A Prospective, Randomized, Parallel-group Single Center Study to Evaluate the Use of Thromboelastometry (ROTEM) in Patients Undergoing Spine Surgeries.

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List of Abbreviations and Definitions

FFP: Fresh Frozen Plasma

RBC: Red Blood Cell

PC: Platelet concentrate

POC: Point of Care

SCT: Standard Coagulation Tests

PT: Prothrombin Time

PTI: Prothrombin Index

aPTT: activated Partial Thromboplastin Time

INR: International Normalized Ratio

TEG: Thromboelastography

ROTEM: Thromboelastometry

ICU: Intensive Care Unit

EXTEM: Extrinsic coagulation pathway

INTEM: Intrinsic coagulation pathway

Ct: Clotting time

CFT: Clot formation time

A10: Amplitude in 10 minutes

MCF: Maximum Clot Firmness

ML: Maximum Lysis

HTC: Hematocrit

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I. Background and Rationale

In patients undergoing neurosurgical procedures, intraoperative blood loss is a very common problem that anesthesiologists encounter. Bleeding can result from dilated epidural venous plexus, soft tissue paraspinal blood vessels, tumor hypervascularity, and even uninvolved bone. [1] This massive amount of blood loss may lead to perioperative coagulopathy, and therefore use of allogeneic blood products such as: blood, platelets, and/or coagulation factors.[2] However, blood product transfusions are associated with significant complications that also need to be taken into consideration when thinking about transfusions; these involve, but are not limited to: infections, acute lung injury, organ dysfunction, and multiorgan failure. Therefore, an early and specific characterization of the cause of bleeding is crucial to achieve an effective and goal directed perioperative hemostatic therapy and reduce these types of complications. [3, 4]

The estimated blood loss is different between surgical procedures; in spinal fusion surgeries it has been documented to be between 650 to 2839 mL per patient, with transfusion requirements in 50% to 80% of the patients analyzed. [2] Patients undergoing surgical procedures for scoliosis had an estimated blood loss of 975.4 ± 318.7 mL [5]; and in spine metastatic disease, a meta-analysis performed by Chen et al. showed blood loss ranges between 1100 ml to 6039 ml, with blood losses greater than 5000 ml present in 12% of the patients. [6]

This amount of bleeding warrants massive transfusion for resuscitation and requires an adequate hemostatic approach in order to prevent massive hemorrhage complications such as acidosis, hypothermia, and coagulopathy. In addition, it can also lead to surgical complications, such as incomplete spinal decompression, inadequate spinal fixation, poor neurologic outcomes, or death. [1]

Coagulopathy and/or uncontrolled bleeding are caused by defects on clot stability and firmness. Deficiency of coagulation factors, fibrinogen, and platelets lead to defects on clot firmness, while hyperfibrinolysis and factor XIII deficiency lead to decrease clot stability. Several studies have underscored the importance of avoiding acidosis, hypothermia, and coagulopathy; these studies have been performed mainly in cardiac surgery and trauma populations. [7]

For years, hemostatic therapy in massively bleeding and/or transfused patients has been guided with standard coagulation tests (SCTs) such as prothrombin time (PT), prothrombin index (PTI), activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, and platelet count. However SCTs limitations include the inability to assess clot strength, fibrinogen functionality; it does not measure the functionability of the red blood cells, and it does not assess the response of all these factors to an injury or surgery. Another potential disadvantage in these tests, includes the turnaround time; which generally is >30 minutes, ranging between 29 to 235 minutes. All these factors contribute to delay the clinical decision in this dynamic setting. [8-10]

Recently, point of care (POC) monitoring has emerged as a valuable alternative in hemostatic therapy algorithms for trauma, transplant, and cardiac surgeries. Thromboelastography (TEG) and thromboelastometry (ROTEM) are viscoelastic coagulation monitors that have shown to have the

potential to provide a more updated and comprehensive overview of the coagulation status. They provide a closer approach to "*in vivo* coagulation", by measuring the entire clot process starting from fibrin formation until clot retraction and degradation (fibrinolysis). [8]

Rotational thromboelastometry (ROTEM) is a POC testing device commonly used to provide a global assessment of the hemostatic status by measuring multiple aspects of blood coagulation, including, the generation of thrombin, factor deficiency, platelet function, fibrinogen, fibrinolysis and the effect of heparin in the coagulation cascade. ROTEM provides the development of the clot via initiation, increased clot firmness and changes of blood clotting under low shear conditions. ROTEM can also monitor the *extrinsic coagulation pathway* in the **EXTEM** assay and the *intrinsic coagulation pathway* in the **INTEM** assay by adding ellagic acid. [11]

Different modifications can be made to both the EXTEM and INTEM in order to assess other various defects of hemostasis:

1. Addition of Cytochalasin-D in the *EXTEM* directly measures the fibrin contribution to the clot and indirectly assesses fibrinogen availability; called **FIBTEM test.**
2. When compared to the *EXTEM* assay, the addition of Plasmin inhibitor confirms fibrinolysis and demonstrate efficacy of antifibrinolytic therapy: **APTEM test**.
3. Addition of Heparinase to *INTEM* assay, can help to discriminate heparin activity from an enzymatic factor deficiency: **HEPTEM test.**

Some other parameters can also be assessed by ROTEM. These include: clotting time, clot formation time, clot firmness, clot lysis, and A10 (which measures the amplitude at 10 minutes after the end of clotting time).

Several studies in trauma, cardiac surgery, postpartum hemorrhage, and scoliosis surgery have shown that maximum clot firmness (MCF) and fibrinogen levels are excellent predictors of perioperative bleeding complications and massive transfusion.[12] FIBTEM-A10 (Clot amplitude at 10 minutes after the end of clotting time) and FIBTEM MCF (maximum clot firmness) predict massive transfusion similarly to standard coagulation tests [13].

In cardiac surgeries, POC testing showed a lower cumulative dosage of packed erythrocytes, lower rate and smaller dose of fresh frozen plasma (FFP) and platelets concentrate (PC) transfusion. As well as reduced postoperative mechanical ventilation time, length of intensive care unit stay, composite adverse events rate, cost of hemostatic therapy, and 6-month mortality [3].

ROTEM standardized massive transfusion protocols have been used to successfully choose the optimal allogeneic blood product or coagulation factor concentrate, reduce transfusion requirements and reduce blood loss in cardiac surgery, transplant surgery, and massive trauma. The rapid ROTEM turnover has shown to impact a timely targeted hemostatic therapy and coagulopathy prevention [11, 14, 15].

The choice and amount of haemostatic therapy is not only highly relevant for patient outcomes but it is also highly relevant economically. Transfusion cost-benefit analysis has shown that the average cost of allogeneic blood replacement is $250 per unit transfused, auto transfusion is $270 per individual, and cell saver is $512 per patient [11]. Recently, the analysis of the cumulative cost of hemostatic therapy comparing POC-guided therapy with conventional coagulation test guided therapy found that the mean cost of therapy is 1,528 € ($1,924) and 3,109 € ($3,914.76) per patient respectively [3].

II. OBJECTIVES

1. Primary objective

Compare the overall amount of intra-operative Red Blood Cells and Fresh Frozen Plasma guided with ROTEM versus laboratory coagulation tests in patients undergoing major spinal surgeries.

2. Secondary objectives

- Compare the amount of Cryoprecipitate and Platelets transfused intraoperative between both groups.
- Compare the amount of all blood products transfused at 6, 12, and 24 hours postoperative.
- Compare the incidence and requirements of fibrinogen concentrate, PCC, antithrombin concentrate, factor XIII concentrate, and activated recombinant factor VII, or any other hemostatic therapy. Compare variables that affect coagulopathy such as acidosis and hypothermia.
- Compare hemodynamic variables (BP, HR, O2, Temperature, Arterial blood gases) during surgery.
- Compare postoperative time of mechanical ventilation
- Compare length of ICU stay and overall hospital stay
- Compare total in hospital need for transfusion
- Compare postoperative coagulation status on days 1 and 3 if available
- Compare overall infection rate
- Compare 30 days mortality

3. Exploratory objectives

Compare the total costs of intra-operative blood transfusion guided with ROTEM versus laboratory coagulation tests in patients undergoing major spinal surgeries.

III. Material and methods

1. Study design:
   This is a prospective, randomized parallel-group, single center study in patients undergoing elective major spine surgery. Patients will be randomized to guide blood transfusion administration with ROTEM or laboratory coagulation tests (ABG, PT, PTT, aPTT, Hb, platelets,

and fibrinogen). Randomization list will be computer-generated using a balanced allocation ratio 1:1.

2. Inclusion and exclusion criteria:

- **Inclusion criteria**

1. Male or female age 18 years or older.
2. Able to provide inform consent.
3. Patients schedule to undergo elective major spinal, orthopedic, or combined procedures under general anesthesia that are expected to receive intraoperative blood products and last greater than 2 hours.

- **Exclusion criteria**

1. Subjects younger than 18 years old.
2. Subjects who are prisoners.
3. Subjects who refuse transfusion of blood products.
4. Subjects unable to participate in the study for any reason in the opinion of the Principal Investigator.
5. Subject with past medical history of uncontrolled coagulopathies.

3. Study population and sample size:

The power analysis has been calculated based on a mean estimated RBC transfusion of 8 units with a conservatively estimated standard deviation of 5. We expect that ROTEM will decrease the RBC transfusion by 3 units. We make the same assumptions for FFP. We will test each main outcome between the ROTEM and control groups at an alpha of 0.025 (adjusted for 2 main outcomes). We need 110 patients; 55 patients in each group to achieve 80% power to detect a difference of 3 units assuming a standard deviation of 5 at an alpha of 0.025.[3,13]

4. **Randomization and study procedures:**

Patients will be randomized in a 1:1 ratio to either laboratory coagulation tests or ROTEM. No changes in surgery or anesthesia technique will be made for study's purposes.

a. Laboratory Coagulation Tests

If the patient is randomized to laboratory coagulation tests, anesthesia care providers will assess the hemostatic status according to OSUWMC standard practices and their own clinical criteria.

Laboratory coagulation tests include but are not limited to the following: hemoglobin, platelet count, fibrinogen concentration, INR, aPTT, and PT. These assessments will be performed at fixed perioperative time points (preoperatively, every 2 hours intraoperatively, end of surgery (EOS), and 24 hours after EOS). Intraoperative arterial blood gases will be performed repetitively

at a fixed range (every hour) based on anesthesia care provider's decision, along with any other common laboratory tests.

b. ROTEM

If the patient is randomized to ROTEM, the anesthesia care provider will be blinded to any conventional intraoperative coagulation test that might be performed during surgery.

ROTEM will be used according to the manufacturer's instructions using equipment and test reagents provided by Tem International GmbH. All tests will be performed at the bedside by a healthcare provider trained to perform ROTEM. A specific algorithm has been created by Dr. Klaus Goerlinger (Clinical Director at Tem International GmbH-ROTEM) and should be followed according to measurements obtained during surgery (Figure 1).

ROTEM monitoring will be performed in patients with signs of clinically relevant diffuse bleeding and in whom blood transfusion is considered (Temp >35^{o}C; pH <7.2; Cai >4.6 mg/dL; Hb $\geq$ 9g/dL, or >10g/dL with anticipated greater blood loss) or at a fixed range every 2 hours or at Anesthesiologist criteria based on patient's clinical situation.

Patient´s clinical situation should be consider as the most important component on the transfusion decision-making process. Packed erythrocytes will be transfused to maintain hemoglobin concentrations >9g/dl or >10g/dl in individuals with underlying cardiovascular disease or anticipated greater blood loss. Individual based dynamics (tachycardia, hypotension, sings of ischemia on electrocardiogram, and lactic acidosis) strongly indicating the need for erythrocyte transfusion will be also part of the decision-making transfusion process by the anesthesia care provider.

5. Data collection

The following data points will be recorded in the interventional and control group patients:

- Demographic information (age, sex, height, weight, BMI, race)
- Medical History (including past and current diagnosis, use of chemotherapy or radiation, type of cancer, medications, surgical history)
- Surgical Information (Procedure type/reason for surgery, length of surgery, perioperative medications, ASA physical classification, type of anesthesia)
- Anesthesia record information
- Baseline (pre-operative) and perioperative coagulation lab values (PT, PTT, INR, HTC, HTC, PLT, FIB) (followed for 24 hours postoperatively)
- Perioperative ROTEM values
- Baseline and perioperative hemodynamics (BP, HR, RR, OXYGEN SATURATION, Temperature).
- Intraoperative arterial blood gases
- Intraoperative blood loss (over time)

- Transfusion information (type of product, number of transfused units, time administered) intraoperative and 6, 12, and 24 postoperative.
- Use of other hemostatic therapy
- Use of antifibrinolytic agents
- Intraoperative fluid management (type, volume, and frequency)
- Urine output for the first 24 hours.
- Postoperative time of mechanical ventilation
- Length of ICU stay and hospital stay
- Other intraoperative and postoperative complications (including respiratory failure, overall infection rate)
- Inpatient mortality
- Postoperative Day 30 phone call follow-up to assess serious adverse events and mortality.
- Hemostatic therapy cost assessment

IV. Assessment and reporting of Adverse Events and Serious Adverse Events

The occurrence of adverse events (AE) and serious adverse events (SAE) will be recorded from the time of consent until discharge. For each AE, the relationship to the study procedures and monitoring, severity, expectedness, outcome will be determined by the PI and recorded in the study source accordingly

If the case a subject withdraws from the study due to a serious adverse event the local IRB will be notified within 10 days.

Adverse Event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigational subject who has undergone an investigational procedure and that does not necessarily have to have a causal relationship with the study treatment. An AE can be any unfavorable or unintended sign, symptom, abnormal laboratory finding, or a temporal disease associated with the study procedure and monitoring, whether or not considered related to the procedure. Planned hospital admissions and/or surgical operations for an illness or disease that existed prior the subject was enrolled in a clinical study are considered part of the subject's medical history and are not considered AEs.

Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening

- Results in persistent or significant disability/incapacity

- Requires in-subject hospitalization or prolongs hospitalization

- A congenital anomaly/birth defect

- Is another medically-significant event that, based upon appropriate medical judgment, may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.

V. Withdrawal criteria from the study

Reasons for premature discontinuation

According with the Declaration of Helsinki, participants have the right to withdraw from the study at any time for any reason. The Principal Investigator also has the right to remove a subject from the study. Reasons that a subject may be removed from the study include:

- An AE or SAE

- The request of the subject, his/her legal representative or caregiver, or investigator, for administrative or other reasons

- Non -compliance with medication, protocol violation, or unreliable behavior

- Any clinically significant abnormalities identified by the Principal Investigator according to his clinical judgment will be followed by appropriate tests and/or procedures until these abnormalities have subsided, returned to to clinically-acceptable levels, or can be attributed to causes other than the study procedure.

The principal Investigator may withdraw an enrolled and treated subject from the study for any of the following reasons:

- Occurrence of a serious or intolerable adverse event

- Emergence of a clinically-significant change in laboratory parameters.

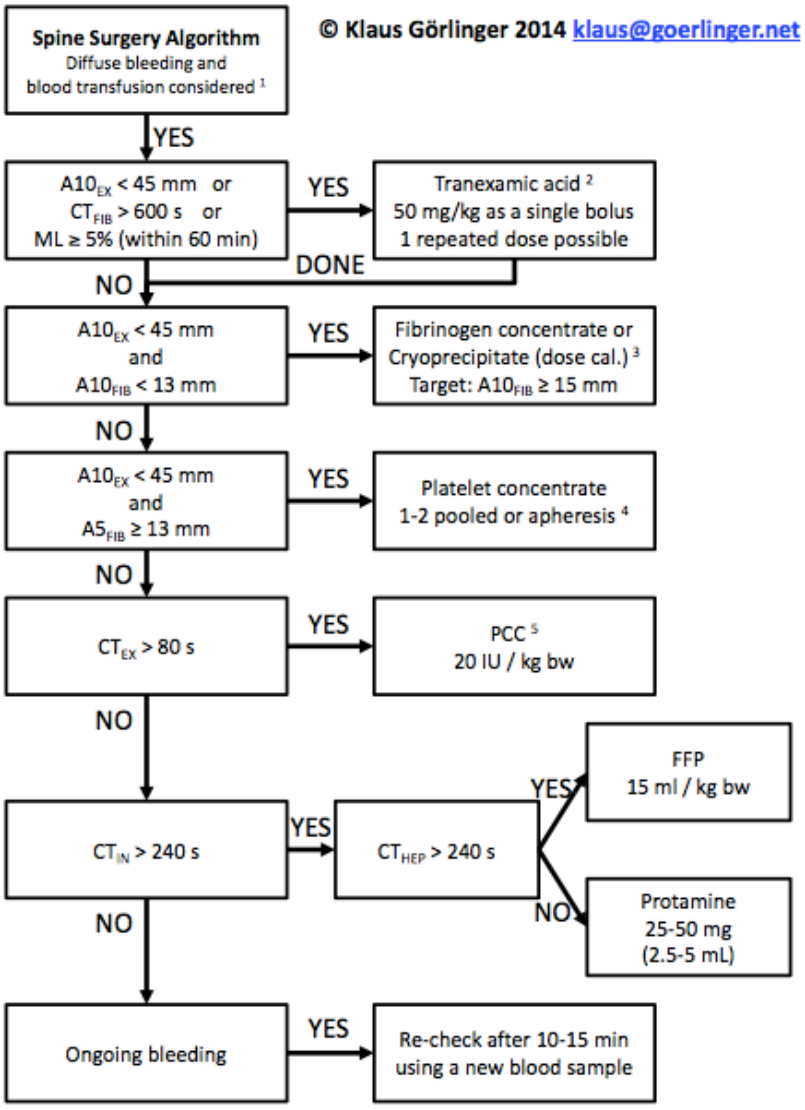
- The subject requests to be discontinued from the study

- A protocol violation sufficiently serious as to require subject withdrawal

- General or specific changes in the subject's condition that render further treatment unreasonable or unsafe within the standards of clinical practice in the judgment of the Principal Investigator or treating physician.

Any subject may leave the study at any time. If a subject decides to stop participating in the study, there will be no penalty. The subject will not lose any benefits to which they are otherwise entitled. Their decision will not affect their future relationship with The Ohio State University.

VI.Figure 1. ROTEM Spine Surgery Algorithm



- [1] Basic conditions:
  - Temp. >35°C; pH >7.2; Cai++ >4.6 mg/dL.
  - Hb ≥ 9 g/dL.
- [2] Antifibrionolytic therapy:
  - Dirkmann et al. Anesth Analg. 2014 (under review)
  - CT_{FIB} > 600 s represents a flat-line in FIBTEM
  - Chapman et al. J Trauma Acute Care Surg. 2013
- [3] Fibrinogen dose calculation:

  - $A10_{FIB}$ 9-12 mm: 50 mg/kg fibrinogen
    (2.5 mL/kg fibrinogen conc. or 5 mL/kg cryoprecipitate)
  - $A10_{FIB} \leq 8$ mm: 75 mg/kg fibrinogen
    (3.75 mL/kg fibrinogen conc. or 7.5 mL/kg cryoprecipitate)
- [4] Platelet concentrate (PC) transfusion:
  - $A10_{EX}$ 35-44 mm: 1 pooled or apheresis PC
  - $A10_{EX} < 35$ mm: 2 pooled or apheresis PC
  - $A10_{EX} \leq 25$ mm: Platelet conc. + fibrinogen
- [5] If Prothrombin-Complex-Concentrate (PCC) is not available:
  - 10-15 mL/kg FFP or
  - 45-90 µg/kg rFVIIa (if $A10_{EX}$ and $A10_{FIB}$ are ok but FFP is not effective)
- Simultaneous interventions:
  - Maximum three interventions at the same time
    (In first analysis and severe bleeding)
  - Maximum two interventions at the same time
    (In second analysis and moderate to severe bleeding)
  - Only one intervention
    (In second or later analysis and mild to moderate bleeding)

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