PROTOCOL and SAP

The Role of Human Fibrinogen Concentrate (RiaSTAP) in Decreasing Blood Loss and the Need for Component Blood Therapy in Infants Undergoing Cardiopulmonary Bypass

National Clinical Trial (NCT) Identification Number: NCT02822599

December 7, 2017

Purpose of Study

The goal of the study is to determine whether the use of Human Fibrinogen Concentrate (RiaSTAP) will decrease blood loss and the need for component blood therapy in neonates and infants undergoing cardiopulmonary bypass. RiaSTAP will be administered after termination of Cardiopulmonary Bypass (CPB) at a dose of 70 mg/kg, in a prospective, randomized, controlled study. We hypothesize that the administration of RiaSTAP in this manner will reduce peri-operative bleeding and transfusion requirements.

Background

Severe postoperative bleeding is a serious complication after cardiac surgery and results in increased morbidity and mortality[12]. The bleeding is often multifactorial and influenced by both surgical factors and impaired hemostasis. The impaired hemostasis after cardiac surgery may be caused by enhanced fibrinolysis, platelet (PLT) dysfunction and coagulopathy secondary to the exposure of blood to artificial surfaces, and the surgical trauma[3].

In children less than 12 months old with congenital heart disease, bleeding after cardiac surgery is further complicated as the fibrinogen of these patients is qualitatively dysfunctional[4]. Moreover, the coagulation systems of neonates and children undergoing CPB are profoundly affected by hemodilution[5] and by consumption[6]. As a result, neonates and young infants undergoing complex cardiac repairs often receive multiple units of blood products, both in the operating room (OR) and intensive care unit (ICU).

Preoperative fibrinogen concentration is an independent predictor of post-operative bleeding volume. Fibrinogen concentration, even when within the normal range, is a limiting factor for post-operative hemorrhage[7]. The prophylactic infusion of fibrinogen concentrate has been shown to reduce bleeding after coronary artery bypass graft (CABG) surgery without evidence of hypercoagulability[8]. Moreover, ROTEM FIBTEM test guided fibrinogen concentrate administration was associated with reduced transfusion requirements and 24 hour postoperative bleeding in patients undergoing aortic valve operations and ascending aortic reconstructions[9].

The goal of the study is to determine whether the use of Human Fibrinogen Concentrate, RiaSTAP, will decrease blood loss and the need for component blood therapy in neonates and infants undergoing cardiopulmonary bypass. We hypothesize that the administration of RiaSTAP after termination from cardiopulmonary bypass will reduce peri-operative bleeding and transfusion requirements.

Fibrinogen replacement therapy is currently indicated as prophylaxis for congenital fibrinogen deficiency and as therapy for acquired fibrinogen deficiency caused by liver failure, disseminated intravascular coagulation, massive transfusion and cardiac surgery. Fibrinogen supplementation can be provided by transfusion of (1) fresh-frozen plasma

(FFP), (2) cryoprecipitate, (3) RiaSTAP or some combination of these three.

FFP has several limitations including the need for ABO compatibility, the time required to thaw it, a low fibrinogen content, which means that large volumes must be given thereby increasing the risk of hemodilution, the risk of transfusion-related complications (i.e., transfusion-related acute lung injury [TRALI] and viral transmission) and the presence of relatively high concentrations of citrate, which can acutely lower ionized calcium, leading to decreased myocardial contractility and hypotension.

Cryoprecipitate is prepared by controlled thawing of frozen plasma to precipitate high molecular weight proteins, which include factor VIII (FVIII), von Willebrand factor (VWF) and fibrinogen. The precipitated proteins are separated by centrifugation, re-suspended in a small volume of plasma (typically 10-20 mL) and stored frozen at –20 °C. Cryoprecipitate is usually administered as a pool of four to six units. Although cryoprecipitate contains a higher concentration of fibrinogen than FFP (usually around 15 g/L), it shares many of the same disadvantages of FFP. For example, the fibrinogen concentration is not standardized among batches of cryoprecipitate and blood group matching is needed prior to transfusion. In addition, cryoprecipitate must be thawed, a clear disadvantage in the setting of massive hemorrhage. Furthermore, like FFP, it contains a relatively high concentration of citrate[10] and carries a risk of viral transmission.

RiaSTAP is a purified fibrinogen concentrate derived from the plasma of healthy donors using the Cohn/Oncley cryoprecipitation procedure[11] . The FDA approved RiaSTAP in 2009 under the accelerated approval regulations for orphan drugs[12]. RiaSTAP is indicated for the treatment of acute bleeding in patients with congenital fibrinogen deficiency (CFD), including afibrinogenemia and hypofibrinogenemia and has several advantages over FFP and cryoprecipitate. First, the fibrinogen concentration is standardized. Second, it is stored as a lyophilized powder at room temperature and can be reconstituted quickly with sterile water. Third, infusion volumes are low, allowing for rapid administration without delays for thawing or cross-matching[13]. Fourth, the manufacturing processing of RiaSTAP includes solvent/detergent exposure or pasteurization, thus minimizing the risk of viral transmission. RiaSTAP is manufactured from cryoprecipitate into a glycine precipitate, which is then further purified by multiple precipitation/adsorption steps. The manufacturing process has been demonstrated to reduce the risk of virus transmission in an additive manner: cryoprecipitation, $Al(OH)_3$ adsorption/glycine precipitation/$Al(OH)_3$ adsorption, heat treatment (60^{o} C for 20 hours in an aqueous solution), and two subsequent glycine precipitation steps (initial and main glycine precipitation steps). These steps have been validated independently in a series of in vitro experiments for their capacity to inactivate and/or remove both enveloped and non-enveloped viruses. However, there is still a small risk of acquiring an infectious disease, despite the testing of plasma donor and the above outlined steps, mostly due to the transmission of prions, the causative agent in Creutzfeldt-Jakob disease. Finally, RiaSTAP does not contain any citrate so the risk of decreased myocardial contractility and hypotension is minimized.

RiaSTAP is contraindicated in patients who have manifested severe, immediate hypersensitivity reactions. Thrombosis has also been reported in patients treated with

RiaSTAP, but the risk appears to be low[14]. However, Jakobsen, Tang and Folkersen reported an increased risk of neurological thromboembolic complications and renal failure in their retrospective review of 1,876 adults undergoing coronary artery bypass graft surgery (CABG) treated with fibrinogen concentrate.

Our institution has been using RiaSTAP on this high-risk patient population since April 2013. In a separate, retrospective analysis our group has compared a group of 50 patients who received RiaSTAP with 50 age, diagnosis and procedure matched patients prior to April 2013. Our analysis demonstrates that there is a statistically significant reduction in the need for FFP and cryoprecipitate, without an increase in thromboembolic events, when RiaSTAP is used at a dose of 70 mg/kg.[15]

Criteria For Subject Selection

Number of subjects: 30

Gender of subjects: There are no gender-based enrollment restrictions for this study. Gender distribution should reflect the gender distribution of the patient population and the gender distribution of Congenital Heart Disease (CHD) in general which is slightly skewed towards male patients in a 60:40 ratio of males to females.

Age of Subjects: Age will range from full term (at least 37 weeks gestational age) newborns to 12 months old, inclusive.

Racial and Ethnic Origin: There are no racial and ethnic restrictions for this study.

[redacted]

Inclusion Criteria: All neonatal and infant cardiac patients presenting for open-heart surgery at Nicklaus Children's Hospital will be eligible for enrollment in the study.

Exclusion criteria: Patients who fall outside of the age range for the study will be excluded. Patients known to have had an anaphylactic or severe reaction to the drug or its components will not be enrolled. At the time of the rewarming ROTEM, any patient with a FIBTEM MCF > 15 mm, will be excluded.

Vulnerable subjects: Patients in the study population are neonatal and infant cardiac surgical patients and are considered vulnerable subjects.

Methods and Procedures

Randomization:

We plan to enroll 30 neonates and infants scheduled for elective cardiac surgery. Patients will be randomized to one of two groups with 15 patients in each group; Group 1 will receive an infusion of RiaSTAP, right after the termination of CPB at a dose of 70 mg/kg and

Group 2 will receive a placebo of Normal Saline 0.9% (NS) during the same time period. The volume of NS will be calculated to be the same volume that would be used IF the patient were receiving RiaSTAP. This will be the only difference between the groups.

Both Groups will receive the normal standard of care both before and especially after this event. This will be the only event that is different for the two groups. To avoid selection bias, the Pharmacy will perform the randomization using Research Randomizer. Briefly, for each patient, a randomly generated integer between 1-30 will be produced. If the number is even, the patient will be assigned to Group 1. If the number is odd, the patient will be assigned to Group 2. The randomization process and schedule will be provided by the Principal Investigator's office, but the actual patient assignment will be done by Pharmacy.

All operating room and ICU personnel will be blinded to the patient's Group assignment. The only persons who will have access to the identity of the Group assignment from the time of randomization until 24 hours after surgery will be members of the Pharmacy staff. NONE of these individuals will be involved in patient care. The DSMB will be unblinded AFTER the study treatment period concludes (24 hours after surgery).

Endpoints:

Primary efficacy endpoints will be estimated as follows:

- postoperative bleeding (EBL) during the first 24 hours (hr) after surgery (cc/kg),
- the identity and total volume of transfused blood products (cc/kg) given in the peri-operative period, separated out into its components,
- hemoglobin concentration 2 hr. and 24 hr. after surgery and
- effects of fibrinogen infusion on global hemostasis 2 hr. and 24 hr. after surgery (PT, PTT, INR, fibrinogen level, platelet count and ROTEM analysis).

Post-operative period begins after the patient leaves the operating room. The need for Factor VII use and dose will also be included as a primary end point. Factor VII is typically used only if there is profuse bleeding not amenable to component transfusion therapy.

Secondary end points will include:

- the number of post-op hours requiring ventilator support,
- Length of Stay (LOSH) in the hospital,
- Length of Stay (LOS ICU) in the Cardiac Intensive Care Unit (CICU) and
- the need for re-exploration for bleeding within the first 12 hours.

The primary safety endpoints that will be monitored are the presence of a clinical adverse events. Clinical adverse events (AEs) are defined as any clinical signs of central or peripheral thromboembolism, respiratory or circulatory failure, or allergic reactions during hospital stay. It will also include infection with a blood-borne pathogen. Thromboembolic phenomenon will include catheter and/or vessel occlusion. Any signs or symptoms of thromboembolism will prompt a Doppler ultrasound examination to confirm the diagnosis. All patients will be monitored for AEs until discharge.

Anesthetic Management:

Standard non-invasive monitors will be employed including Electrocardiogram (EKG), Non-invasive blood pressure (NIBP), Pulse Oximetry (SaO_2), capnography, and Near Infrared Spectroscopy (NIRS).

For patients greater than six months of age, premedication with midazolam will be used. Dose will be 1 mg/kg Per Os (PO), with a maximum of 20 mg. Anesthesia will be induced with Propofol 2 mg/kg or fentanyl 5 mcg/kg, if the patient already has an indwelling IV catheter. Otherwise an inhalational induction with Sevoflurane 5% will be done. Anesthesia maintenance will be with Sevoflurane and dexmedetomidine 1 mcg/kg/hr. No more than 10 mcg/kg of fentanyl will be used. Once the patient is anesthetized and intubated a Foley catheter will be placed along with an Arterial line (A-line) and a double lumen Central venous line (CVL). Hemodynamics will be maintained by adjusting the Sevoflurane concentration in increments of 0.5% to maintain blood pressure within 20% of baseline. Propofol 0.5 mg/kg will also be used for this purpose.

Cardiopulmonary Bypass (CPB) Management:

After purse strings sutures are placed, heparin 300 International Units (IU) will be administered by the surgeon directly into the right atrium (RA) in order to maintain an ACT greater than 400 seconds. After CPB, the heparin will be reversed by the administration of protamine (1 mg protamine/100 IU of residual heparin activity as measured by the Medtronic Hepcon) to an ACT of <130 s. The CPB circuit included a membrane oxygenator and centrifugal pumps. Standard non-pulsatile CPB technique with moderate hypothermia (bladder temperature 28–30°C) or deep hypothermia (bladder temperature 18–20°C) and hemodilution will be used depending on the surgical repair. Cardioprotection will be achieved with antegrade cold blood cardioplegia. Weaning off CPB will be performed after rewarming to a bladder temperature of at least 36°C. We will use the Medtronic Hepcon Hemostasis Management System Plus to optimize and monitor heparin and protamine dosing.

Patients under 10 kg in body weight will have the CPB pump primed with one unit of Packed Red Blood Cells (PRBC) and 200 cc Fresh Frozen Plasma (FFP). In patients over 10 kg a pure crystalloid prime will be used. Target hemoglobin (Hg) while on CPB will be 9 gm/dL, but the transfusion trigger for additional units of PRBC will be 7 gm/dL.

Drug protocol:

The following laboratory studies will be obtained prior to surgery: Complete Blood Count (CBC), Prothrombin time (PT), International Normalized Ratio (INR), Partial Thromboplastin time (PTT), Platelet count, and a Fibrinogen level; an electrolyte profile will also be done. An Activated Clotting Time (ACT) and a Thromboelastometry analysis [redacted], a device that assesses the viscoelasticity of whole blood and other parameters, will be done after an A-line is placed (Figure 1).

A blood products transfusion algorithm was developed based on four previous studies published in the literature, modified for pediatrics[16171819] (Figure 2). Blood is measured in the cell saver reservoir and the suction canister every fifteen minutes while in the OR. Clinically significant bleeding, requiring treatment, will be defined as a rate in excess of 10 cc/kg/hr calculated every 15 minutes while in the OR. Calculations will be done every 60 minutes in the CICU.

After rewarming, but prior to the termination of CPB a ROTEM analysis will be done. Platelets or FFP will be administered at this time, while still on CPB, if the ROTEM results indicate a deficiency of either component. Then immediately after the termination of CPB, RiaSTAP or NS will be administered depending on the group assignment. Then, as per routine care, a ROTEM analysis and fibrinogen level will be assessed and the transfusion algorithm will be continued. *If the ROTEM indicates a fibrinogen deficiency, cryoprecipitate will be given.* Thereafter, as per routine care, a ROTEM analysis will be done at least every 30 minutes while in the OR or sooner at the discretion of the OR team. Once the patient leaves the OR a ROTEM will be done at least every 60 minutes for the first six hours or until clinically significant bleeding has stopped, whichever comes first; ROTEMs can be done more frequently at the discretion of the ICU staff caring for the patient. The blood products transfused after separation from CPB will be based on the protocol below (Figure 3). Dosing amounts of the required component therapy will be based on the formula below:

PRBC: Volume required = Blood volume (V) x desired Hct increase / Hct of red cell unit (70%)
FFP: 20 cc/kg
Plateletpheresis: 20 cc/kg
Cryoprecipitate: 10 cc/kg

The ROTEM analysis algorithm is below (Figure 4).

Four main scenarios based on clinical observation and TEM results were possible:
1. Insignificant bleeding—normal TEM ⇒ no transfusions
2. Insignificant bleeding—abnormal TEM ⇒ no transfusions
3. Significant bleeding—normal TEM ⇒ surgical reevaluation
4. Significant bleeding—abnormal TEM ⇒ transfusion of blood products as indicated by:
    a. fib-TEM MCF < 7 mm ⇒ cryoprecipitate
    b. hep-TEM MCF <50 mm ⇒ platelets,
    c. hep-TEM CT > 240 seconds ⇒ FFP,
    d. hep-TEM CFT > 110 seconds ⇒ cryoprecipitate and /or platelets depending on MCF

If clinically indicated (continuing bleeding) or to verify the treatment effect and control heparin reversal, a second set of in-TEM, hep-TEM, and fib-TEM analyses will also be performed during wound closure. ACT will be tested in all patients to control for heparin reversal. If patients have both a pathological ACT and TEM, protamine will be administered.

Postoperative bleeding in the ICU will be defined as the total amount of chest tube drainage after closure of the sternum and during the first 24 postoperative hours. If the sternum is not closed, it will be defined at the total chest tube drainage during the first 24 postoperative hours. An intensive care nurse blinded to group assignment will record the bleeding every hour. The amount of transfused red blood cells (RBC), FFP, cryoprecipitate and platelets during the hospital stay will be recorded in cc/kg. The transfusion triggers will be as described above. The CICU physicians and nurses will not be informed of the preoperative fibrinogen concentration or group assignment.

Patient Assessment:

Primary efficacy endpoints will be postoperative bleeding during the first 24 hours (hr) after surgery (cc/kg), the total volume and identity of transfused blood products (cc/kg), hemoglobin concentration 2 hr. and 24 hr. after surgery and effects of fibrinogen infusion on global hemostasis 2 hr. and 24 hr. after surgery (PT, PTT, INR, fibrinogen level, platelet count and ROTEM analysis). Secondary end points will include the number of post-op hours requiring ventilator support, Length of Stay (LOS) in the Cardiac Intensive Care Unit (CICU), the need for re-exploration for bleeding within the first 12 hours, and LOS in the hospital. The need for Factor VII use and dose will also be included.

The primary safety endpoint is a clinical adverse event. Clinical adverse events are defined as:

1. Any clinical signs of central or peripheral thromboembolism. This then will be confirmed by Doppler ultrasound. Assessments will be made once per shift (once every eight hours)
2. Respiratory or circulatory failure. Parameters of respiration, like respiratory rate (RR), end-tidal CO_2 ($ETCO_2$) and circulation, like heart rate (HR), rhythm, blood pressure (BP), arterial oxygen saturation (SPO_2) are monitored continuously while in the ICU. Respiratory failure will be defined as the need for reintubation after extubation. Circulatory failure will be defined as cardiac arrest.
3. Allergic reactions during hospital stay. These will include signs or symptoms like urticaria, wheezing, angioneurotic edema, and anaphylaxis.
4. Infection with a blood borne pathogen. Manifestation of an infection with a blood borne pathogen is unlikely to occur during the study treatment period, which ends 24 hours after the end of surgery. If this were to occur, it would not manifest itself for weeks or even months.

Patients will be assessed once per shift (once every eight hours) for signs of thromboembolism. Any evidence of thromboembolism will warrant a vascular ultrasound to assess the integrity of the vessel.

Adverse events will be monitored until discharge.

All patients will be assessed for signs and symptoms of thromboembolism, per routine care. Specifically, patients will be assessed for signs and symptoms of central and arterial

line thrombosis. These include edema, leg pain and tenderness, erythema, and discoloration for venous thrombosis, as well as loss of distal peripheral pulses, pain, pallor, paresis, paresthesias, decreased skin temperature for arterial thrombosis. If any of these signs and symptoms appear, Doppler Ultrasound examinations of the affected area will be performed.

The Safety Team, which consists of the Cardiac Intensive Care Unit physicians, will evaluate each event when it occurs; they will not be blinded to patient assignment after 24 hours. Please see safety assessments and timing below. These represent minimums as prescribed by the protocol. Assessments may be more frequent (See table 1).

Stopping Criteria:

A statistically significant increase in thromboembolic phenomenon between Group 1 and Group 2 will trigger a stop in enrollment. This will be monitored by the Safety Team.

Table 1: Assessments

Assessment	**Timing in OR**	**Timing in ICU**
EBL	q 15 min	hourly
ROTEM	q 30 min as needed	hours 2 and 24, or as needed hourly until bleeding ceases
peripheral thromboembolism	N/A	q8 hrs, or as needed
hemoglobin	as needed	hours 2 and 24
PT/PTT, platelets, fibrinogen	prior to surgery if not previously done	hours 2 and 24

Schedule of Events

	Pre-Operative	Intraoperative	2 hours Post-Operative	24 hours Post-Operative	When occurs	60 ± 14 days
Informed Consent/Assent	x					
Eligibility Assessment	x					

Demographic Data	x					
Medical History	x					
Baseline Assessment [1]	x					
Body Weight and Height	x					
Concomitant Medications[4]	x	x				
Randomization		x				
Administration of Study Drug		x				
Pharmacy Prep of Study Drug		x				
Laboratory Studies [2]	x		x	x		
Adverse Events		x	x	x	x	x
Surgical and Cardiopulmonary Bypass Data[3]		x				
Estimated Blood loss (EBL) [5, 6]		→	→	→		
ROTEM Analysis[9,11]	x	X[7, 10]	x	x	X[8]	
Identification of total transfused blood products [12]				x		
Thromboembolitic Assessment [13]		→	→	→	x	
Factor VII					x	
Length of Stay ICU and Hospital					x	
Mechanical ventilation duration					x	
Need for Re-exploration first 12 hours			x	x		
Phone assessment						x

1. Assessment includes allergies, diagnosis, procedure(s)
2. Laboratory collection and assessment includes CBC, prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen level. Pre-Operative includes complete platelet count, and electrolyte profile.
3. Time in/out, sternal closure time, bypass start/stop time, total bypass time, total cross clamp time, total regional low perfusion time, blood components administered for patients under 10 kg in body weight, and pure crystalloid prime for patients over 10 kg in body weight, activated clotting time (ACT), thromboelastometry analysis after A-line assessment.
4. During intraoperative period concomitant medications include anesthesia induction medication, heparin, and protamine.
5. Estimated blood loss will be assessed every 15 minutes while in the OR and every 60 minutes in the CICU. Clinically significant bleeding defined as a rate in excess of 10 cc/kg/hr.
6. Total EBL at 24 hour time point.
7. Prior to Termination of CBP
8. If bleeding occurs
9. If fibrinogen deficiency noted on ROTEM, administer cryoprecipitate
10. Every 30 minutes as routine or sooner as per OR team discretion.
11. Assess post-operatively for every hour for 6 hours or until clinically significant bleeding ceases and additionally as per ICU team's discretion.
12. Includes total prime, total CPB, total Anesthesia, total CICU, total platelets, total PRBC, total FFP, total Cryo, total cell saver.
13. Assess every 8 hours central and arterial line for signs and symptoms. Thrombosis including edema, leg pain and tenderness, erythema, and discoloration for venous thrombosis, loss of distal peripheral pulses, pain, pallor, paresis, paresthesias, decreased skin temperature for arterial thrombosis. Confirmed by Doppler Ultrasound. Report when occurs.
14. Any untoward event reported from the time subject signs consent. Should be reported as soon as the study team becomes aware.

Data Analysis and Data Monitoring

Safety Monitoring

For the safety monitoring, adverse events will be documented. Aggregate and individual subject data related to safety, data integrity and overall conduct of the trial will be reviewed after enrollment of 10, 20 and 30 subjects.

Methods to Minimize Bias

To avoid selection bias, patients will be randomized to their treatment assignment group by the research pharmacists using the Research Randomizer. The randomization procedures are detailed in the Methods and Procedures section of this protocol. All operating room and ICU personnel will be blinded to the patient's Group assignment. An intensive care nurse blinded to group assignment will record postoperative bleeding every hour. Since the study is blinded and the practitioners caring for the patient will not know if the subject received the study drug or placebo, for the study treatment period (ending 24 hours after surgery), the Cardiac Intensive Care Unit staff will monitor the incidence of adverse thromboembolic events and intervene with routine care, if necessary. In order to maintain patient safety, the ROTEM analyses must be interpreted by the anesthesiologist caring for the patient in order to guide transfusion therapy. This is the standard of care and an integral part of the protocol. The hospital staff anesthesiologists are also investigators in the study including the Principal Investigator. As part of routine care, if the ROTEM results indicate a deficiency of platelets or FFP, either component will be administered while still in the OR. In addition, if the ROTEM indicates a fibrinogen deficiency after termination of CPB, cryoprecipitate will be given. After review of the ROTEM values, the identity of the study drug may be discernable. In order to avoid the ascertainment bias from this knowledge, study data will be analyzed by a biostatistician independent of the investigator prior to any presentation or publication of study results. The biostatistician will be blinded to the study treatment assignment.

Statistical Analyses

All quantitative measures will be analyzed using descriptive statistics [mean +/- standard deviation (SD), etc.]. Treatment and placebo group comparisons will be made with the Student's t-test (continuous variables) or Fisher's exact test (categorical variables). A p-value of ≤ 0.05 will be considered statistically significant. For group comparisons of variables that will be analyzed at more than onetime point, Analysis of Variance (ANOVA) for repeated measurements will be used followed by Student's t-test if the ANOVA (group or interaction between group and time) indicated a statistically significant difference ($p \leq 0.05$).

Data Storage and Confidentiality

All data for the study will be stored on a Nicklaus Children's Hospital password protected computer. Access to the data will be limited to the Investigators and study personnel. All subject identifiers will remain strictly confidential. After the study closure, all consent forms and study data will be kept in a locked cabinet in the Research Institute Clinical Research Coordinators' office at Nicklaus Children's Hospital.

Transition From Research Participation

The study treatment period ends 24 hours after surgery. All patients will be provided routine care within the CICU. A follow-up phone call will be made 60 (± 14) days after the end of the study treatment period.[20] Subjects will be asked about any adverse events or

hospitalizations.

We will maintain surveillance for blood borne infections (Cytomegalovirus, HIV, Hepatitis, etc.) by contacting the parents of the study participants and asking them if their child has been diagnosed with any blood borne illness since they took part in the study.

We will also ask if their child received any additional blood products aside from the one received during their participation in the study.

We will again provide the parents our study team's contact information and advise them that it is important to notify us if their child develops any of the above referenced illnesses.

Figure 1 ROTEM Assays

ROTEM® Assays

Assay	Indicatons for Use	Principle	Storage/Stability
ap-tem®	Provides information on clot firmness after blocking hyperfibrinolysis by aprotinin	Plasmin antagonist Aprotinin prevents fibrino-lysis in vitro. Evidence of fibrinolytic activity is obtained by comparing the results of ex-tem® and ap-tem®	- Store at +2 - +8°C - Stable until the expiration on label. Vials must be used within 14 days after opening
ex-tem®	Used to monitor the coagulation process via the extrinsic pathway and its interaction with throm-bocytes in citrated blood	Reagent contains concen-tration of tissue factor and phospholipids used for a mild extrinsic activation of the coagulation system	- Store at +2 - +8°C - Stable until the expiration on label. Vials must be used within 8 days after opening
fibt em®	Provides information on fibrinogen level and quality of fibrin polymerization in citrated blood by inhibiting thrombocytes	Reagent contains thrombocyte inhibitor and recalcification reagent. Used in conjunction with ex-tem® test	- Store at +2 - +8°C - Stable until the expiration on label. Vials must be used within 14 days after opening
hep-tem®	Used to monitor the coagulation process via the intrinsic pathway, in the presence of unfraction-ated heparin, in citrated whole blood specimens	Reagent contains heparinase that inactivates heparin in vitro. Also contains an opti-mized calcium ion concen-tration in a buffer to start the coagulation reaction	-- Store at +2-+8°C - Stable until expiration on label. - Reconstituted reagent is stable for 30 days at +2 - +8°C
in-tem®	Used to monitor the coagulation process via the intrinsic pathway in citrated whole blood specimens	Reagent contains an concentration of ellagic acid creating a standardized mild activation of the contact phase through negatively loaded surface. Sample is recalcified with star-tem®	Store at +2-+8°C - Stable until expiration on label. Vials must be used within 8 days after first opening

BR-2011-18-v02

thromboelastometry ROTEM®
The bleeding management system

Figure 2 Transfusion Algorithm

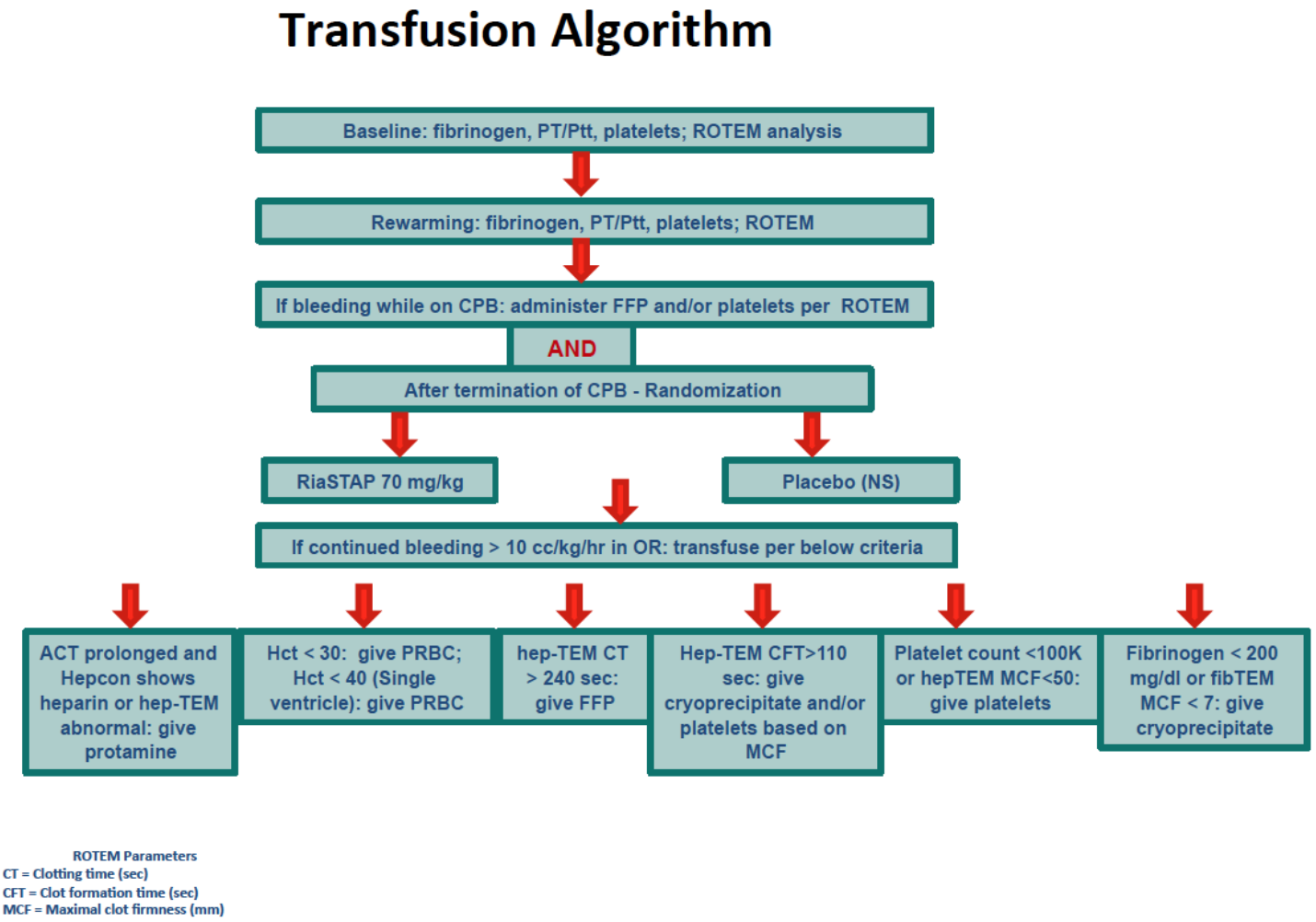


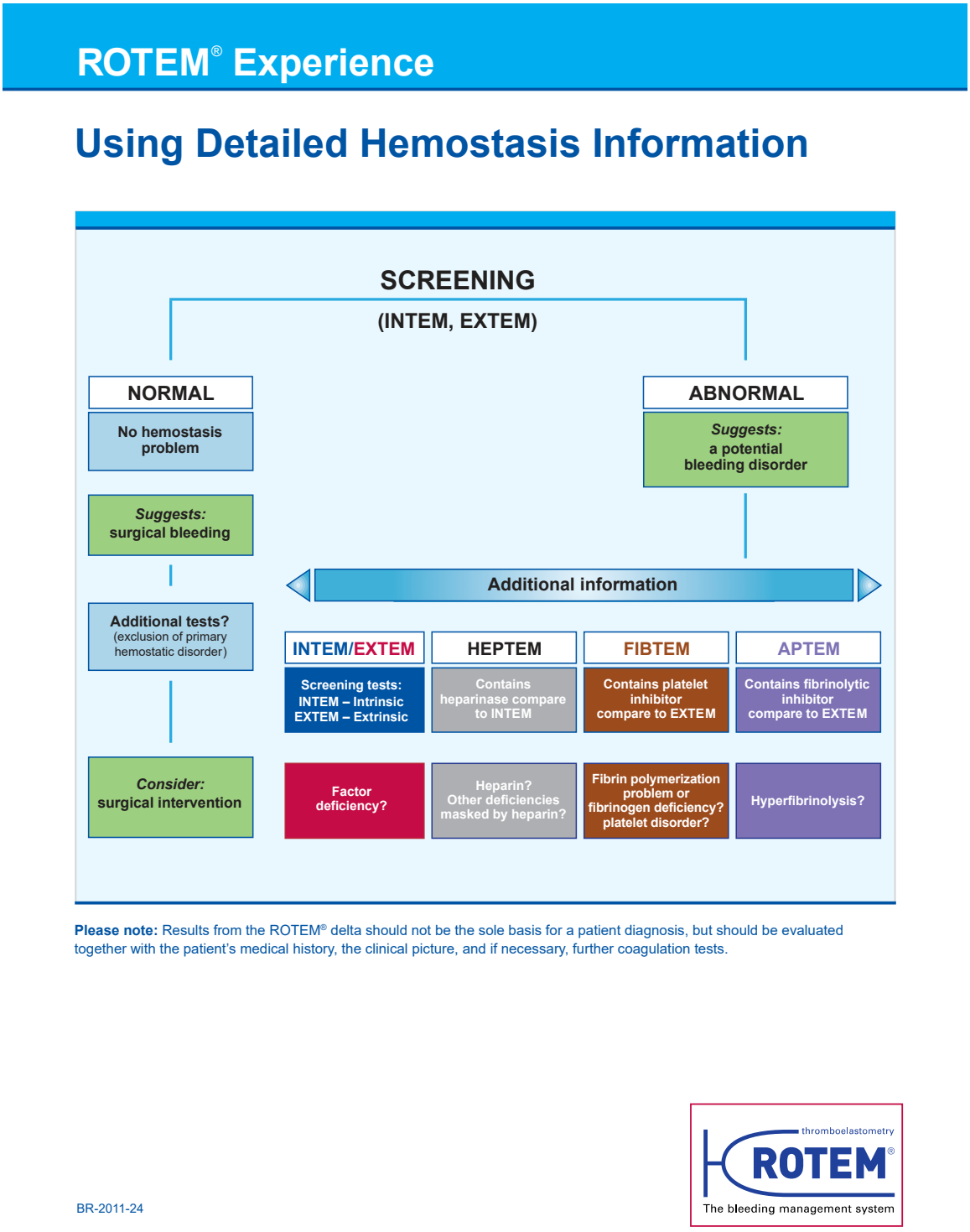
Figure 3. Blood Transfusion Protocol

Dosing amounts of the required component therapy will be based on the formula below:

PRBC: Volume required = Blood volume (V) x desired Hct increase / Hct of red cell unit (70%)

FFP: 20 cc/kg
Plateletpheresis: 20 cc/kg
Cryoprecipitate: 10 cc/kg

Figure 4. Rotem Experience



Risk/Benefit Assessment

Risk Category: Greater than minimal.

Potential Risk: According to the manufacturer RiaSTAP is "contraindicated in patients known to have had an anaphylactic or severe reaction to the drug or its components". "Thrombotic events have been reported in patients receiving RiaSTAP. The most severe adverse reactions observed are thrombotic episodes (pulmonary embolism, myocardial infraction and deep vein thrombosis. The most common adverse reactions observed in clinical studies (frequency > 1%) were fever and headache". Moreover, "RiaSTAP is made from pooled human plasma. Products made from human plasma may contain infectious agents, i.e., viruses and, theoretically, the Creuzfeldt-Jakob disease (CJD) agent."

Protection against risks: The patients will be assessed for thromboembolic events at least once per shift. If symptomatic evidence exists that a venous or arterial occlusion has occurred an Ultrasound will be ordered. Assessment for anaphylactic reactions will be made at the time of drug administration by the anesthesiologist. There is no additional surveillance for blood borne infectious agents. As with any patient, bloodborne illnesses will be diagnosed and treated at the time of occurrence.

Potential Benefits to the Subjects: The study drug can potentially decrease blood loss and decrease the need for transfusion therapy.

Alternative to Participation: Usual standard of care will be employed for all patients not participating.

Subject Identification, Recruitment and Consent

Method of Subject Identification and Recruitment

All neonatal and infant patients scheduled for open-heart surgery will be recruited.

Process of Consent

Principal Investigator, Sub-Investigators, Clinical Research Coordinators, and Cardiac Nurse Practitioners will be authorized to obtain consent. No undue coercion will be employed on any potential patients and families to enroll.

Subject Capacity

Since the study patients will be neonates and infants, consent will be obtained from the parents or legal guardian of the child.

Subject/Representative Comprehension

The person obtaining consent will provide a detailed overview of the study protocol to all prospective patients/families. All potential risks and benefits of the study drug will be discussed with the family. All questions will be answered and no enrollment will be allowed unless the study subjects/families have a complete understanding of the protocol.

Consent Forms

Informed consent will be obtained for all study patients. The parent or legal guardian will sign the consent form.

Documentation of Consent

The Principal Investigator, Sub-Investigators, Clinical Research Coordinators, and Cardiac Nurse Practitioners will be responsible for the documentation of consent.

Costs to the Subject

Study participants will not incur any additional costs due to enrollment in the study.

Payment for Participation

Payments will not be made to study participants.

References

[1] Dacey LJ, Munoz JJ, Baribeau YR, Johnson ER, Lahey SJ, Leavitt BJ, Quinn RD, Nugent WC, Birkmeyer JD, O'Connor GT. Reexploration for hemorrhage following coronary artery bypass grafting: incidence and risk factors. Northern New England Cardiovascular Disease Study group. Arch Surg 1998; 442-7.

[2] Moulton MJ, Creswell LL, Mackey ME, Cox JL, Rosenbloom M. Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. J Thorac Cardiovasc Surg 1996; 111: 1037-46.

[3] Paparella D, Brister SJ, Buchanan MR. Coagulation disorders of cardiopulmonary bypass: a review. Intensive Care Med 2004; 30: 1873-81.

[4] Miller B, Tosone S, Guzzetta N, miller J, Brosius K. Fibrinogen in Children Undergoing Cardiac Surgery: Is It Effective? Anesth Analg 2004; 99: 1341–6

[5] Kern FH, Morana NJ, Sears JJ, Hickey PR. Coagulation defects in neonates during cardiopulmonary bypass. The Annals of Thoracic Surgery, Vol. 54: 541-546

[6] Chan AK, Leaker M, Burrows FA, Williams WG, Gruenwald CE, Whyte L, Adams M, Brooker LA, Adams H, Mitchell L, Andrew M. Coagulation and fibrinolytic profile of paediatric patients undergoing cardiopulmonary bypass. Thromb Haemost. 1997 Feb; 77 (2): 270-7.

[7] Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A. Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: a prospective observational study. Transfusion 2008; 48: 2152-2158.

[8] Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Flinck A, Skrtic S, Jeppsson A. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. Thromb Haemost 2009; 102:

[9] Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, WInterhalter M, Piepenbrock S, Tanaka KA. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. British Journal of Anaesthesia 102 (6): 785–92 (2009)

[10] Franchini M, Lippi G. Fibrinogen replacement therapy: a critical review of the literature. Blood Transfus 2012; **10**: 23-7.

[11] Rahe-Meyer N, Sørensen B. Fibrinogen concentrate for management of bleeding. J Thromb Haemost 2011; *9*: 1-5.

[12] U.S. Food and Drug Administration (FDA). FDA approves RiaSTAP for treatment of bleeding in patients with rare genetic defect. FDA News. Rockville, MD: FDA; January 16, 2009. Available at: http://www.fda.gov/bbs/topics/NEWS/2009/NEW01948.html.

[13] Fenger-Erikson C, Ingerslev J, Sørenson B. Fibrinogen concentrate - a potential universal haemostatic agent. Expert Opin Biol Ther 2009; **9**: 1325-33.

[14] Dickneite G, Pragast I, Joch C, Bergman G. Animal model and clinical evidence indicating low thrombogenic potential of fibrinogen concentrate (Haemocomplettan P). Blood Coagulation and Fibrinolysis 2009, 20: 535–540

[15] Tirotta CF, Lagueruela RG, Madril D, Ojito J, Balli C, Velis E, Torres M, Alonso F, Hannan RL, Burke RP. Use of human fibrinogen concentrate in pediatric cardiac surgery patients. Int J Anesthetic Anesthesiol 2015, 2:1-6

[16] Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, WInterhalter M, Piepenbrock S, Tanaka KA. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. British Journal of Anaesthesia 102 (6): 785–92 (2009)

[17] Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg 1999; 88: 312–9

[18] Birgitta S. Romlin, Håkan Wåhlander, Håkan Berggren, Mats Synnergren, Fariba Baghaei, Krister Nilsson, and Anders Jeppsson. Intraoperative Thromboelastometry Is Associated with Reduced Transfusion Prevalence in Pediatric Cardiac Surgery. Anesth Analg January 2011 112:30-36

[19] Romlin BS, Wahlander H, Berggren H, Synnergren M, Baghaei F, Nilsson K, Jeppsson A. Intraoperative thromboelastometry is associated with reduced transfusion prevalence in pediatric cardiac surgery. Anesth Analg. 2011; 112:30–36