**Use of ROTEM guided blood product utilisation in cirrhotic patients undergoing interventional procedures (PROTEM Trial)**

Investigator-led Trial

Flinders Medical Centre

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written authorisation of Assoc. Prof Alan Wigg.

Statement of Compliance

This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-E6).

# INVESTIGATORS

The project team will include the following investigators:

**Flinders Medical Centre**

* A/Professor Alan Wigg – Hepatologist, Coordinating Principal Investigator, FMC.

A/Professor Alan Wigg will assume overall responsibility for the study.

* A/Professor David Roxby - Chief Medical Scientist of Transfusion Services, Principal Investigator, FMC
* Dr Magdalena Sobieraj-Teague – Haematologist, Principal Investigator, FMC
* Dr Yasmina Tashkent – Hepatology/Gastroenterology Advanced Trainee, Study Coordinator, FMC
* Dr Sumudu Narayana – Hepatology Department Clinical Research Scientist, FMC

**Royal Adelaide Hospital**

* A/Professor Edmund Tse - Hepatologist, Principal Investigator, RAH
* Dr Tsai-Wing Ow – Hepatologist, RAH

**Lyell McEwin Hospital**

* Dr Biju George - Hepatologist, Principal Investigator, LMH

**Sir Charles Gardiner Hospital**

* A/Professor Leon Adams - Hepatologist, Principal Investigator, SCGH

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# Background

The Australian Liver Association (2013) estimates that over 5 million Australians are affected by chronic liver disease (CLD). Patients with CLD frequently require invasive interventional procedures during routine care, which can be associated with an increased risk of bleeding. Traditionally the risk of bleeding in cirrhotic patients has been assessed using platelet count and international normalized ratio (INR). Patients with low platelet counts or elevated INR are given platelet transfusions or clotting factors (fresh frozen plasma (FFP) or cryoprecipitate) to reduce the risk of bleeding. However, routine coagulation studies, such as INR and platelet count, do not accurately reflect the risk of bleeding in these patients due to the complex changes in the coagulation system that occurs in CLD. Subsequently, the use of blood products in this setting is resource intensive and not evidence based. It is suggested that newer technology, such as rotational thromboelastometry (ROTEM), can predict the risk of thrombosis and bleeding in liver disease, which has led to its widespread use in liver transplantation to guide transfusion (Hartmann, Szalai and Saner, 2016). ROTEM measures the viscoelastic properties of blood to assess clot formation time, clot dissolution time and clot firmness, and can identify defects in coagulation (Forkin et al, 2018)

Overall, there are no prospective trials investigating whether ROTEM can be used to reduce the use of blood products in patients with CLD undergoing invasive procedures. A randomized controlled trial by De Pietri et al (2016) using similar point of care testing called thrombelastography (TEG) on patients with CLD undergoing invasive procedures showed that following a transfusion strategy based on TEG reduced the use of blood products with no increase in bleeding nor adverse events. However, the paper was compromised by the inclusion of low risk procedures and the potential overuse of blood products in the standard of care arm.

An observational study by Venon et al. (2015) on whether ROTEM could be used to identify bleeding risk in patients with cirrhosis undergoing invasive procedures and a case control study on liver transplant patients (Alamo et al, 2013) have suggested that blood product use can be reduced by using ROTEM guidance in patients with CLD. Rocha et al (2017) are currently conducting a randomized controlled trial to investigate three blood product transfusion protocols, including ROTEM, in critically unwell patients with cirrhosis before undergoing central venous catheterization (CVC). However, their study is only investigating patients undergoing CVC insertion and does not include other invasive procedures.

Overall there is an evidence gap, with no high quality studies demonstrating safety and cost effectiveness of ROTEM based protocols. Trials are needed to establish a new standard of care for these patients, which may also reduce precious and expensive blood product use. To further investigate this, a protocol has been developed by the Flinders Medical Centre Transfusion Service and Haematology Department for this trial to study the effects of a ROTEM-guided blood product protocol in patients with CLD undergoing interventional procedures. Based on this algorithm, patients will receive bloods products (FFP, cryoprecipitate or platelets) depending on certain ROTEM parameters (Figure 1.).

**Aim**

The aim of this proposal is to study the effects of a ROTEM-guided blood product protocol in patients with chronic liver disease undergoing interventional procedures associated with a moderate to high risk of bleeding.

**Study endpoints**

Primary endpoint

* Number of patients in each group requiring blood products

Secondary endpoints

* Number of units of blood products used (red cells, FFP, platelets, cryoprecipitate)
* Cost of blood products in each arm of trial
* Total number of procedure-related bleeding events in each group
* Serious adverse events including transfusion related adverse events
* Rate of unnecessary blood product usage in standard of care arm (based on ROTEM profile)

Power analysis for primary endpoint

Assume 50% reduction (conservative relative to 85% reduction seen in De Pietri paper)

5% alpha error

20% beta error

Minimum recruitment target is 16 patients (8 per group)

**Inclusion Criteria**

* Aged ≥ 18 years
* Able to give informed consent
* Patients with coagulopathy (INR≥1.8 OR Platelet count ≤50,000) who require procedures with moderate to high risk of bleeding

Definitions of moderate and high risk procedures:

Transcatheter arterial chemoembolization (TACE), percutaneous ablation, transthoracic liver biopsy, endoscopic sphincterotomy, endoscopic polypectomy, tunnelled central venous catheter (CVC) placement, liver resection, abdominal surgery. Definitions are per as defined by (Patel et al, 2012)

**Exclusion Criteria**

* Known overt encephalopathy or cognitive impairment from other aetiologies
* Non-English speakers

**Withdrawal Criteria**

* Wish of patient to discontinue due to procedure discomfort
* Occurrence of serious adverse events

**Design and Plan for Study**

Patients will be identified by the principal site investigators during organisation of elective admissions for invasive procedures at the four participating sites - Flinders Medical Centre (FMC), Royal Adelaide Hospital (RAH) the Lyell McEwin Hospital (LMH) and Sir Charles Gardiner Hospital. A total of sixteen consecutive patients with CLD who require invasive procedures will be offered the opportunity to enrol in this prospective, multicentre trial. Patients will be given a patient information sheet and informed consent will be obtained on the day, prior to the procedure or earlier if feasible. The information sheet will have details pertaining to the use of ROTEM, as well as any potential complications.

The study will be conducted in a randomized controlled manner. Allocation to one of two treatment groups (ROTEM guided or standard of care arms) will occur on a 1:1 ratio across sites. Patients will be randomized 1:1 to ROTEM guided or standard of care arms, via a call to the FMC randomization centre upon patient consent. Participant allocation, using unique study ID, will be recorded by the independent researcher and details stored in a secure cabinet. Blood samples will be collected on the day of the procedure from all consenting patients. Patients in both arms will have blood sent for ROTEM testing, fibrinogen level, coagulation studies, platelet count, full blood examination and crossmatch.

Patients randomized to the ROTEM arm will receive blood products guided by the ROTEM algorithm (*Figure 1*) prior to their invasive procedure. As per the ROTEM algorithm patients will receive FFP, cryoprecipitate, platelets or no blood products based on the ROTEM EXTEM Clotting Time (CT), EXTEM (i.e. assessment of clot formation, fibrin polymerisation and fibrinolysis via the extrinsic pathway) amplitude at 10 minutes (A10) and FIBTEM (i.e. qualitative assessment of fibrinogen status) A10. The blood products given in the ROTEM arms will be compared to those used in the standard of care arm at each of the participating sites.

Standard of Care (SOC) arm

This will be the existing practice on the day associated with each hospital team and individual interventional radiologists, and local protocols if available. SOC at each site will be recorded for each patient. It is accepted that the standard practice may vary across different institutions and radiologists, reflecting the lack of current evidence based guidelines. The study is not designed to enforce a standard of care but rather to reflect real world current practice.



***Figure 1. ROTEM algorithm to guide blood product usage.*** *CT, clotting time (seconds); A10, amplitude at 10 minutes (mm); EXTEM, assessment of clot formation, fibrin polymerisation and fibrinolysis via the extrinsic pathway; FIBTEM, qualitative assessment of fibrinogen status; AD, Adult Dose; FFP, fresh frozen plasma; Developed by Dr M. Sobieraj-Teague and A/Professor D Roxby, Haematology Department and Transfusion Services, Flinders Medical Centre, Adelaide, South Australia, 2019.*

Principal site investigators or delegate will collect the following information:

1. Number of units of blood products used (red blood cells, FFP, platelets, cryoprecipitate)
2. Bleeding events defined as per standard definitions
3. Serious adverse events including transfusion related adverse events as per standard definitions.

**Follow-up**

Patients will be followed up 48hrs post-procedure via a telephone call by the study coordinator. Information regarding adverse events will be collected. Electronic records will also be used to assist with assessment of adverse events as per standard definitions. Costs will be calculated using SA Health costing data for blood products.

**Data Analysis/Storage**

Patient anonymity will be maintained throughout this study, and patient name or any other identifying information will not be collected. De-identified patient data will instead be labelled with a unique study number. De-identified data will be entered into an Excel spreadsheet for analysis and reporting onto a password protected computer. Data will then be entered, collated and analysed using a Statistic Package for Social Sciences (SPSS).

The sample size has been calculated on the basis of the prior study by De Pietri et al (2016) that identified an 85% reduction in patients receiving blood products using a similar functional clotting assay named Thromboelastography (TEG).  We have conservatively assumed a 50% reduction in patients receiving bloods products together with the following assumptions; 5% alpha error and 20% beta error. This provides a minimum recruitment target of 16 patients (8 per group). Standard statistical analyses, in consultation with our  statistical investigator, Professor Richard Woodman, to compare differences between the ROTEM and SOC groups for the primary and secondary endpoints will be used. Differences for endpoints between groups will be assessed using Mann-Whitney’s U test which will be applied to compare nonparametric variables and chi-square test will be performed for categorical parameters. A two-tailed t test will be used for normally distributed data.

**Patient Recruitment**

Patients undergoing elective admission for invasive procedures will be identified by principal site investigators at four sites - Flinders Medical Centre, Royal Adelaide Hospital the Lyell McEwin Hospital, and Sir Charles Gardiner Hospital.

**Patient Consent**

Specific consent will be sought from participants for the duration of the PROTEM trial. The information sheet will include information about ROTEM and any potential adverse reactions related to venepuncture and blood products. Patients will have the option to withdraw from the trial at any time.

**Sample Size**

* 16 patients

**Ethical Considerations**

All aspects of this study will be discussed with each patient during the recruitment process. Each participant will be given written, informed consent and will be free to withdraw from the study at any time.

The study protocol will be submitted to the Southern Adelaide Clinical Research Ethics Committee for approval. This study will be performed in accordance with the National Statement on Ethical Conduct in Human Research 2007. The Chairman of the Research Ethics Committee will be notified within 72 hours should any serious adverse event occur. Confidentiality will be maintained beyond study parameters.

**Anticipated outcomes**

It is anticipated that the study will show a significant reduction in blood product usage and costs associated with the ROTEM arm, without any increase in procedure-related adverse events. It is hoped that findings from this study will be published in a high impact journal and help to stimulate further high quality studies in this area with the aim of establishing improved evidence based guidelines.

**References**

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