups (Supplemental Table).

INR increased significantly in patients by the end of parenchymal transection, and continued to rise by the morning of post-operative day 1 (POD1) (Figure 1). Fibrinogen levels decreased steadily during operation, reaching a trough of 2.77 ± 0.71 g/L after parenchymal division then increasing by the morning of POD1, although they did not return to baseline (Figure 2). PAP complex levels mirrored this trend, increasing steadily to peak at more than twice normal (1106 ± 407 μg/L) following parenchymal transection then decreasing by the following morning (Figure 3). There were no differences noted in any of these measurements in patients treated with TXA at either dose.

Plasma TXA concentration increased rapidly immediately following the bolus to peak at 204 ± 36 μg/mL. After approximately one hour during TXA infusion, the concentration reached a steady concentration of 37 ± 3 μg/mL in the Dose I group and 70 ± 12 μg/mL in the Dose II group (Figure 4). All TXA was eliminated by 24 hours following surgery.

DISCUSSION

This trial examining hemostatic function during major liver resection demonstrated no evidence of hyperfibrinolysis by thromboelastography. However, fibrinogen levels decreased and PAP, a marker of fibrinolysis, increased modestly during liver resection. The use of TXA employing the dose used in the CRASH-2 study or the dose routinely used in liver transplantation had no detectable impact of fibrinogen levels or degradation. Importantly, the

serum concentration of TXA was maintained throughout the perioperative period at concentration in excess of 10 mcg/ml; the concentration demonstrated in vitro to be required to completely inhibit fibrinolysis.

Liver resection remains a major undertaking, with hepatic dysfunction combined with a profound systemic inflammatory response. These two factors have the potential to substantially alter the systemic hemostatic function through a number of mechanisms, potentially including activation of hyperfibrinolysis. Conventional laboratory measures of hemostatic function including INR and PTT are frequently elevated following major liver resection due to impaired hepatic synthetic function, and are not accurate measures of hemostatic function in this setting. Furthermore, elevations in INR typically occur 24-48 hours following resection, whereas the majority of bleeding (and hence the opportunity for intervention) generally occurs intraoperatively. In this study, INR was increased slightly 24 hours following liver resection. Similarly, although fibrinogen levels decreased slightly during the course of hepatic transection, they are not sensitive enough to be relied upon for assessment of fibrinolytic function during major surgery.

Thromboelastometry has been studied in a number of settings where hyperfibrinolysis may occur, including multisystem trauma[41]. A major advantage of TEG is its ability to provide real-time information regarding a patient's hemostatic function. However, massive near-fatal trauma is required to produce detectable changes in TEG, so it may not be sensitive enough to identify patients undergoing elective surgery with moderate hyperfibrinolysis who may benefit from antifibrinolytic therapy[42]. In this study of patients undergoing major liver resection, TEG failed to identify any abnormalities in fibrinolytic function.

In contrast, PAP complex levels may be elevated in patients with modest, but clinically significant hyperfibrinolysis. In one study of patients with multisystem trauma, PAP complex levels were significantly elevated in 57% of patients with moderate or severe injuries, while TEG detected abnormalities in only 5% of patients[42]. TEG detected clot lysis only when PAP complex levels were increased to 30 times normal. Furthermore, PAP complex levels were independently associated with need for red blood cell transfusion, ventilator-free days, length of hospitalization, and 28-day mortality. In our study, PAP complex levels increased modestly by the end of transection. PAP complex levels had returned to baseline by the morning following surgery, indicating that the fibrinolytic activity is transient.

The transient fibrinolysis that occurs around the time of liver resection presents a potential opportunity to intervene and improve hemostatic function, thereby reducing blood loss and transfusion. TXA has been well studied in various settings including multisystem trauma, orthopedic surgery, spine surgery, cardiopulmonary bypass, and liver transplantation.[7,27-31] The most compelling evidence of the effectiveness of TXA comes from the large multicentred, multi-national CRASH-2 trial.[27] This prospective randomized controlled trial included more than 20,000 patients with multisystem trauma in 40 countries. Patients randomized to receive TXA within one hour of trauma had a 32% reduction in death due to bleeding compared to placebo.

In a recent meta-analysis of 95 surgical randomized controlled trials (N=7838 patients), TXA reduced the probability of receiving a blood transfusion by one third (risk ratio 0.62, 95% confidence interval 0.58 to 0.65; P<0.001).[43] The majority of these trials were in cardiac and orthopaedic surgery however, where the mechanism of bleeding is significantly different than

abdominal surgery. Four small trials have been performed in patients having liver transplantation; TXA did not result in significant reduction of allogenic blood transfusion, although the confidence interval was wide and there was a trend towards improvement.[44] Only one randomized controlled trial has examined the role of perioperative parenteral TXA in patients undergoing liver resection.[33] Among 212 patients who underwent liver resection, the blood transfusion rate was 16% in the control group and 0% in patients who received preoperative TXA ($p < 0.001$). This trial included mainly patients undergoing minor liver resection, with only 18% of patients having major liver resection (greater than two segments), and the results have not changed practice in North America[32].

The trials included in the meta-analysis all evaluated the impact of TXA on clinical outcomes, but only a few of them examined the impact of TXA on laboratory measures of hemostasis. In one trial of TXA in patients undergoing total hip arthroplasty with concomitant hydroxyethyl starch, patients randomized to the control group demonstrated significant fibrinolysis on TEG, and this effect was attenuated by TXA.[45] Two trials have examined the impact of TXA on TEG markers of fibrinolysis in cardiac surgery, yielding conflicting conclusions.[46, 47] To our knowledge, none of the trials identified measured the impact of TXA on PAP complex levels.

In our study, TXA did not impact the extent of fibrinolysis as measured with TEG or PAP complex levels. It is possible that neither of these measures are sensitive enough to detect clinically relevant changes in fibrinolysis that TXA impacts. Another possibility is that TXA acts through a different mechanism that is not accurately assessed by TEG or PAP complexes. Further research is warranted to elucidate the mechanism of action of TXA, and to investigate

the impact of other antifibrinolytic agents on the hemostatic system in this setting. Furthermore, given the compelling evidence of TXA's effectiveness in other settings, trials examining the impact of TXA on clinical outcomes (bleeding and blood transfusion) following liver surgery would be beneficial.

Our study provides pharmacokinetic information that may be used to design future trials of TXA in patients undergoing liver resection. The two most commonly used doses of TXA are 1 g bolus followed by 1 g over 8 hours (from the CRASH-2 trial) and 1 g bolus followed by 10 mg/kg/hr in liver transplantation studies.[27,43] In a meta-regression analysis, the effectiveness of TXA was stable over a wide range of doses, suggesting that the impact of TXA is not dose-dependent at the concentrations used clinically. In contrast, more complications (most notably seizures) were observed at higher doses. The plasma tranexamic acid concentration reported to inhibit fibrinolysis *in vitro* is 10 μg/mL in cardiac surgery.[48] Thus, our study suggests that a dose of 1 g bolus followed by 1 g over 8 hours is sufficient to inhibit fibrinolysis in this setting.

This study is most limited by the relatively low sample size. It was not powered to identify relationships between extent of fibrinolysis and clinical outcomes; although this would be an interesting area for future study. We did not include a comparator group of patients undergoing other types of operations, so it is difficult to determine the impact of the liver resection on fibrinolysis compared with any other major operative interventions.

In summary, this trial demonstrated no evidence of hyperfibrinolysis during liver resection by thromboelastography and only modest increases in PAP, a more sensitive marker of fibrinolysis. Neither of these hemostatic parameters was altered by TXA, despite serum concentrations in excess of 10 mcg/ml; the concentration demonstrated in vitro to be required

to completely inhibit fibrinolysis. Although there does not appear to be substantial systemic hyperfibrinolysis in patients undergoing major liver resection, there may be excessive fibrinolysis locally at the parenchymal surface, and inhibition of this process with TXA may strengthen clot. Further research is warranted to elucidate the mechanism of action of TXA and to examine the impact of TXA on clinical outcomes (bleeding and blood transfusion) following liver surgery.

Declaration of Interests

All authors have no relevant conflicts of interest to declare.

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Author's Contributions

PJK – Study design, patient recruitment, data collection, data analysis, writing first draft of manuscript, critical revisions, approved final version

YL – Study design, data analysis, critical revisions, approved final version

JT – Study design, data analysis, critical revisions, approved final version

CHL – Study design, patient recruitment, data collection, critical revisions, approved final version

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JH – Study design, patient recruitment, data collection, critical revisions, approved final version

BN – Study design, data analysis, critical revisions, approved final version

JP – Data collection, data analysis, critical revisions, approved final version

SAM – Study design, data analysis, critical revisions, approved final version

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Tables

Table 1. Baseline characteristics of included patients

	Total (18)	**Control (6)**	**TXA Dose I (6)**	**TXA Dose II (6)**
Age, Median (IQR)		68 (61-73)	66 (63-69)	62 (54-68)
K-W p-value		0.59		
Male, N (%)		4 (67)	3 (50)	3 (50)
F-E p-value		1.00		
Weight – kg, Median (IQR)		76 (60-84)	82 (79-86)	62 (51-75)
K-W p-value		0.20		
Diagnosis, N (%)				
Colorectal Metastases	16 (89)	6 (100)	5 (83)	5 (83)
Hepatocellular Carcinoma	1 (6)	0 (0)	1 (17)	0 (0)
Cholangiocarcinoma		0 (0)	0 (0)	1 (17)
F-E p-value		1.00		
Operation, N (%)				
Extended Right Hepatectomy	5 (28)	2 (33)	1 (17)	2 (33)
Right Hepatectomy	4 (22)	1 (17)	2 (33)	1 (17)
Left Hepatectomy	1 (6)	0 (0)	0 (0)	1 (17)
Other		3 (50)	3 (50)	2 (33)
F-E p-value		1.00		
Number of Segments Resected, Median (IQR)		4 (4-4)	5 (3-5)	4 (3-5)

K-W p-value		0.87		
Operative Time – minutes, Median (IQR)		268 (184-290)	313 (275-350)	306 (283-330)
K-W p-value		0.32		
Parenchymal Transection Time – minutes, Median (IQR)		60 (49-119)	93 (72-122)	64 (40-87)
K-W p-value		0.54		
Inflow Occlusion (Pringle), N (%)		5 (83)	6 (100)	4 (67)
F-E p-value		0.74		
Intraoperative Blood Loss – mL, Median (IQR)		650 (300-1500)	1200 (500-1450)	500 (400-1000)
K-W p-value		0.05*		

Table 2. Clinical outcomes of included patients

	Total (18)	**Control (6)**	**TXA Dose I- (6)**	**TXA Dose II (6)**
Red Blood Cell Transfusion*, N (%)		0 (0)	1 (17)	0 (0)
F-E p-value		1.00		
Complications, N (%)				
Confusion	2 (11)	0	2 (33)	0
Fever	1 (6)	0	0	1 (17)
Ileus	1 (6)	0	1 (17)	0
Urinary	1 (6)	0	0	1 (17)
Ascites	1 (6)	0	1 (17)	0
Length of Stay – days, Median (IQR)		4 (4-4)	11 (4-15)	6 (4-15)
K-W p-value		0.11		
Readmission, N (%)		0	0	2
F-E p-value		0.29		

*No other blood products were transfused to any patients

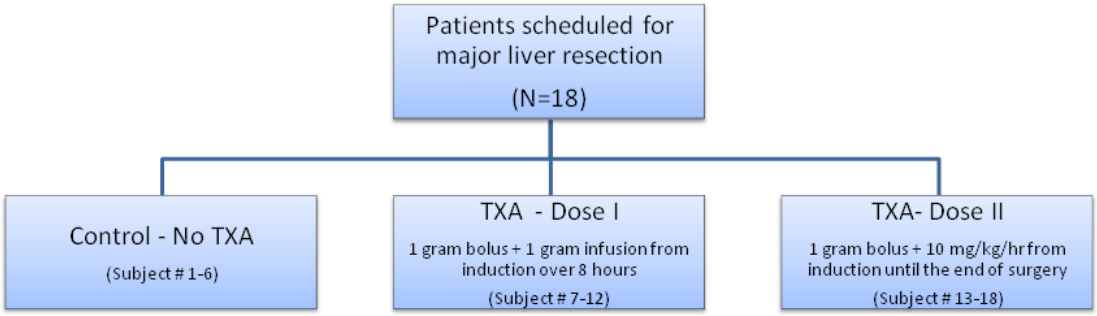
Figure Legends

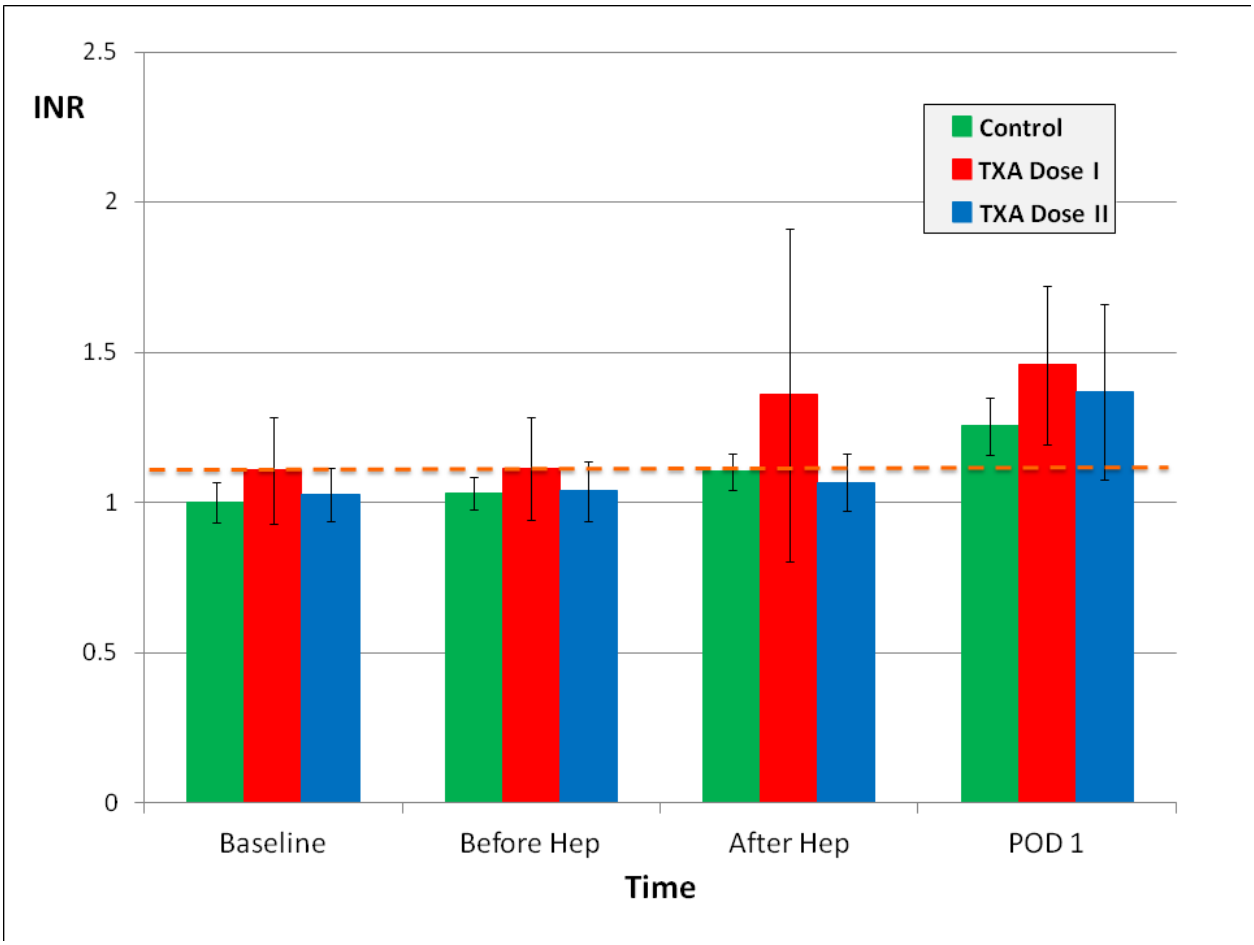
Figure 1. Trend in INR values at different time points (error bars represent standard error). Dashed line represents upper limit of normal range (1.10).

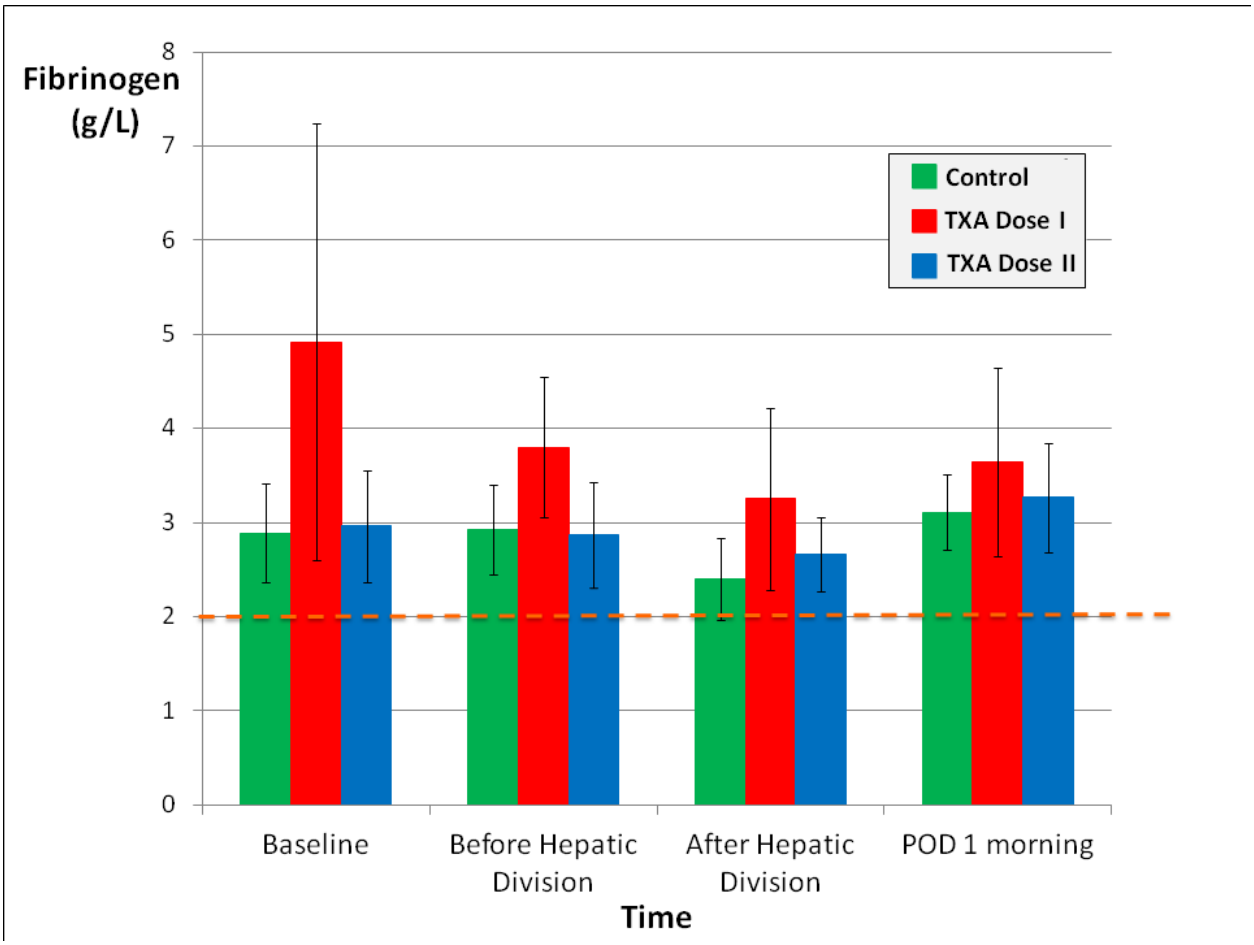
Figure 2. Trend in fibrinogen values at different time points (error bars represent standard error). Dashed line represents lower limit of normal range (2 g/L).

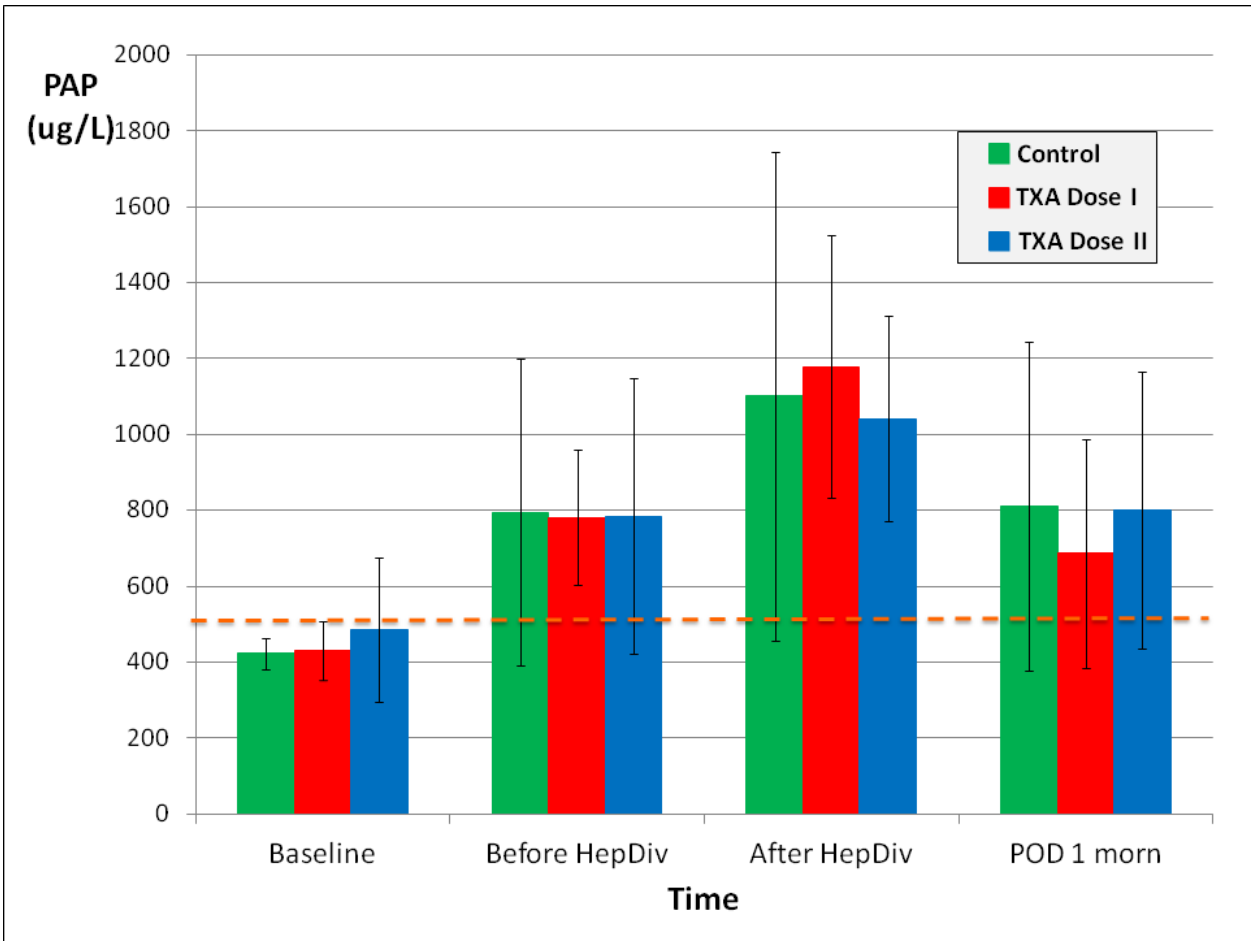
Figure 3. Trend in plasmin-antiplasmin (PAP) complex values at different time points (error bars represent standard error). Dashed line represents upper limit of normal range (512 ug/L).

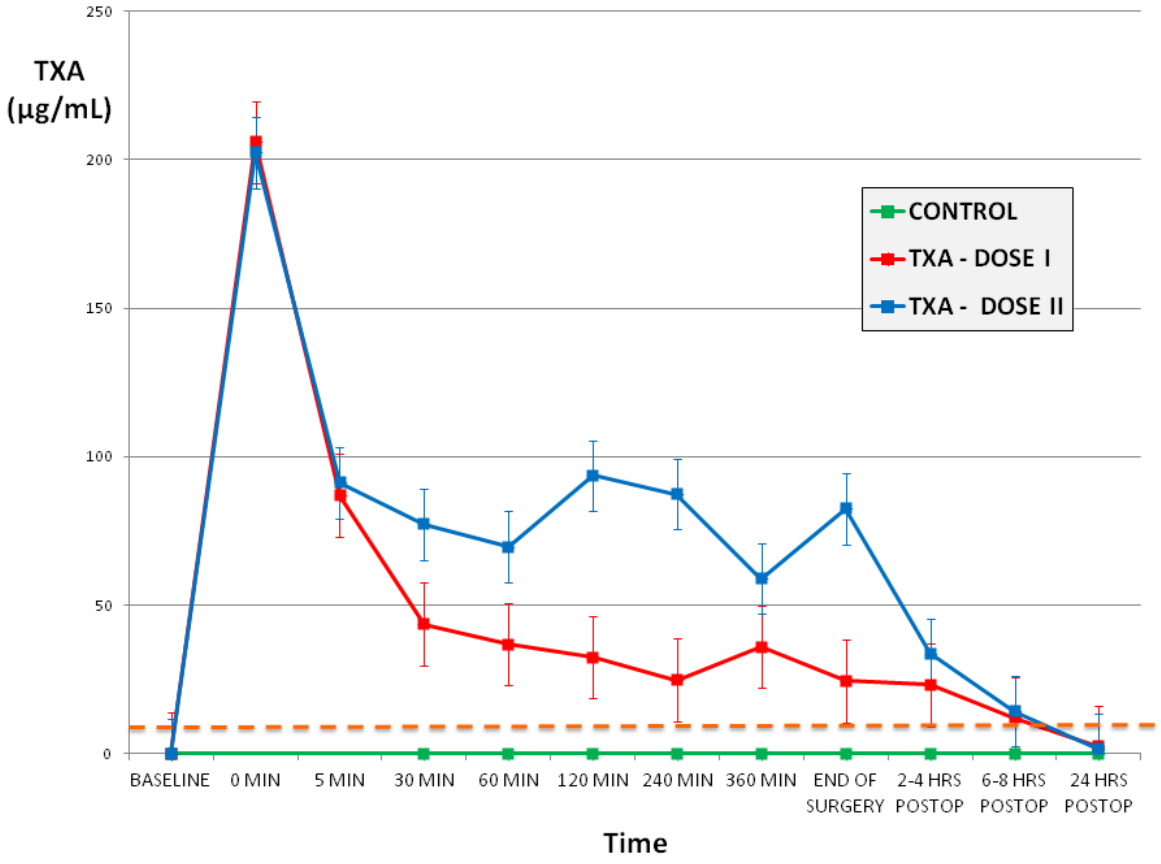
Figure 4. Plasma concentration of TXA at different time points relative to bolus and infusion of TXA in patients (error bars represent standard error). Dashed line represents in-vitro therapeutic level of TXA (10 µg/mL).


Patients scheduled for major liver resection
(N=18)
Control - No TXA
(Subject # 1-6)
TXA - Dose I
1 gram bolus + 1 gram infusion from induction over 8 hours
(Subject # 7-12)
TXA- Dose II
1 gram bolus + 10 mg/kg/hr from induction until the end of surgery
(Subject # 13-18)


INR
2.5
2
1.5
1
0.5
0
Control
TXA Dose I
TXA Dose II
Baseline
Before Hep
After Hep
POD 1
Time


Fibrinogen (g/L)
8
7
6
5
4
3
2
1
0
Control
TXA Dose I
TXA Dose II
Baseline
Before Hepatic Division
After Hepatic Division
POD 1 morning
Time


PAP (ug/L)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Control
TXA Dose I
TXA Dose II
Baseline
Before HepDiv
After HepDiv
POD 1 morn
Time


TXA
(µg/mL)
250
200
150
100
50
0
CONTROL
TXA - DOSE I
TXA - DOSE II
BASELINE
0 MIN
5 MIN
30 MIN
60 MIN
120 MIN
240 MIN
360 MIN
END OF SURGERY
2-4 HRS POSTOP
6-8 HRS POSTOP
24 HRS POSTOP
Time