COVER LETTER

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Comparison of Blood Product Use and Bleeding Events During and After Endoscopic or Neurosurgical Procedures in Patients with Cirrhosis and Coagulopathy: Rotational Thromboelastometry Versus Conventional Therapy

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SCARLET: A Prospective, Randomized Clinical Trial Comparing Blood Product Use and Bleeding Events During and After Endoscopic or Neurosurgical Procedures in Patients with Cirrhosis and Coagulopathy: Rotational Thromboelastrography (ROTEM) versus Conventional Therapy.

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I. Objective

This is a prospective, single center, randomized clinical trial in patients with cirrhosis and associated coagulopathy undergoing endoscopic or neurosurgical intervention, investigating outcomes including blood product use and bleeding events in patients who receive Rotational Thromboelastography (ROTEM) versus conventional, laboratory-based coagulation methods.

II. Background

The liver produces most of the proteins involved in coagulation and those that regulate it [1]. In liver disease, production of procoagulants and anticoagulants is impaired, fibrinolysis is altered, and there is a reduction in platelet number and function [2]. These various abnormalities of the coagulation system in liver disease can be characterized by measuring individual components. However, this does not give a global account of blood coagulation and the risk of spontaneous or iatrogenic bleeding. Standard coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen, and platelet count are limited in their inability to assess clot strength and the functionality of fibrinogen or hyperfibrinolysis that may be present, especially in the presence of liver disease. There is also a lack of real time monitoring. This is one of the greatest benefits of using ROTEM point of care testing, as changes in coagulation can be evaluated throughout a procedure. ROTEM monitors viscoelastic properties of clot formation and degradation, allowing for a comprehensive view of the entire coagulation process. The viscoelastic reaction in the clot formation processes are assessed by ROTEM as follows: clotting time measures the start of clot formation, clot formation time measures the initial rate of fibrin polymerization and clot formation dynamics and kinetics, A10 measures the amplitude at 10 minutes after the end of clotting time, maximum clot firmness measures the maximal viscoelastic strength of the clot, and maximum lysis measures the percentage in the decrease of amplitude in relation to the maximum clot firmness. A maximum lysis value of greater than 15% is used to diagnosis hyperfibrinolysis or premature clot lysis.

Several studies utilizing ROTEM have shown that maximum clot firmness and fibrinogen levels are reliable predictors of perioperative bleeding complications and need for massive transfusions of blood products [3]. In patients undergoing liver transplantation, use of ROTEM guided hemostatic therapy correctly predicted hypofibrinogenemia, thrombocytopenia, and decreased clot firmness [4]. Furthermore, researchers suggest that while PT and INR are used as a prognostic indicator and to guide blood product management, that these tests are poor predictors of bleeding risk in liver disease [5]. This is an important realization, which challenges the current practice of correcting an abnormal INR with fresh frozen plasma prior to invasive procedures, even though INR cannot accurately predict bleeding risk, as it measures only one of the many components of coagulation and clot stability. Used in other scenarios where coagulopathy is encountered, studies have revealed the utility of ROTEM use in liver transplantation, significant hemorrhage, cardiac surgery, and detecting coagulation disorders in trauma [6].

Application of ROTEM hemostatic therapy and algorithm-guided blood products resuscitation before and during endoscopies may lead to more judicious use of blood products for cirrhotic patients with coagulopathy, as point of care testing will reveal information on the coagulation status of the patient to guide transfusions. In cardiac surgery patients who also had coagulopathy, point of care ROTEM testing resulted in lower cumulative blood product usage (including packed red blood cells, pooled platelets, and fresh frozen plasma), as well as lower post-operative mechanical ventilation time, length of intensive care unit stay, and six month mortality [7]. Cirrhosis-related coagulopathies represent an even more significant derangement in natural clotting and anticoagulation factors, and ROTEM may provide a more holistic approach to understanding where a particular patient lies on the spectrum from a high bleeding risk to a high clotting risk.

III. Procedures

A. Research Design

The objective of this study is to investigate blood product use, bleeding events, hospital length of stay, and health care costs in hospitalized patients with cirrhosis and coagulopathy undergoing endoscopy or neurosurgical procedures utilizing ROTEM compared to conventional therapy. Data will be extracted from charts in the electronic medical record (IHIS). Data from charts will be used to construct a secure database of information on risk factors and pre-procedure testing (see Appendix 1). This database will allow analysis of clinical outcomes in patients with cirrhosis undergoing an endoscopic or surgical procedure.

In this prospective study, patients will be randomized into one of two groups:
-Study Group: those who receive blood product transfusions based on ROTEM-guided protocol (Appendix 2).
-Control Group: those who receive blood product transfusions based on conventional, laboratory-guided parameters (Appendix 3).

The randomization list will be computer-generated using a balanced allocation ratio of 1:1. The endoscopist or surgeon performing the procedure will be blinded to the patient's group.

B. Hypothesis

The ROTEM- guided transfusion protocol will significantly decrease blood product usage without any increase in procedural bleeding complications versus the conventional, laboratory-based transfusion protocol in patients with cirrhosis undergoing endoscopy and neurosurgical procedures.

C. Objectives

Primary Objective

To compare the total amount of pre-procedure blood products transfused between the ROTEM-guided transfusion protocol and conventional, laboratory-based transfusion protocol in patients undergoing endoscopy and neurosurgical procedures. Endoscopy procedures include esophagogastroduodenoscopy, colonoscopy, flexible sigmoidoscopy, endoscopic retrograde cholangiopancreatography, and endoscopic ultrasound. Neurosurgical procedures may include bedside procedures (e.g. placement of an external ventricular drain or placement of an intracranial pressure monitor), or any neurosurgical cranial or spinal procedure that occurs in the operating room

during the patient's admission (e.g. craniotomy for evacuation of hematoma or a spinal fusion procedure to address spinal instability).

Secondary Objectives

1. Compare the rate of bleeding events between ROTEM vs. conventional therapy:
    - Clinically significant peri-procedure blood loss as documented by the endoscopist or surgeon performing the procedure
    - Major bleeding during the 24 hours post-procedure, defined as a decrease in hemoglobin of $\geq$ 2 g/dL or requiring a transfusion of $\geq$ 2 units of packed red blood cells.
2. Compare length of stay between ROTEM vs. conventional therapy
3. Compare hospitalization costs between ROTEM vs. conventional therapy

D. Sample

202 patients with cirrhosis and coagulopathy who are undergoing an endoscopic or neurosurgical procedure, at The Ohio State University Wexner Medical Center will be enrolled into the study using the inclusion/exclusion criteria below. Coagulopathy will be corrected by ROTEM-guided transfusion protocol (Appendix 2) or conventional, laboratory-based transfusion protocol (Appendix 3) prior to procedure using a 1:1 randomization.

For the primary aim, a total sample size of 202 patients (101 patients in both the non-ROTEM and ROTEM groups) is required to achieve 80% power for a two-sample t-test to detect a 100% increase in the geometric mean of the non-ROTEM group over the ROTEM group. Significance is defined as a two-sided p-value of less than 0.05. This calculation was based off of pilot data which contained 8 ROTEM and 8 non-ROTEM patients. The secondary aim, demonstrating that the proportion of bleeding events in ROTEM patients is equivalent to or less than the proportion in non-ROTEM patients requires a sample size of 446 patients per group. This calculation assumed that both ROTEM and non-ROTEM patients experience a bleeding event 10% of the time. It was further assumed that the proportion of bleeding events in the ROTEM group will be considered to be equivalent to that of the non-ROTEM group if the proportion is no more than 5% larger. The secondary aim is exploratory in nature for the purposes of this protocol as the sample size for the current study is only 202 patients.

No changes in procedural or anesthesia technique will be made for the purposes of the study. All transfusion protocols are currently in use and have been approved by the Ohio State University Wexner Medical Center. Cutoff values and transfusion guides in this protocol have been designed for patients with cirrhosis undergoing liver transplantation based on the currently available evidence in liver transplantation. There are no globally accepted clinical practice guidelines for blood product transfusion in patients with chronic liver disease who undergo invasive procedures. For the purposes of this study, we are incorporating the conventional transfusion protocol utilized by the endoscopy unit, providing a standardized approach to pre-procedure transfusion/s. For the purposes of this study, peri- and post-procedure bleeding events were estimated to occur 10% of the time. This was extrapolated from a study evaluating patients with coagulopathy undergoing bronchoscopy where bleeding rates occurred in 7-11% of procedures. [1] No standard, reported bleeding event rate exists for patients with cirrhosis undergoing endoscopy.

Inclusion criteria

1. Patients of any gender aged 18 years or older

2. Patients who have clinically-documented cirrhosis
3. Patients are coagulopathic (INR > 1.5 and/or platelets < 50,000 K/uL)
4. Patients are undergoing an endoscopic procedure (esophagogastroduodenoscopy, colonoscopy, flexible sigmoidoscopy, endoscopic retrograde cholangiopancreatography, endoscopic ultrasound), or neurosurgical procedure (placement of an external ventricular drain or placement of an intracranial pressure monitor, or any neurosurgical cranial or spinal procedure that occurs in the operating room during the patient's admission [e.g. craniotomy for evacuation of hematoma or a spinal fusion procedure to address spinal instability])

Exclusion criteria

1. Patients must not be pregnant or < 18 years of age
2. Patients must not be taking any anticoagulant or antiplatelet medications, except for Aspirin 81 mg daily
3. Patients must not have an active infection (per PI discretion)
4. Patients must not have any known hemostatic disorder

E. Measurement/Instrumentation

The requested data fields include demographic data, clinicopathologic data, and procedure/operative reports. Please see Appendix 1 for all variables that will be extracted from charts. Any PHI that is collected as part of this prospective study will be maintained in the secure database.

Standard coagulation tests

Conventional coagulation tests (hemoglobin, platelet count, fibrinogen concentration, INR, aPTT, and PT) will be performed in both groups (ROTEM vs. conventional therapy) at two fixed time points (enrollment and within 3 hours after transfusion [which is also within 12 hours of procedure]) in order to compare both groups reliably. Transfusion of blood products (if indicated per the transfusion protocols) will occur within 24 hours of enrollment in both groups. In the post-procedure setting, tests will be performed if any bleeding occurs per the treating physician's discretion.

ROTEM

ROTEM will be performed according to the manufacturer's instruction, using equipment provided by Tem International GmbH. All tests will be performed at the bedside by a clinical perfusionist or study staff member trained to perform ROTEM. The point of care treatment will be guided with the Spine Surgery Algorithm based on the EXTEM, INTEM, FIBTEM and HEPTEM assays. ROTEM will be performed in both groups (ROTEM vs. conventional therapy) at two fixed time points (enrollment and within 3 hours after transfusion [which is also within 12 hours of procedure]) in order to compare both groups reliably.

F. Data Analysis

We will analyze blood product usage, peri- and post-procedure bleeding events, and hospital length of stay comparing ROTEM-guided transfusion protocol versus conventional, laboratory-based transfusion protocol. We will calculate any significant differences between these two cohorts using standard T-Test and multivariate analysis (ANOVA) with support from our Internal Medicine biostatistician.

All study patients will be continuously monitored by the study PI and sub-I's on the inpatient hepatology services. Safety monitoring will be performed on an ongoing basis throughout the entirety of the study. Based on our retrospective study using ROTEM in liver transplantation, we expect FFP transfusion rate to decrease by 50% and cryoprecipitate transfusion rate to increase in the ROTEM group with an overall decrease in blood product use. We expect bleeding rates to be similar in both groups.

IV. References

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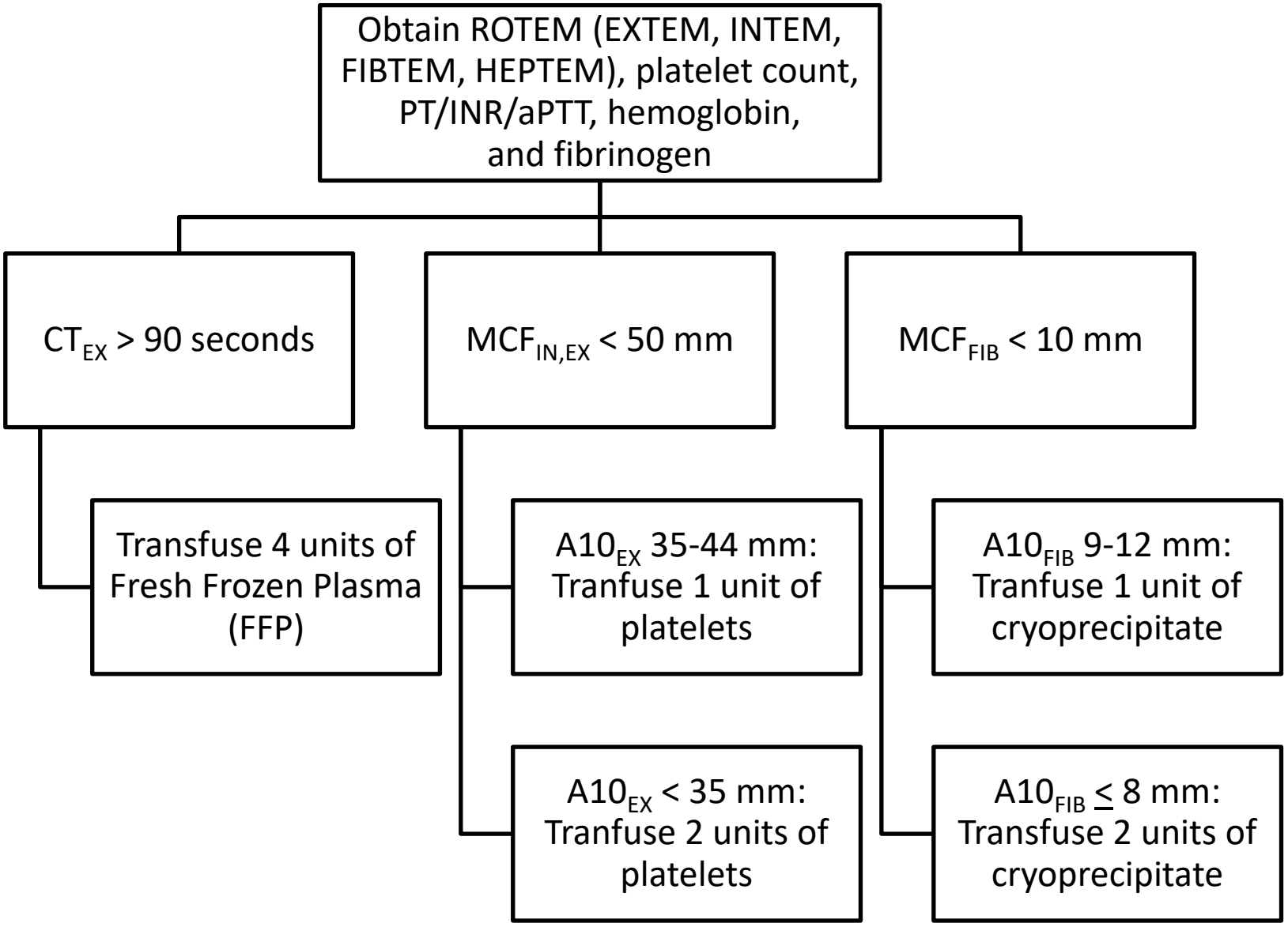
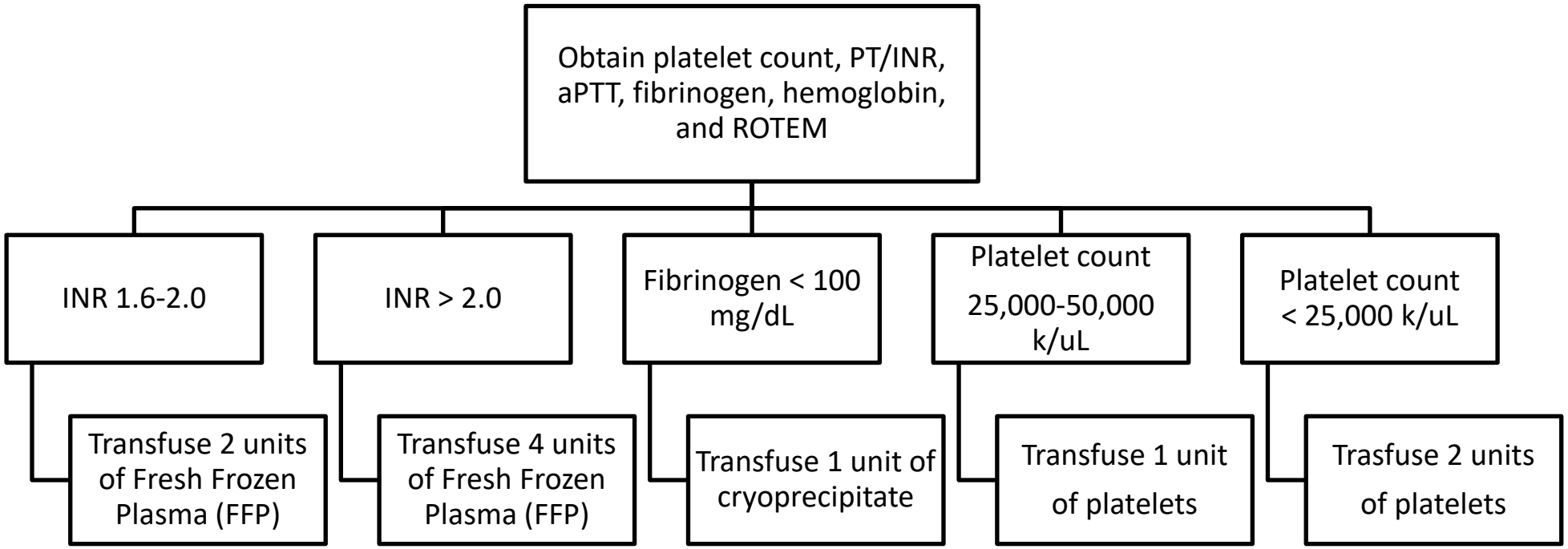
Appendix 1

Age	Age
Sex	Female = 1; Male = 2
Race	Caucasian = 1, African-American = 2, Hispanic = 3, Asian = 4, Other = 5
Obesity	Body Mass Index > 30, No=0, Yes=1
Model for End-Stage Liver Disease (MELD)	Model for End-Stage Liver Disease (MELD) score (number)
Diagnosis/Etiology	Hepatitis C Virus = 1, Hepatitis B Virus = 2, Alcohol = 3, Non-Alcoholic Steatohepatitis = 4, Primary Biliary Cirrhosis= 5, Autoimmune = 6, if other please type out diagnosis (e.g. Acetaminophen)
Hemoglobin Pre procedure	Hemoglobin (number)
Hemoglobin Post procedure	Hemoglobin (number)
Platelets Pre transfusion	Platelets (number)
Platelets Post transfusion	Platelets (number)
Fibrinogen Pre transfusion	Fibrinogen (number)
Fibrinogen Post transfusion	Fibrinogen (number)
International Normalized Ratio (INR) Pre transfusion	International Normalized Ratio (INR) (number)
International Normalized Ratio (INR) Post transfusion	International Normalized Ratio (INR) (number)
Procedure performed	esophagogastroduodenoscopy = 1, colonoscopy = 2, neurosurgical procedures = 3, other endoscopy procedures = please type out procedure (e.g. endoscopic ultrasound)
Blood product use prior to procedure	Number of Units
Type of blood product given prior to procedure	Fresh Frozen Plasma (FFP) = 1, platelets = 2, cryoprecipitate = 3
Packed Red Blood Cells (pRBC) use post-procedure	Number of units
Total blood product use post-procedure	Number of units
Significant blood loss peri-procedure	No = 0, Yes = 1
Bleeding event 24 hours post-procedure	No = 0, Yes = 1
Hospital Length of Stay	Number of Days
Cost	Total cost of ROTEM reagents and supplies used and lab tests (number)

Appendix 2: ROTEM Transfusion Protocol



Appendix 3: Conventional, Laboratory-Based Transfusion Protocol



Appendix 4: Schedule of Events

	Enrollment	≤ 3 hours after transfusion and ≤ 12 hours of procedure	Peri-procedure	24 hours post-procedure
Consent	✓			
Randomization	✓			
ROTEM[1]	✓	✓		
Blood Collection[2]	✓	✓		
Assess for Bleeding			✓	✓

[1] Includes INTEM, EXTEM, HEPTEM, FIBTEM; [2] Includes fibrinogen, PT/INR/aPTT, Hemoglobin;