Cover Page for Study Protocol

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Prospective, randomized, double blind study on the effects of tranexamic acid on intraoperative blood loss during lumbar spinal fusion and instrumentation

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Primary Aim of this proposal is to demonstrate that tranexamic acid (TXA) reduces intraoperative blood loss and transfusion requirements during and following posterior lumbar spinal fusions

Primary Hypothesis:
TXA reduces intraoperative and postoperative (up to 7 days) blood loss and transfusion requirements.

Primary Objective:
1. To test the effect of TXA on the need for red blood cell (RBC) transfusion (intraoperatively and postoperatively) in patients undergoing lumbar spinal fusion compared to placebo (Normal Saline). This will be adjusted for number of levels to fuse, duration of surgery and patient's weight.
2. To test the effect of TXA on blood loss adjusted for weight, duration and number of level fused

Secondary Objectives:
1. To test the effect of TXA on the following:
    a. Duration of surgery (Skin to skin)
    b. Length of hospitalization (LOH)
    c. Cost/effectiveness analysis
2. To assess the safety of TXA.

Exploratory objectives:

1. To test the effect of TXA on the required duration of subcutaneous drain placement (Hemovac)
2. To assess the effect of TXA on incidence of postoperative delirium.

Study Design:
Phase 2B randomized, single-center, double-blinded, placebo vs. TXA clinical trial with 1:1 randomization.

Primary endpoints:
1. The amount of RBC transfusion intraoperatively
2. The amount of RBC transfusion up to 7 days postoperatively
3. Measurement of intraoperative blood loss, postoperative blood loss, and total blood loss.

Secondary endpoints:
1. Safety analysis: thromboembolic events and worsening renal function in TXA vs placebo
2. LOH

3. Cost effectiveness analysis: cost saving from reduction in transfusion and LOH vs. cost of TXA administration

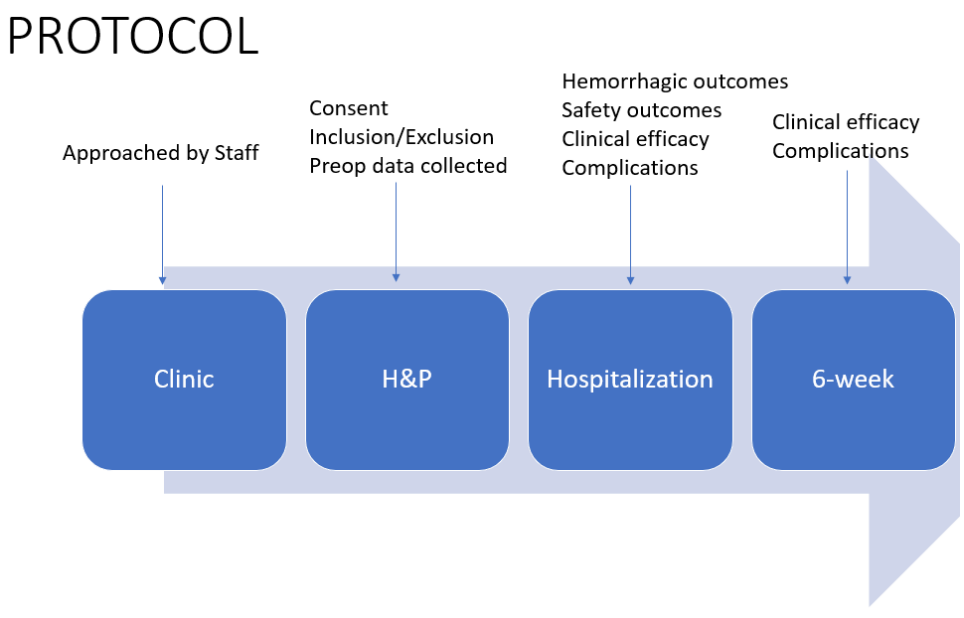
Exploratory endpoints:
1. Duration of drain in place
2. Postop wound complication incidence
3. Incidence of postoperative delirium based on CAM-3D and CAM-ICU delirium screening tools.
4. Effect of delirium on cognitive function.

Intervention:
An intravenous infusion of 10mg/kg of TXA (Amchafibrin VR 500mg; Rottapharm S.L., 5-mL vials) is administered for 20min before the surgical incision, followed by perfusion of 2mg/kg/h up to surgical wound closure at completion of surgery vs. a saline solution (placebo) administered according to the same infusion pattern and timing as in the TXA.

Drug: TXA is a synthetic reversible competitive inhibitor to the lysine receptor found on plasminogen. The binding of this receptor prevents plasmin (activated form of plasminogen) from binding to and ultimately stabilizing the fibrin matrix. TXA used for hereditary angioedema works by its indirect effect of reducing complement activation. By reducing plasmin activity, it reduces the consumption of C1 esterase inhibitor. The half-life of TXA is 2 to 11 hours. The duration of action is 3 hours after the initial dose.

Dose: 10mg/Kg bolus 20 min prior to infusion followed by 2mg/kg/h up to closure

Protocol:



Patients of ages 18 to 90 years old with ASA class I-IV undergoing elective lumbar interbody fusion (PLIF or TLIF) for degenerative disc disease (DDD) are considered eligible for inclusion in this study. Patients are screened for the inclusion/exclusion criteria below. Patients will enroll

in the study at the time of signing consent for surgery at their preoperative visit. Participation in the study has no bearing on their consent for surgery. After the patient signs consent at the preoperative visit, they will complete the baseline cognitive assessment (TICS-m, COWAT, TMT, BDI, 3D-CAM). Patients will have from the first visit until the day of surgery to withdraw from the study (2-6 weeks) and from the first visit to the preop visit to consent (1-4 weeks). Once patients are consented, they are considered enrolled. Patients can withdraw out of the study at any time prior to surgery. Once they withdraw, they will no longer be considered participants in the study. Patients will be randomized (blind randomization) using SPSS to placebo vs TXA. The primary surgeon, anesthesia care provider, investigator, and outcomes assessor will be blinded to the treatment and control arms. The intraoperative estimated blood loss in milliliters will be recorded routinely by the anesthesiologist participating in the case. All patients will be discharged to the neurosurgical or orthopedics wards postoperatively. Twice daily (~8am and ~4pm) a study member will administer the 3D-CAM or CAM-ICU delirium screening assessments to determine delirium status. Patients are followed until their second postoperative visit to clinic, approximately 3 months after the surgery. At the first visit, patients will be screened for any adverse events. At both the first and second visit postoperatively, the patients will complete the cognitive testing (TICS-m, COWAT, TMT, BDI, 3D-CAM).

Baseline Demographics/Data	
Age	**Chronic Liver Disease**
Sex	**History of DVT, PE, TEE**
Height	**Oral anticoagulation (and reason for it)**
Weight	**Oral antiplatelet therapy (and reason for it)**
BMI	**Visual impairment**
Smoking (Yes/No)	**Number of levels fused**
DM	**Number of Interbody fused**
Coronary Artery Disease	**ASA classification**
Peripheral Vascular Disease	**OB/GYN: breast feeding, OCP or pregnant**

Chronic Kidney Disease **Chronic anemia (Hb<8)**

Inclusion Criteria

1) Age 18-90 years
2) ASIA anesthesia risk of I to IV
3) Patients undergoing posterior lumbar spinal fusion for DDD.
4) Patients have failed conservative management, which include PT/OT and/or injections.

Exclusion:

1) ASIA class V
2) Patient unable to consent
3) Patient with chronic kidney disease stage III or above: baseline plasma creatinine>1.5mg/dL
4) Patient with known liver failure
5) Patients on anticoagulation or dual antiplatelets (presence of vascular stents).
6) Patients with artificial valves.
7) Patients with allergy to TXA
8) Patients with platelet count < 150 000
9) Patients with PT>15s
10) Patients with APPT>38s
11) History of stroke or (an) unprovoked thromboembolic event(s).
12) History of intracranial bleeding,
13) Pregnancy
14) known defective color vision
15) history of venous or arterial thromboembolism or active thromboembolic disease
16) Patients with severe pulmonary or cardiac disease.
17) Patients who refuse transfusion of blood products
18) Patients with chronic anemia with Hg<8
19) Patients undergoing lumbar fusion for disease other than DDD (neoplasm)
20) Patients undergoing lumbar fusion by anterior or lateral approach.
21) Minimally invasive TLIF are excluded.
22) Emergent cases.
23) Women on hormonal contraception
24) Retinal vein or artery occlusion
25) Hypercoagulability
26) Seizure disorder
27) Current use of tretinoin
28) Current use of chlorpromazine
29) Breast feeding

Variables	Preop	Hospitalization	6-week f/u	3-month f/u
Demographics	X			
BHCG				
LFT *	X			
Coags (PTT/PT/INR)	X			
GFR	X	POD1		
SF Rand/ PROMIS	X		X	X
CBC	X	X		
Complications (DVT,PE,SSI,TE)		X	X	
Visual testing *	X	POD1		
New deficit		POD1		
	X	Intraop 1h postop (PACU) POD1,2,3		
Drain output/duration		X		
Blood Loss		X		
3D-CAM/CAM ICU*	X	X	X	X
TICS-m*	X		X	X

COWAT*	X	X	X
TMT*	X	X	X
BDI*	X	X	X

Safety analysis:
Adverse events occurring in the intraoperative period, immediate postoperative period and up to 4-8 weeks after the procedure will be recorded. We will collect specific adverse events that might be related to TXA treatment, including incidence of TTE, impaired renal function (plasma creatinine increase>20% of baseline level), and neurological complications, such as seizures and vision abnormalities. Adverse events apparently unrelated to use of the drug will also be recorded. The plasma creatinine will be obtained on POD1 and preoperatively. Sever adverse events are DVT and PE.
Sections including description of the anesthesia technique, transfusion requirements and blood loss, and venous thromboembolism prophylaxis are described in the Appendix. A comparison of the frequency and severity of adverse events occurring up to the 4-8-week follow-up period will be analyzed. Any SAE will be reported to the DSMB as they occur.

Stopping rules or safety triggers for the study: impairment in renal function and thromboembolic events will trigger a meeting of the DSMB to discuss the events and decide on the continuation of the trial. The study will automatically be placed on hold until the investigators and the DSMB can conduct a review of events. All AEs will be collected, recorded, and analyzed. Safety oversight for this study will be provided by both the DSMB and an independent Medical Safety Monitor. If the rate of thromboembolic events or impaired renal function crosses the literature threshold or the control group with 95% probability, the study will stop.

Postoperative drain management: The Hemovac drain is removed when the 8h output is <50 cc. The output is recorded for every 8 hour and charted.

Indication for transfusion
- Hb <7.0 mg/dl
- Anemic symptoms developed:
    - A decrease in blood pressure to <100 mmHg systolic,

- tachycardia greater than 100 beats/min
- Orthostatic hypotension , lightheadedness, Chest pain/palpitation, confusion (due to a low bp)

- Low urine output of <30 ml/h, after initial fluid challenge with 500 ml normal saline in patients with a hemoglobin level between 7.0 and 8.0 mg/dl.

Calculations and measurement of blood loss

Visible blood loss = intraoperative blood loss + postoperative drainage amount; intraoperative blood loss = weight of liquid in the suction bottle – weight of intraoperative rinsing fluid + increased weight of intraoperative gauges and towers.

Hidden blood loss is calculated based on the linear equations provided by Gross.[7] The formula is as follows:

1)Hidden blood loss = total blood loss before and after surgery – visible blood loss.

2)Total blood loss before and after surgery = preoperative blood volume × (HCT difference before and after surgery/mean HCT before and after surgery).

3)Preoperative blood volume = K1 × height (m)3 + K2 × body weight (kg) + K3, where K1 = 0.3669, K2 = 0.0322, and K3 = 0.6041 in male patients, and K1 = 0.3561, K2 = 0.0331, and K3 = 0.1833 in female patients.[8]

Outcome assessment:
1) hemorrhage assessment:

- intraoperative blood loss,
- Total blood loss (Calculated) and Hidden Blood loss (Calculated)
- postoperative drainage amount (per 8 h shift),
- days of drain in place, HGB level (before surgery and 1, 24h, 48 and 72 hours after surgery),
- hematocrit (HCT; same),
- prothrombin time (PT), PPT before,
- number of blood transfusions

2) clinical efficacy evaluation:

- length of hospital stay
- visual analogue scale (VAS) measurement before and after surgery; duration of surgery.
- SF Rand/ PROMIS preop, 6 weeks and 3 month follow-up.
- Duration of the procedure

3) cognitive evaluations

- CAM-ICU/3D-CAM & 3D-CAM-S will be collected preop, during the hospitalization, and 6 weeks and 3 month follow-up
- TICS-m, TMT, COWAT, and BDI preop, 6 weeks and 3 month follow-up.

Venous thromboembolism prophylaxis
Patients received antithrombotic prophylaxis according to the institutional guidelines and protocols of each participating service and the individual risk estimated by the investigator. The study protocol includes evaluation of the probability that a patient would experience venous thromboembolism (VTE) using the Wells clinical prediction guide for deep venous thrombosis (DVT) and pulmonary embolism (PE) or the Geneva criteria for PE. DVTs are diagnosed by using US and PEs by using CTA. Clinically and radiologically confirmed DVT or PE are considered severe adverse events. LWMH or USQH were used after 24h of the procedure (adjusted to weight and renal function). Patients are mobilized as early as possible with Physical and occupational therapy.

Study design:

Measures to minimize bias: randomization and blinding: Randomized block design with variable block sizes will be used to randomize subjects to the 2 groups with a 1:1 ratio. Randomization will be generated by a randomization coding software (SAS Version 9.4). Randomization schema will be distributed to the pharmacy and sequence numbers will be identified to match patient enrollment. We will use triple masking: Concealment of randomization, blinding of treatment (placebo and TXA are indiscernible) and blinding of data analysis. Unmasking will be performed at the end of the trial. We will allow for unplanned masking in case of severe adverse events by the DSMB. (See Adverse events section).

Sample Size Determination Based on Primary Endpoint (Blood loss and transfusion)
We are planning a study of continuous response variable from independent control and experimental subjects with 1:1 allocation ratio. Primary calculations are based on the mean difference from a meta-analysis of RCT studies between patients who received TXA and those who received placebo. The amount of blood loss per patient significantly decreased with TXA with a mean difference (MD) of 681.81 ml (95% CI: 214.49 to 1149.12 ml). The pooled weighted MD for blood transfusion per patient between TXA group and placebo group is −234.61 ml (95% CI: −383.23 to −85.99 ml). However, there was significant heterogeneity within the selected studies. The TXA use could decreased 44% risk of blood transfusion compared with the placebo group with an OR of 0.56 (95% CI: 0.36 to 0.87). Based on the previous studies, we will need to study 40 experimental subjects and 40 control subjects to be able to reject the null hypothesis (i.e. the population means of the experimental and control groups are equal) with a probability of 0.9 (power = 90%) (Table 2). The Type I error probability associated with this test is 0.05. We will thus recruit 50 subjects per group and assume at least a 10% loss to follow-up. thrombosis complications and the use of TXA with an OR of 0.99 (95% CI: 0.06 to 16.07).

Sample size calculation for Secondary endpoints:

1. We do not anticipate any difference in thrombosis complications as a meta-analysis showed an OR of 0.99 (95% CI: 0.06 to 16.07).
2. Analyses for LOH will be based on the difference in mean hospital stay between the 2 groups. This will be adjusted on the number of level fused, presence of a neurological deficit, and BMI
3. Cost effectiveness analysis: The cost of TXA has to be compared with the cost reduction from shorter LOH and reduction in transfusion requirements.

Analysis of Primary End Point:

The primary endpoint is the mean difference in total blood loss, intraoperative blood loss and postoperative blood loss. An ANOVA will be used to compare between the 2 groups. A type I error rate of 0.05 will be utilized. An exploratory GLM ANOVA will be used to test for interaction for the subgroups with number of level fused, BMI and duration of surgery.

Analysis of Secondary End Points:

1. LOH: LOH will be defined from the day of surgery until the patient is medically ready for discharge. The 'actual LOH' will be defined as the duration from the day of surgery to actual discharge. The discharge will depend on the patient insurance and facility availability. The 'actual LOH' will reflect the duration of hospitalization in the general community, while the LOH will reflect the effect of TXA on improving the postoperative course of the patient. We will test for difference in mean between the 2 groups for both LOH and 'actual LOH'. A multivariable linear regression model will be used to adjust for factors related to longer LOH such as BMI, higher ASA score preoperatively, SF-36/PROMIS, and number of level fused.
2. We will analyze the cost-effectiveness of TXA by computing the cost reduction from the decreased in transfusion and LOH and the cost increase from treating TXA related side-effects: additional thromboembolic complications (cost of diagnosis and treatment). We will test for the difference in the mean between the two groups.
3. The other endpoints (cognitive assessments) are exploratory.

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