Prothrombin complex concentrate compared to fresh frozen plasma for post-cardiopulmonary bypass coagulopathy and bleeding, a prospective randomized trial at large US medical center

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Prothrombin complex concentrate compared to fresh frozen plasma for post-cardiopulmonary bypass coagulopathy and bleeding, a prospective randomized trial at large US medical center.

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Abstract

Background:

Post-cardiopulmonary bypass coagulopathy and bleeding represents one of the largest areas of blood product transfusion in surgical practices today. Abnormal bleeding after cardiopulmonary bypass has been shown to be present in about 11% patients.[1] Current literature shows lower transfusion rate and blood loss in patients receiving prothrombin complex concentrate (PCC) when compared to fresh frozen plasma (FFP) after cardiac surgery.[2]

Specific Aim:

Determine best practice in management of postcardiopulmonary bypass coagulopathy and bleeding. Our aim is to compare administration of PCC (Kcentra) to FFP for patients with post bypass factor mediated coagulopathy and clinically significant microvascular bleeding. Primary endpoints for the study will be allogenic blood product transfusion rate and 24 hour postoperative blood loss.

Hypothesis:

Patients receiving PCC (Kcentra) will have same or decreased allogenic blood product transfusion rate and blood loss after cardiac surgery compared to patients receiving fresh frozen plasma.

Significance:

This will be the first prospective randomized controlled clinical trial directly comparing PCC to FFP for post cardiopulmonary bypass microvascular bleeding and factor-mediated coagulopathy.

1. Background and Significance:

Post-cardiopulmonary bypass coagulopathy and bleeding represents one of the largest areas of blood product transfusion in surgical practices today. Abnormal bleeding necessitating blood product transfusion occurs in about 11% of cardiac surgical patients.[1] Bleeding after cardiopulmonary bypass is multifactorial and related largely to blood exposure to bypass circuit components. Consequential coagulation aberrations include thrombocytopenia, platelet dysfunction, clotting factor consumption and dilution, hyper-fibrinolysis, and hypofibrinogenemia.[3] Surgical field and bypass circuit blood which is processed through cell salvage processing and then transfused to the patient is devoid of remaining coagulation factors.[4,5] Standardized transfusion algorithms for patients with post-cardiopulmonary bypass bleeding are not utilized across all healthcare institutions; however, algorithm based transfusion is standard practice at our institution.[1] Currently, patients with factor mediated coagulopathy and bleeding after cardiopulmonary bypass at our institution receive transfusion of fresh frozen plasma.[1] Factor concentrations within FFP are variable, and large volumes of transfused product are often necessary to correct factor deficiencies. In addition FFP transfusion carries the risk of transfusion related lung injury, transfusion related circulatory overload, infectious and allergic complications among others.[6]

Prothrombin complex concentrate use in hemophiliac patients dates back several decades, and has recently become the treatment of choice for management of bleeding in patients taking vitamin K antagonists (warfarin).[7-9] Current formulations of inactivated PCC available in the United States include Bebulin (Baxter) which contains factors 2, 9, 10, and Kcentra (CSL Behring) which contains factors 2, 7, 9, 10. PCC administration in the perioperative setting including post-cardiopulmonary bypass coagulopathy and bleeding is common in European countries. Studies evaluating the efficacy of PCC's in this patient population have demonstrated faster normalization of INR, lower blood loss, and lower transfusion requirements.[2,10,11] Historically, PCC use in the perioperative setting has been limited due to fear of thrombotic complications. Newer formulations of PCC's include a variety of anti-coagulants such as heparin, protein C & S, and anti-thrombin 3. Such additives are felt to reduce thrombotic risk when compared to PCC formulations void of these additives.[12] Thromboembolic events remain a concern when using any procoagulant including PCC's, especially formulations with activated factors such as FEIBA (Baxter), which contains activated factor 7. Inactivated PCC use has not been directly linked to significantly higher rates of adverse outcomes or thrombotic complications when compared to conventional therapies in surgical patients.[2,10,13] Large prospective randomized trials comparing PCC and FFP in cardiac surgical patients to assess clinical outcomes and safety have not been performed. Distinct advantages to PCC administration compared with FFP include higher factor concentration despite significantly less infusate volume, ambient storage with rapid reconstitution, unnecessary blood group compatibility, lower risk of transfusion related complications such as acute lung injury and infection, along with potential cost savings.[14] Current transfusion practices in European countries involve use of inactivated PCC in lieu of FFP.

The significance of this study is related to the potential for reduction in allogenic transfusion requirements and hence associated transfusion related complications. Transfusion reduction would also lead to institutional cost savings which in busy cardiac surgical practices could be

substantial. In addition, massive bleeding after cardiac surgery is associated with higher rates of reoperation, morbidity, and mortality.[3] Current practice per our institutional transfusion algorithm is to use fresh frozen plasma as first line therapy for factor mediated coagulopathy and bleeding after cardiopulmonary bypass.

Large prospective randomized studies directly comparing PCC to FFP in the setting of factor-mediated bleeding after cardiac surgery have not been conducted.

We hypothesize that PCC use will show a reduction in allogenic transfusion requirements in cardiac surgical patients with factor mediated postcardiopulmonary bypass bleeding.

2. Specific Aims:

Our aim is to conduct a prospective randomized controlled trial of patients undergoing elective cardiac surgery. We plan to preoperatively consent and enroll sufficient patients to reach a goal of 200 randomized patients (100 patients per arm) that demonstrate clinically significant microvascular bleeding and factor mediated coagulopathy after cardiopulmonary bypass. Randomized patients with clinically significant factor mediated bleeding will receive transfusion of PCC (Kcentra) (100 patients) or fresh frozen plasma (100 patients). Factor mediated coagulopathy will be defined per our current transfusion algorithm as PT >16.6 sec/ INR >1.6 sec. Primary outcome measures for efficacy will be total units of allogenic blood product transfused, and 24 hour postoperative blood loss. Outcome measure for safety will be rate of serious adverse outcomes. Analysis of coagulation factor levels will also be conducted prior to cardiopulmonary bypass, post cardiopulmonary bypass, and after product administration (PCC or FFP).

Hypothesis:

PCC arm will have same or decreased allogenic blood product transfusion rate and blood loss after cardiac surgery compared to patients receiving fresh frozen plasma.

3. Research Design and Methods:

A. Study Overview

All patients enrolled in the study will have a perioperative anesthetic care plan standardized as much as possible conforming to the current institutional protocol utilized for intraoperative medication administration. Patients will be anticoagulated according to institutional practice with heparin 400 units/kg with goal ACT >400 prior to initiation of cardiopulmonary bypass. After cardiopulmonary bypass, patients will receive protamine at dose 0.01 mg/unit of heparin given with target ACT within 10% of baseline value. If ACT >10% baseline additional protamine will be given at the anesthesiologists discretion. Evaluation and determination of excessive microvascular bleeding in the surgical field will occur 10 minutes after return of ACT to within 10% of baseline. Determination for treatment with PCC or FFP will be based off of the current algorithm used at our institution.[1] Specifically this study will focus on patients with a PT >16.6 sec/ INR >1.6 sec, or aPTT > 57 sec with clinical evidence of excessive microvascular bleeding

in the surgical field as determined by the surgical team. All other coagulopathies will be treated as per the current institutional transfusion protocol.

B. Study Population

Consecutive adult patients undergoing cardiac surgery at St. Marys Hospital will be potentially eligible for the study. All of the cardiac surgeons at Mayo Clinic Rochester will be asked to participate in the study.

Inclusion Criteria
All subjects eligible for enrollment must:

1. Be ≥ 18 years of age
2. Be undergoing a cardiac surgical procedure utilizing cardiopulmonary bypass
3. Have an INR ≤ 1.3 if warfarin was not held for 5 days

Exclusion Criteria
All subjects with one of the following are not eligible for enrollment:

1. Are unable to grant informed consent or comply with study procedure
2. History of hypercoagulable condition (e.g. Factor V Leiden, AT-3 deficiency, Prothrombin gene mutation, Anti-phospholipid antibody syndrome, etc.) or previous unprovoked thromboembolic complications
3. Coagulopathic conditions such as factor deficiencies, factor inhibitors, heparin induced thrombocytopenia, or use of intravenous anticoagulants other than heparin at the time of cardiovascular surgery
4. Thromboembolic event with past 3 months
5. Received oral therapy with ELIQUIS (apixaban) or Xarelto (rivaroxaban) within 3 days prior to planned surgical procedure
6. Received oral therapy with clopidogrel, prasugrel, or dabigatran within 5 days prior to planned surgical procedure
7. Are undergoing emergency open heart-surgery
8. Cardiopulmonary bypass time is expected to be <30 minutes
9. Are pregnant
10. Heparin allergy
11. ECMO post op
12. Life threatening bleeding necessitating transfusion of hemostatic products (FFP or PCC) prior to the study intervention time point
13. Circumstances for which the safety of the patient could be jeopardized by continued adherence to the study protocol

Enrolled subjects must meet additional criteria in order to receive study treatment:
Inclusion Criteria

1. Have evidence of excessive microvascular bleeding in the surgical field as determined by the surgical team
2. PT >16.6 sec/ INR >1.6 sec, or aPTT > 57 sec. on initial post cardiopulmonary bypass labs

Exclusion Criteria

1. Fibrinogen < 144 mg/dL on initial post cardiopulmonary bypass labs

C. Enrollment

Subjects will be enrolled at the time of pre-operative visit with cardiothoracic surgery if they meet the eligibility criteria. Informed written consent will be obtained and randomization performed to one of the two study arms.

We estimate approximately 1000 subjects will be need to consented with intent of having 100 patients receive treatment (50 patients in each treatment arm). This study will terminate once 50 patients in each study arm have received treatment. Our data and safety monitoring board (DSMB) will provide oversight and monitoring to the study to ensure the safety of participants and validity and intensity of data. The DSMB will consist of 2 physicians and a statistician not affiliated with study. They will review data from the study and meet at the 50% and 75% enrollment milestones or every 6 months from previous meeting date whichever comes first. The DSMB will provide aggregated data summaries to the Mayo IRB with explanations of seriousness and relatedness of adverse events to the study. In addition to the above, the authors will inform the National Institute of Health (NIH) of any actions taken by the IRB as a result of its continuing review.

The primary adverse event of concern in this study would be thromboembolic events. DSMB (anesthesiologist, hematologist, and statistician) will meet quarterly, and review all data from each study arm. Thromboembolic complications will be reviewed and clinical judgment will used to determine necessity of study termination. No formal stopping rules are feasible given the study size and low incidence of TEE.

Early termination of the study will ensue if adverse events in either study arm exceed acceptable level.

D. Randomization and Blinding

Upon consent for study participation enrolled patients will be randomized via computer-generated blocks and with stratification according to the surgical procedure to either receive PCC or FFP during cardiac surgery should they develop excessive microvascular bleeding in the

surgical field as determined by the surgical team in addition to a PT >16.6 sec/ INR >1.6 sec after cardiopulmonary bypass. The randomization assignments will be concealed in opaque envelopes and disclosed to the anesthesiologist caring for the patient. The surgical and intensive care personnel will not be blinded to the treatment arm, as transparency of transfusion product is necessary to prevent overdosage of PCC and potential thrombotic complications.

E. Interventions

Patients will be consented and enrolled in the study until 50 patients have received treatment in each arm of the study. Patients will be anticoagulated according to institutional practice with heparin 400 units/kg with goal ACT >400 prior to initiation of cardiopulmonary bypass. After cardiopulmonary bypass, patients will receive protamine at dose 0.01 mg/unit of heparin given with target ACT within 10% of baseline value. After protamine administration the ACT, CBC, PT/ INR, and fibrinogen, will be collected via preexisting arterial access. If ACT >10% baseline additional protamine will be given at the anesthesiologists discretion. Evaluation and determination of excessive microvascular bleeding in the surgical field will occur 10 minutes after return of ACT to within 10% of baseline. Patients with clinical evidence of excessive microvascular bleeding in the surgical field as determined by the surgical team, along with a PT >16.6 sec/ INR >1.6 sec will receive randomized treatment with either PCC or FFP.

PCC (Kcentra) Dosage: Patients randomized to the PCC arm with evidence of microvascular bleeding and PT >16.6 sec/ INR >1.6 sec will have Kcentra 15 units/kg prepared from pharmacy.

Patients who have received **PCC** and continue to demonstrate microvascular bleeding 10 minutes after the full PCC dose has been administered will undergo repeat laboratory evaluation of PT/INR +/- CBC, and fibrinogen depending on previous lab results and product administration other than PCC. Therapy will ensue following our institutions current transfusion algorithm. Patients who received full dose PCC and continue to have microvascular bleeding in addition to a PT >16.6 sec/ INR >1.6 sec will receive FFP at a dose of 10-15 mL/kg rounded up to the nearest unit.

FFP dosage: Patients randomized to the FFP arm will continue with standard therapy per our institutional algorithm at a dose of 10-15 mL/kg rounded up to the nearest unit. Patients who have received **FFP** by randomization per the above dosage protocol and continue to demonstrate microvascular bleeding 10 minutes after product administration will undergo repeat laboratory evaluation of PT/INR +/- CBC, APTT, and fibrinogen depending on previous lab results and product administration other than FFP. Therapy will ensue following our institutions current transfusion algorithm. Patients who receive FFP per randomization and continue to have microvascular bleeding 10 minutes after product administration in addition to a PT >16.6 sec/ INR >1.6 sec, or aPTT > 57 sec will receive additional FFP.

Transfusion of coagulation products other than PCC or FFP (e.g. platelets and cryoprecipitate) will be determined by laboratory abnormalities requiring treatment within our institutions current algorithm in the presence of excessive microvascular bleeding.

Resolution of microvascular bleeding within the surgical field as determined by the surgical team is the endpoint for necessitation of transfusion, not normalization of coagulation testing. Examples of this are as follows:

1. A patient with an INR of 1.9 and evidence of microvascular bleeding who receives either PCC or FFP, for which the microvascular bleeding resolves but the INR remains elevated at 1.7 would not receive additional transfusion.
2. In the absence of laboratory deviations, continued bleeding is most commonly secondary to surgically related issues. The extremely rare instance that bleeding persists despite normalization of laboratory indices and there is no identifiable surgical cause for bleeding (thus presumed to be continued microvascular bleeding), the decision to transfuse blood component products, PCC, or potentially salvage therapy with activated PCC will be left to the discretion of the anesthesiologist and surgeon caring for the particular patient.

Red blood cell transfusion (PRBC) threshold will be a hemoglobin concentration of 8g/dL (Hct 24%) for patients enrolled in this study, as this threshold was not inferior to a threshold of 10 g/dL (Hct 30%) in the TRACS trial.[15] PRBC transfusion threshold deviations from this recommendation may occur at the discretion of the anesthesiologist caring for the patient in rare instances (e.g. severe surgical bleeding). Transfusion of PRBC in intensive care setting will also target a hemoglobin transfusion threshold of > 8 g/dL. Resolution of microvascular bleeding is the endpoint for necessitation of transfusion, not normalization of coagulation testing.

Thrombin generation testing

A blood sample will be collected to analyze thrombin generation prior to cardiopulmonary bypass, post-cardiopulmonary bypass after protamine administration, after transfusion of product (either FFP or PCC), 24 hours postoperative, 3 days postoperative, and 5 days postoperative or day of discharge . This sample will be collected in conjunction with other standard laboratory tests. Thrombin generation testing is not performed at Mayo Clinic. These samples will be stored at -20 degrees Celsius and sent batched to a specialized laboratory for testing. All samples will be deidentified and contain no PHI. Study participants will not be charged for this testing. No genetic analysis or testing other than AT-3 and Thrombin generation testing will occur with these samples.

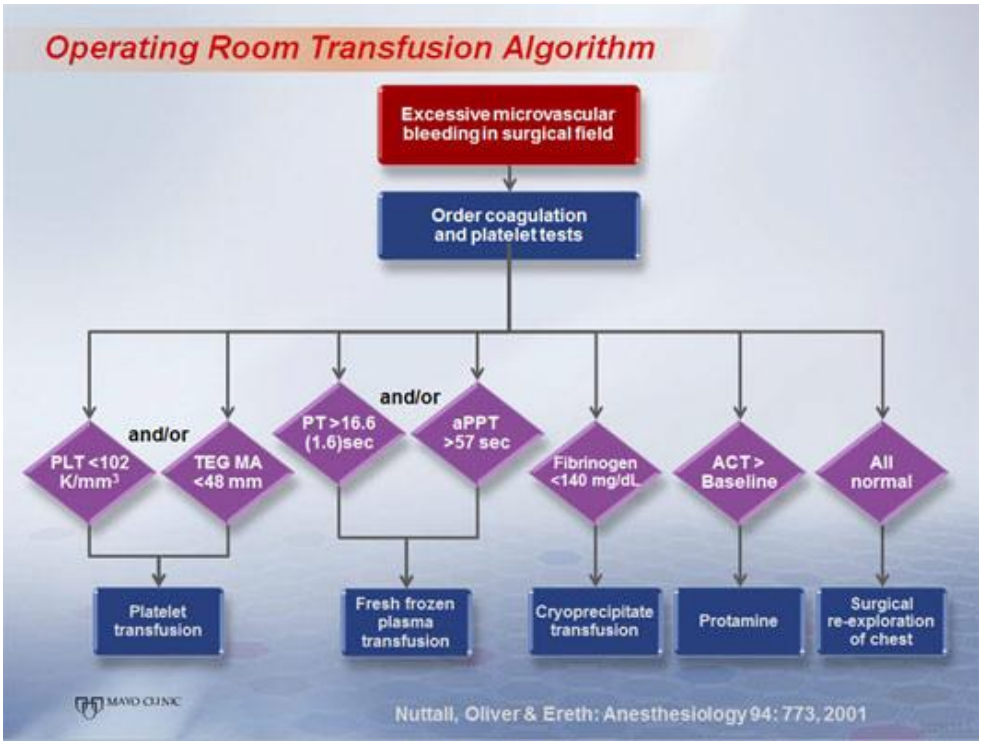
Antithrombin III Level

AT-3 levels will be drawn at time periods that mirror thrombin generation testing below: prior to cardiopulmonary bypass, post-cardiopulmonary bypass after protamine administration, after

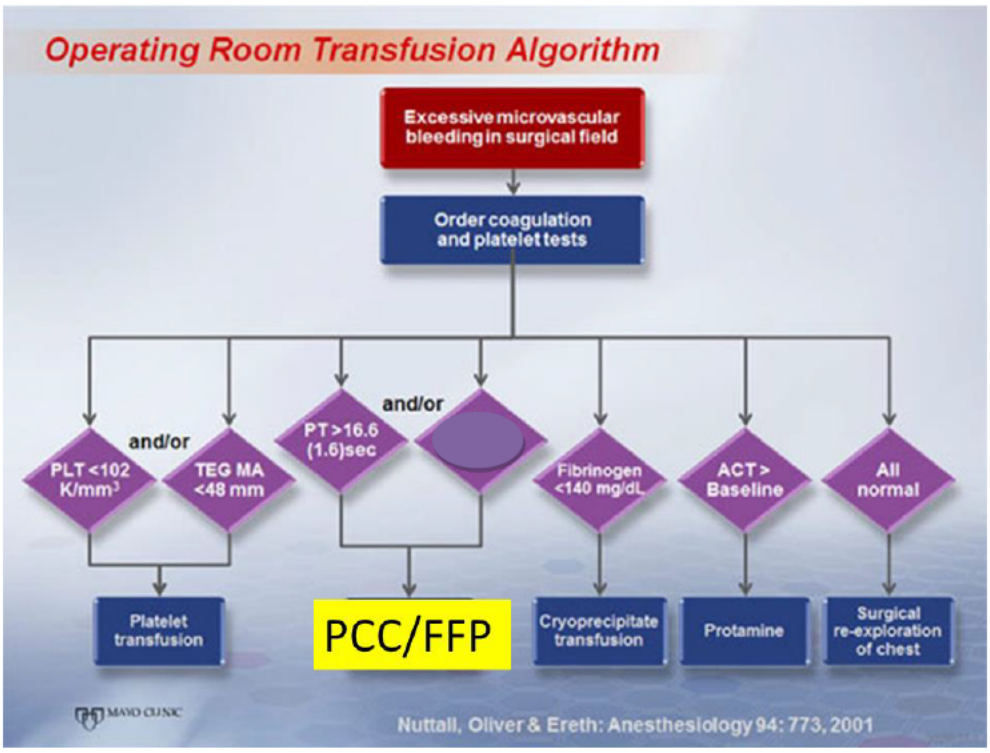
transfusion of product (either FFP or PCC), 24 hours postoperative, 3 days postoperative, and 5 days postoperative or day of discharge . Patients will not be charged for this testing. AT-3 levels will be collected in the same sample tube as Thrombin generation testing and shipped to a facility capable of performing such testing. All samples will be deidentified and contain no PHI. No genetic analysis or testing other than AT-3 and Thrombin generation testing will occur with these samples.

Coagulation Factor Levels

A blood sample will be collected to analyze coagulation factors 1-12 and protein C & S levels prior to cardiopulmonary bypass, post-cardiopulmonary bypass after protamine administration, and after transfusion of product (either FFP or PCC). This blood sample will be collected through an arterial catheter which is routinely placed as standard practice for cardiovascular operations. The collected coagulation factor level results will not be available to alter treatment in either study arm. Analysis of coagulation factor levels will focus on changes in factor levels resultant of cardiopulmonary bypass, and changes in factor levels resultant of product administration (either FFP or PCC). Study participants will not be charged for coagulation factor laboratory analysis. These samples will be batch shipped to CSL Behring's central laboratory in Germany for testing. All samples will de-identified and contain no PHI (Protected Health Information). No genetic analysis or testing other than the factor levels will occur on these samples.



Current intraoperative transfusion algorithm



Proposed study intraoperative transfusion algorithm

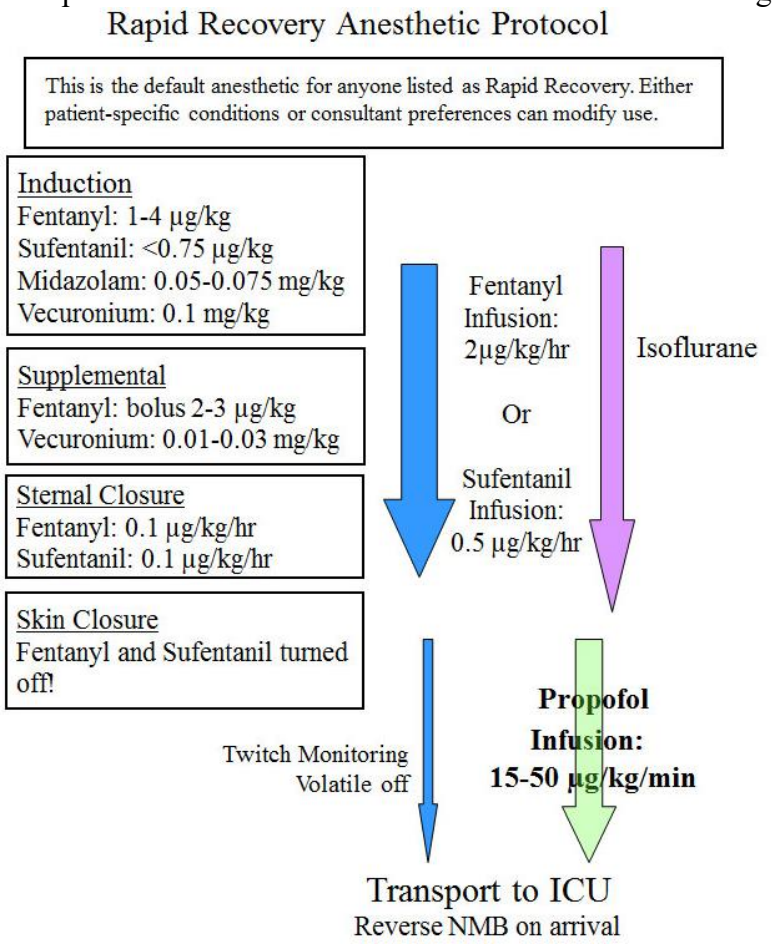
F. Protocols of care

Anesthesia

All patients will have perioperative anesthetic care plan standardized as much as possible conforming to the current divisional protocol utilized for intraoperative medication administration and consistent with the practice of the majority of anesthesiologists in the cardiovascular anesthesia division (see rapid recovery anesthetic protocol below). Patients will receive routine monitoring for cardiac surgery including an indwelling arterial catheter, and central venous catheter. Crystalloid and colloid solutions will be administered in order to maintain adequate volume status and hemodynamics. All patients will have a propofol or dexmedetomidine infusion prior leaving the operating room and continued into the ICU for sedation and pain control.

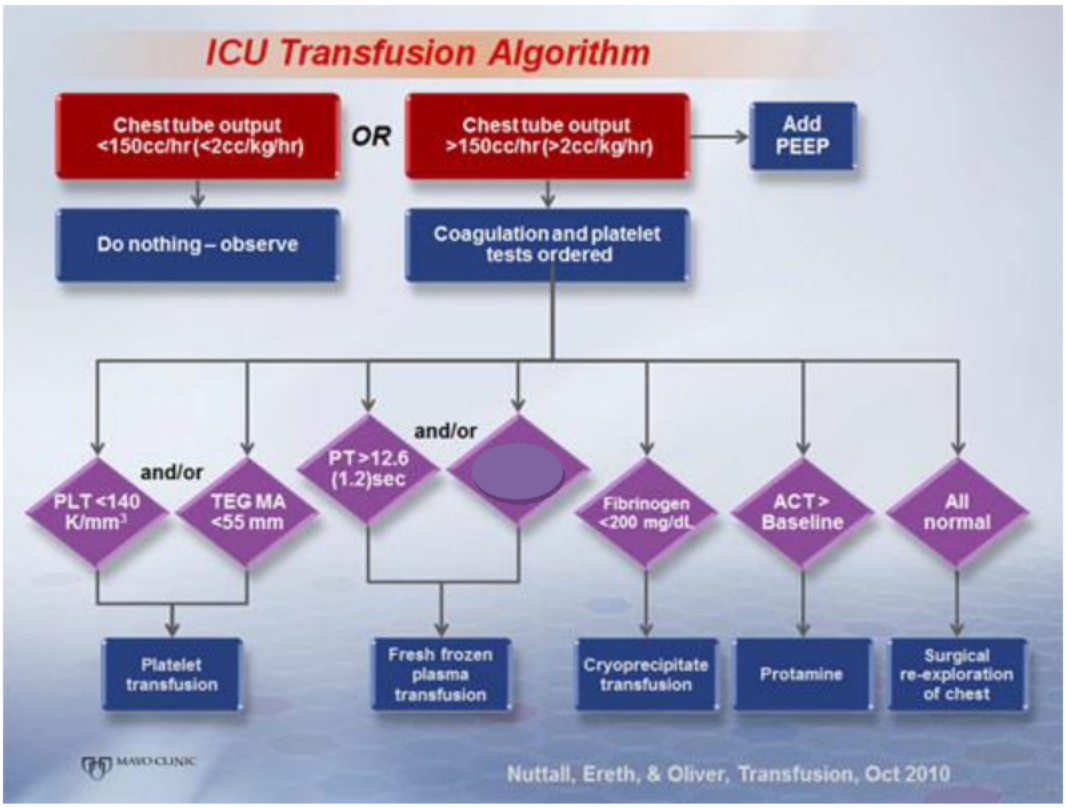
All patients will undergo median sternotomy with myocardial preservation. Anticoagulation will be with heparin, patients unable to receive heparin will be excluded from the study. The priming solution for the venous reservoir of the extracorporeal circuit will contain a standard crystalloid solution. Packed red blood cells (PRBC) will be added if the patient is predicted to have a hematocrit (HCT) less than 19% once CPB is initiated. Mean perfusion pressure will be maintained during CPB between 50-90 mm Hg. During CPB, the HCT will be maintained at ≥ 19%. Most patients will undergo normothermic CPB, although some may be cooled further depending on the planned operation (e.g 18°C for deep hypothermic circulatory arrest). All

patients will be at a nasopharyngeal temperature of >36°C prior to discontinuation of CPB. Anticoagulation will be reversed with protamine as previously described. The patient will be transported intubated on a monitored cart to the cardiac surgical ICU.



Postoperative ICU transfusion

Current postoperative ICU transfusion requirements will follow the institutional algorithm (see ICU transfusion algorithm below). Deviation from the protocol in rare circumstances is left to the discretion of the ICU consultant and Surgeon. Transfusion of PRBC in intensive care setting will aim for a hemoglobin transfusion threshold of > 8 g/dL.



Ventilator weaning and extubation protocol

Current conventional ventilator weaning and extubation of the trachea criteria protocols will be used in this study. Patients will be ventilated in the ICU to maintain a $PaCO_2$ of 32-42 mmHg. Arterial blood gases (ABG) will be obtained on admission to the ICU, with further ABG assessment directed by the ICU consultant. Hemodynamic measurements (heart rate (HR), blood pressure (BP), Pulmonary artery pressure (PAP), right atrial pressure (RAP), cardiac index (CI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) will be obtained on admission to ICU and at intervals directed by the ICU consultant and the patients clinical course. All decisions regarding weaning and extubation of the patient will be made by ICU consultant. Weaning of the ventilator may begin after these previously standardized criteria have been fulfilled or as instructed by the critical care consultant:

1) Mediastinal chest tube output must be $\leq$ 3 ml/kg/hr and 2 ml/kg/hr the first and second hour respectively, and 1 ml/kg/hr thereafter.
2) Hemodynamically stable.
3) Urine output $\geq$ 1 ml/kg/hr.
4) Normothermia (>36°C)
5) Respiratory parameters fulfilled
   - pH $\geq$ 7.35 and $\leq$ 7.55
   - $PaCO_2 \geq$ 30 mmHg and $\leq$ 50 mmHg
   - $PaO_2 \geq$ 80 mmHg
   - SpO2 $\geq$ 92%

Respiratory rate ≤ 25/min

Discharge from the intensive care unit and hospital criteria
Current conventional discharge from the intensive care unit criteria and hospital will be used.

ICU discharge time will be recorded and traditionally assumes following criteria:
- Alert and cooperative
- No inotropic support
- No hemodynamically unstable dysrhythmia
- Adequate respiratory status
- Minimal chest tube drainage
- Urine output ≥ 0.5 ml/kg/hr

Discharge from the hospital will be recorded and traditionally assumes following criteria:
- Hemodynamically stable
- Stable cardiac rhythm
- Noninfected incisions
- Afebrile
- Ability to void and bowel movements
- Independent ambulation and feeding.

G. Data Collection

The following variables will be entered into a database:

1. Demographic:
    a. Age
    b. Sex
    c. Society of Thoracic Surgeons (STS) risk score (where applicable)

2. Comorbidities:
    a. History of cerebrovascular accident
    b. History of vascular thromboembolic disease (arterial or venous thrombosis, organ ischemia secondary to thromboembolic phenomenon).
    c. Coronary artery disease
    d. History of atrial fibrillation
    e. GFR < 60 mL/min/1.73 m^2

3. Preoperative laboratory variables:
    a. CBC, and the following if available preoperatively PT/ INR, APTT, Fibrinogen

4. Preoperative medications:
    a. Anticoagulant medications

5. Intraoperative variables:
    a. Procedure performed

b. Initial or Redo-Sternotomy
c. Cardiopulmonary bypass time
d. Aortic cross clamp time (if applicable)?
e. Presence and (if present) duration of deep hypothermic circulatory arrest
f. Allogenic blood product utilization after cardiopulmonary bypass
g. Laboratory variables (CBC, PT/ INR, APTT, and Fibrinogen)
h. Anticoagulant (Heparin +/- other) and anti-fibrinolytic use (aminocaproic acid or tranexamic acid)
i. Direct transfusion related complications/reactions
    1. TRALI (Transfusion related acute lung injury) by standard definition[16]
    2. ABO/Non-ABO hemolytic reaction
    3. Anaphylactic or Allergic reaction

6. Postoperative variables:
    a. Allogenic blood product transfusion
    b. Mediastinal and chest tube output for 24 hours after chest closure
    c. **Serious Adverse Events** occurring within 30 days of operation:
        i. Thromboembolic events (new DVT or arterial thrombosis diagnosed by Doppler ultrasound, cerebrovascular accident or transient ischemic attack, new myocardial infarction, end organ ischemia secondary to thromboembolic phenomenon, all-cause mortality)
            1. The concern for thromboembolic complications is certainly present, and will be monitored closely as an adverse event in both treatment arms. The presence of clinically significant thromboembolic complications will be diagnosed as per current clinical practice in this patient population. It is assumed that clinical symptomatology or suspicion to such diagnoses will trigger diagnostic testing when deemed appropriate, and any confirmed diagnoses of thromboembolic complications will be noted. No specific screening tests will occur in patients enrolled for this study.
        ii. Renal failure necessitating unplanned initiation of dialysis or hemofiltration
        iii. Acute Respiratory Distress Syndrome (ARDS) by Berlin definition[17]
        iv. Direct transfusion related complications/reactions
            1. TRALI (Transfusion related acute lung injury) by standard definition16
            2. ABO/Non-ABO hemolytic reaction
            3. Anaphylactic or Allergic reaction
    d. Length of stay (ICU and total hospital stay)

H. Outcomes

All suspected outcome events will be evaluated in a standardized way by an adjudication panel that will be unaware of the patients' assignments.

In the study, outcome measures for efficacy will be total allogenic blood products transfused and 24 hour postoperative blood loss. Outcome measure for safety will be rate of serious adverse events.

Length of stay in the ICU and hospital will also be recorded in both groups.

I. Follow-Up

A telephonic assessment will be made by a study nurse at 30 days + 7 days. A standardized phone survey will be used to obtain information for assessing events of interest (Attached below).

J. Statistics/Power Analysis

Power Analysis was determined from a study by Arnekian et al that retrospectively presented a reduction in blood loss in patients receiving PCC over those receiving FFP.[2] In that study, the distribution of 24-hr chest tube drainage was highly skewed, but the observed difference between the two groups was at least 0.65 standard deviation units. Using a non-parametric test, a sample-size of **N=50 per group should provide statistical power of >85% to detect a difference of this magnitude. Therefore we suggest a sample-size of at least 50 per group**. In the paper, they also found a dramatic difference in ICU red cell transfusions. If the true difference is as large as they observed a sample-size of N=50 per group would also provide adequate statistical power for this endpoint.[2]

Primary endpoints in this study will be units of allogenic blood product administration, and 24 hour postoperative blood loss. Exploratory endpoints will include rate of serious adverse outcomes.

Baseline patient characteristics, including demographics, comorbidities, preoperative laboratory values, and cardiovascular variables will be reported and compared across treatment groups. Categorical variables will be reported as counts and percentages, and compared across groups using chi-square or Fisher's exact tests. Continuous variables will be reported as median and interquartile ranges, and compared across groups using Wilcoxon rank sum tests.

K. Feasibility and Time Frame

This study with the combined collaboration of divisions of anesthesiology and cardiovascular surgery is quite feasible. Approximately 2200-2500 cardiopulmonary bypass procedures are done annually at St. Mary's Hospital. Making the conservative estimate that 50% will consent 1000 patients should be consented within 1 year. Given that approximately 11% of patients

receive transfusion; this would result in approximately 100-110 patients to be treated within 12 months. We expect to get IRB approval within the next one month. The study and data collection will take about 1 year with approximately two months for data analysis.

L. Strengths and Limitations

Strengths: This will be the first prospective randomized controlled trial in the United States directly assessing the effect of PCC compared to FFP in the setting of postcardiac surgery coagulopathy and bleeding in patients undergoing elective cardiac surgery.

Limitations: If the study demonstrates lower transfusion requirements and blood loss in the PCC arm, further studies will need to address optimal dosing requirements. Current PCC dosing is based on INR and weight for patients on warfarin therapy. Should no difference be found between groups, or lower transfusion rate and/or postsurgical blood loss is found in the FFP arm, the question as to whether this represents a superior result of FFP or underdosing of the PCC arm will remain.

M. Anticipated Results

a. PCC administration will reduce the amount of allogenic blood product transfused and amount of postoperative bleeding in patients undergoing cardiac surgery.

b. Adverse event rate will be similar between the 2 treatment arms, representing the known risk associated with cardiovascular surgery.

c. Perioperative transfusion related costs will be similar or lower in patients receiving PCC compared with FFP

N. Estimated Costs

Kcentra will be supplied and funded by CSL Behring (Melbourne, Australia). FFP if administered will be covered by the patient/payer as this treatment is the current practice standard. All laboratory testing not routine to this patient population will be funded by CSL Behring and is outline within the budget.

O. Research Materials

All data forms will be stored in individual patients study folders and handled securely for patient confidentiality. This data will be entered into an access database that is password protected.

P. <u>Human Subjects</u>

We will obtain informed consent from all participants prior to initiation of the study. Informed consent will meet the requirements of the code of federal regulations 21CFR 50.25 (elements of informed consent) and the IRB of this center. During informed consent for the study cardiac

surgical patients will be told that the chance of needing a transfusion in the perioperative period is around 11%. Should they meet criteria by our current transfusion algorithm to receive FFP, they would have been randomized to receive either FFP or the study PCC infusion. A copy of the consent form will be placed in the patient's medical records. The study will be stopped when 50 patients have received treatment in each study arm. Efficacy will be defined as either a statistically significant reduction in transfusion of allogenic blood products or 24 hour postoperative blood loss. Safety will be defined as similar rate of serious adverse outcomes in the PCC study drug arm to the standard therapy FFP arm.

The trial will be conducted in accordance with the Declaration of Helsinki.

Q. Institutional IRB training Narrative

The institution has established a formal program entitled the Mayo Investigator Training Program or MITP. The MITP is a web based educational course designed to provide all personnel involved in human subject research with training about human subject protection. All Mayo personnel engaged in human subject research are required to complete the course. The primary objectives of the course are to provide the historical framework for current human subject protection regulations and to explore the evolving issues related to human subject research. The course is divided into four sections:

- Course introduction and general overview
- History section which explores examples of unethical behavior in human subject research
- Review of major human subject protection issues
- Discussion of the various roles and responsibilities of individuals involved in human subject research
- At the conclusion of the instruction, individuals are required to complete a thirty-question assessment.

R. Confidentiality

Every effort will be made to ensure strict patient confidentiality. Research records are stored securely and are separate from hospital records. No patient identifier will be used in any publication resulting from this study.

S. Recruitment

Volunteers will be recruited by study personnel during their preoperative medical evaluation. The investigators will review the purpose, the procedures risks and discomforts, benefits alternatives, costs, participation and termination, treatment for research related injury and confidentiality issues of the study in person with all potential volunteers. Before participation, all volunteers are given adequate time to read the consent form before written informed consent is obtained. The original consent form is placed in the subject's study file. A copy is provided to the participant and sent to HIM scanning to include in the electronic medical record.

T. Gender/Minority Mix

We expect an equal distribution of male and female study participants. The study population will comprise patients mainly from Olmsted County, MN and a few referred patients from throughout the country. We expect the racial/ethnic characteristics of the group to reflect the communities in Olmsted County, MN and are anticipated to be 95% white, 3% Asian and 2% other minorities. No efforts will be made to alter these characteristics, as there are no data that suggest differences in outcomes that we are studying in different genders or ethnic groups.

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PCC vs. FFP Telephone script

Good morning/afternoon. This is Dr./Ms./Mr. _____ calling from the Mayo Clinic-Rochester. May I please speak to _____? (If the participant is there proceed to the following; if the participant is not there, see below***)

I am contacting you to ask you some questions in regard to the research study that we are doing here at the Mayo Clinic involving people who have had heart surgery. You had provided consent to participate in this study prior to your heart surgery. Please understand that your current care and future care at the Mayo Clinic will not be affected by whether or not you participate. Specifically, your care will not be jeopardized if you choose not to answer the questions. Would you be willing to answer some questions regarding your surgery?
If yes: Is now a good time or would you like me to call you back?
If no: Thank you for your time.

1. Have you seen a doctor for any reason since being discharged from the hospital after your surgery?

If yes: Could you please tell me the reason.
If no: go to question 2

_____
_____

2. Have there been any changes in your health status since being discharged from the hospital after your heart surgery?

If yes: document
If no: go to question 3

_____
_____

3. Have you had any problems specifically with blood clots, heart attack, stroke, or damage to your kidneys requiring dialysis?

If yes: document

_____
_____

******If the participant you wish to speak with is not available, ask:*** When would it be a good time to call to speak with _____? Thank you, I will return the call at that time.

******If there is any indication that the patient is deceased:*** I'm truly sorry to hear that. Mr/Mrs _____ agreed to participate in a study concerning his/her recent

heart surgery. If you are willing to answer some questions, we may be able to collect some information that is helpful to the study. Would you be willing to share the circumstances of Mr/Mrs _____ death?

If yes: document. If not stated by call recipient, pose question number three phrased for a third party.
If no: I can certainly understand. Thank you very much for your time. (end call)

Closing: Thank you for participating in our research study. Please understand that your answers to the questions will be kept confidential and when the data from this research study is reported your data will be included in a summary without your name or any other identifying information.