Repurposing of Fibrinogen Concentrate as a Cost-Effective and Safe Hemostatic Agent in Infants Undergoing Cardiac Surgery on Cardiopulmonary Bypass

Study Protocol

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Study Title: Repurposing of Fibrinogen Concentrate as an Efficacious and Safe Hemostatic Agent in Infants undergoing cardiac surgery on cardiopulmonary bypass

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Abstract

Neonates and infants undergoing cardiac surgery are at high risk for perioperative bleeding and massive transfusion due to immature coagulation systems, cardiopulmonary bypass effects, hemodilution, and the complexity of surgeries. The current treatment for post-bypass bleeding includes transfusion of multiple rounds of blood products, which increases the risk of volume overload, immunologic burden, morbidity, and mortality. The average number of donor exposures for a neonate undergoing cardiac surgery requiring CBP at Children's Healthcare of Atlanta is nine exposures. Targeting transfusion strategies and alternative hemostatic agents that would reduce bleeding and transfusions would be a significant benefit to these patients.

The most common hemostatic derangement after CPB is an acute acquired hypofibrinogenemia, which compromises fibrin clot generation and platelet aggregation, resulting in increased bleeding and need for allogenic blood product transfusions. Currently, management of this acquired hypofibrinogenemia is replaced with a blood product, cryoprecipitate. Fibrinogen concentrate, RiaSTAP (CSL Bering), is a commercially available product that is being used off-label in cardiac and pediatric surgery to reduce bleeding and transfusions. However, a study specifically targeting neonates undergoing open-heart surgery with CPB has not been done to determine the efficacy of RiaSTAP in this population.

In this study, we plan to complete a multi-center randomized, control trial comparing cryoprecipitate to fibrinogen concentrate in reducing allogenic blood transfusions in infants undergoing cardiac surgery with CPB. Secondary outcomes will evaluate perioperative laboratory values, length of mechanical ventilation, length of ICU and hospital stays, as well as adverse events. Overall, we hope to use the results of this study to develop alternative transfusion strategies to treat post-CPB bleeding in infants.

Introduction and Background

In patients undergoing open-heart surgery (OHS), transfusion of allogenic blood products is independently associated with increased morbidity and mortality (1,2). In response to this, research in adult cardiac anesthesia has focused on blood product usage and developing algorithms to limit blood product exposure. Due to the smaller population, considerable variability in patient characteristics, and wide range of procedures performed in pediatric cardiac patients, the literature regarding blood conservation strategies for pediatric cardiac patients is limited. In children undergoing OHS, there are no published algorithms even though product exposure, particularly in neonates, is significant. The National Heart, Lung and Blood Institute (NHLBI) has determined pediatric transfusion medicine (PTM) to be a high priority for clinical and translational

research, specifically targeting transfusion strategies that could reduce short and long term morbidity and mortality (3).

Approximately 10,000 babies born with congenital heart disease require OHS during the first year of life. Excessive bleeding after CPB is an independent predictor of increased adverse events and massive transfusions in neonates (4). Higher perioperative transfusions of allogenic blood products during pediatric cardiac surgery are associated with increased mortality, increased pulmonary complications, prolonged mechanical ventilation, prolonged hospital stays, increased risk of hospital acquired infections and other adverse events (5,6). Many children with failed single-ventricle surgical palliation become higher-risk heart transplantation candidates because of the allo-sensitization after donor blood exposure. Finally, exposure to blood borne infections is a potential complication from receiving human derived blood products. Therefore, developing strategies to reduce bleeding and standardize blood transfusions for pediatric patients during CPB is an urgent need with a potential to reduce short and long-term morbidity and mortality.

Neonates and infants undergoing cardiac surgery are at high risk for perioperative bleeding and massive transfusion due to immature coagulation systems, cardiopulmonary bypass (CPB) effects (deep hypothermia, extreme hemodilution, large non-endothelialized surfaces) and complexity of surgery. The most common hemostatic derangement after CPB is an acute acquired hypofibrinogenemia, which compromises fibrin clot generation and platelet aggregation, resulting in increased bleeding and need for allogenic blood product transfusions. Recent studies suggest that qualitative and quantitative fibrinogen deficiencies may contribute to impaired hemostasis in neonates and infants (7). Using confocal microscopy, Brown et al demonstrated neonatal clot formation before and after cardiopulmonary bypass is more porous and less dense than clots from adults. However, the addition of adult fibrinogen was able to establish more effective clot formation in neonates (7). In conjunction with the decreased function of neonatal fibrinogen, the acute acquired hypofibrinogenemia after OHS contributes to impaired fibrin clot generation and platelet aggregation. Currently, fresh frozen plasma and cryoprecipitate are used to supplement fibrinogen in pediatric cardiac patients, thus increasing the allogenic transfusion exposures.

RiaSTAP (fibrinogen concentrate (FC)), an FDA-approved medication for congenital hypofibrinogenemia, is being used off-label for treatment of acute acquired hypofibrinogenemia associated with massive bleeding and CPB in adult and pediatric patients (8-10). Fibrinogen concentrate has many potential advantages for pediatric patients including 1) smaller volume to achieve target levels of fibrinogen, 2) decreased exposure to allogenic blood products, 3) decreased risk of infectious transmission, immunologic or allergic reactions, and 4) no required cross-matching or thawing process that makes it rapidly available for all patients. Recent studies found that FC was as effective as cryoprecipitate in reducing bleeding and transfusions for pediatric patients undergoing craniofacial and open-heart surgery (9,10). However, these studies did not specifically examine the neonatal and infant population, who are most vulnerable to the affects of hypofibrinogenemia, excessive bleeding and large transfusions associated with

OHS. We propose that FC poses many advantages over current options, but there is a clear need for a randomized, prospective study in this population. After communication with the Center for Biologic Evaluation and Research (CBER) and the Office of Blood Research and Review (OBRR) at the FDA, an IND exemption was granted for this study. A grant from The Child Health Research Institute at Stanford University and SPARK has supported the initial work on this study and will help support the center at Children's Healthcare of Atlanta.

Significance:

Specific Aim #1:
Demonstrate that fibrinogen concentrate can reduce allogenic donor exposures when compared with cryoprecipitate in infants undergoing cardiac surgery with CPB. The most common cause of post-bypass coagulopathy in infants after bypass surgery is from an acquired hypofibrinogenemia due to hemodilution from the bypass circuit. Secondly, immature neonatal fibrinogen does not function as well as adult fibrinogen in forming stable clots. This acquired hypofibrinogenemia is currently treated with cryoprecipitate, a human derived blood product, which requires blood type matching and time to obtain from the blood bank. The FDA has approved fibrinogen concentrate, a lyophilized protein with minimal side effects, for use in pediatric and adult patients with congenital hypofibrinogenemia. Fibrinogen concentrate is being used off-label for treatment of acute acquired hypofibrinogenemia associated with massive bleeding and CPB in pediatric patients. No studies have been done specifically in cardiac surgery patients <12 months, who are most at risk for hypofibrinogenemia due to their small circulating blood volumes, immature coagulation systems, and potential long-term effects of transfusion related risks. Therefore, we have received an IND exemption from the FDA to conduct this randomized, control trial comparing fibrinogen concentrate to cryoprecipitate in hemostatic management of post-bypass coagulopathy in patients <12 months. We propose that replacing cryoprecipitate with reconstituted fibrinogen concentrate will be as effective as cryoprecipitate in treating post-CPB bleeding and decrease total donor exposures by 20%.

Specific Aim #2:
Comparison of fibrinogen concentrate to cryoprecipitate as a safe and effective hemostatic agent:
By evaluating the laboratory values, transfusion requirements, and outcomes, we will examine the effectiveness of FC in reducing transfusion related risks, such as 1) length of mechanical ventilation time, 2) length of ICU stay, 3) length of hospital stay, 4) adverse events within seven days of surgery, 5) preoperative and post-operative coagulation laboratory values.

Experimental Design and Methods

Design:

This study will be a multi-center prospective, randomized control trial. After informed and written parental consent, a total of 60 neonates and infants (<12 months) will be enrolled at Children's Healthcare of Atlanta or Lucile Packard Children's Hospital at Stanford Hospital.

Study Population:

The following criteria will be used to determine patient eligibility:
Inclusion Criteria:

- Full term neonates (32-42 weeks gestational age)
- weight ≥ to 3 kg at time of surgery
- Infants less than 12 months of age
- Infants and Neonates undergoing elective cardiac surgery requiring CPB at Children's Healthcare of Atlanta or Lucile Packard Children's Hospital at Stanford Hospital
- No known patient or family history of coagulation defect or coagulopathy
- Parents willing to participate and able to understand and sign the provided informed consent

Exclusion Criteria:

- Preterm neonates (less than 32 weeks gestation)
- Patients less than 3 kg at time of surgery
- Patients ≥12 months of age
- Patients undergoing emergent procedure
- Patients undergoing cardiac surgery not requiring CPB
- Patients with known coagulation defect or coagulopathy
- Family history of coagulation defect or coagulopathy
- Parents unwilling to participate or unable to understand and sign the provided informed consent

Enrollment/Consent Process:

The Institutional Review Board will approve informed consent documents prior to commencement of the study. Only those patients who meet the entry criteria will be considered as possible study candidates. Patients will be enrolled consecutively and randomized per protocol as they present to Children's Healthcare of Atlanta.

The parent(s) or legal guardian of the neonate will be approached on a day prior to surgery by the principal investigator, or a member of the IRB approved study team to discuss the goals, benefits and risks of the project. A thorough discussion between the parent(s) or legal guardian and the IRB approved study team will occur during the study consent process. Written informed consent will be obtained following this discussion.

For the occasions when parent(s) or legal guardian does not arrive at the hospital until the day of surgery, they will be approached only if there is sufficient time to allow for their full consideration. No study related procedure will occur prior to obtaining appropriate informed consent.

Patients undergoing emergent/urgent procedures or when there is insufficient time for the parent(s) or legal guardian to fully consider the goals, benefits and risks of this project will not be approached for enrollment.

Study Description:

This study is a prospective, randomized trial designed to evaluate the role of fibrinogen concentrate versus cryoprecipitate in reducing allogenic donor exposures in infants undergoing cardiac surgery with CPB. Prior to surgery, we will randomize infants undergoing cardiac surgery to receive cryoprecipitate (standard of care) or fibrinogen concentrate (study arm) as part of a post-bypass transfusion algorithm.
For patients enrolled in the study, we will follow our standard anesthetic management, cardiopulmonary bypass protocol, and transfusion thresholds in the operating room and ICU.

In each patient, results from our standard of care labs will be obtained at seven different time points:

1) Preoperative labs (for outpatients, preoperative baseline labs are obtained in the preoperative clinic; for inpatients, baseline labs are obtained in the hospital the day before surgery) (CBC, Coagulation tests, Fibrinogen, Chemistry),
2) After induction of anesthesia but prior to surgical incision (ABG, TEG),
3) 10min after initiation of CPB (TEG, Fibrinogen, ABG),
4) After termination of CPB, protamine reversal and first cryoprecipitate/FC administration (ABG, TEG, fibrinogen),
5) After chest closure or placement of silastic patch if chest remains open (ABG, TEG),
6) Coagulation labs on immediate arrival to the ICU as per ICU protocol (ABG, Fibrinogen, Coagulation studies, CBC, Chemistry), and
7) On the morning of the first post-operative day in the ICU as per ICU protocol (fibrinogen, ABG, coagulation studies, chemistry, CBC).

Blood samples drawn prior to surgery (i.e time number 1) will be done either by our clinical laboratory for outpatients or by hospital protocol for inpatients. For all other time points, blood samples will be drawn from an indwelling line placed for the surgery.

After separation from bypass, patients will receive either cryoprecipitate or FC, depending on their randomization group. For patients randomized to the study arm, the fibrinogen level measured on bypass will be used to calculate the appropriate dose of fibrinogen concentrate to achieve a level of 300mg/dL after separation from bypass. In these patients, FC will replace cryoprecipitate in our post-bypass transfusion algorithm

for the first dose only. If a patient in either arm continues to have post-bypass bleeding, the anesthesiologist will use point of care testing and the transfusion algorithm to determine appropriate products for transfusion. Patients on the study arm will only receive the initial dose of FC; cryoprecipitate should be used for subsequent low fibrinogen levels.

Data regarding patient demographics, CPB variables, intraoperative and post-operative laboratory values, intraoperative and post-operative transfusion requirements, chest tube output, adverse events, length of ventilation time, ICU and hospital length of stay will be recorded and maintained in a HIPPA secure database.

Fibrinogen Concentrate (RiaSTAP) Dose:

Hypofibrinogenemia is one of the main reasons for the perioperative coagulopathy in major pediatric surgeries. This hemostatic derangement is amplified in the pediatric population undergoing cardiac surgery due to the hemodilutional effects of the cardiopulmonary bypass machine. Therefore, post-bypass transfusion guidelines often include cryoprecipitate to maintain an adequate fibrinogen level.

Haas et al (10) found that maintaining a higher fibrinogen concentration level (FIBTEM <13mm vs <8mm) significantly decreased bleeding and transfusion requirements for patients undergoing craniosynostosis (median age 10months), but not scoliosis patients (mean age 12 years). Brown et al (7) recently demonstrated that clots formed with neonatal fibrinogen are more porous and less dense than adult clots. The addition of adult fibrinogen to neonatal fibrinogen in higher concentrations creates a more three-dimensional structure than neonatal fibrinogen alone. Using these studies and our historical data that neonates undergoing cardiac surgery had a median post-operative fibrinogen level of 345mg/dL (258-469) (unpublished data), we chose to target a post-transfusion fibrinogen level of 300mg/dL.

Fibrinogen Concentrate (RiaSTAP)

Fibrinogen concentrate can be dosed two ways. For unknown fibrinogen levels, the RiaSTAP dose is 70mg/kg. However, the dose of FC can be calculated to reach a target fibrinogen level.

Dose = (Target Level-Measured Level)/1.7 x weight (kg)

As we have chosen a target fibrinogen level of 300mg/dL, we will use the above equation to calculate the RiaSTAP dose for each patient in the study arm. In order to account for the hemodilutional effects of the bypass prime on fibrinogen levels, the "measured level" will be the fibrinogen level measured after 10min on the CPB machine, time point #2.

Specific Aim #1:

Rational: The goal of Aim #1 is to determine if fibrinogen concentrate can decrease overall allogenic donor exposure in infants undergoing CPB surgery. By targeting a higher level of fibrinogen, we hope to mitigate the effects of the acquired hypofibrinogenemia in post-bypass coagulopathy, while also decreasing the hemodilutional effects of additional blood products during post-bypass transfusion. As massive transfusion in infants is associated with worse outcomes, we hope that reducing transfusions will reduce the short and long term risks associated with allogenic donor exposures.

Specific Aim #2:
By evaluating the laboratory values, transfusion requirements, and short-term outcomes, we will examine the effectiveness of FC in post-bypass hemostasis. We will evaluate hematocrits, fibrinogen levels, and thrombelastogram values to determine if FC is at least as effective as the standard of care in post-bypass transfusion management. Secondly, we will evaluate secondary outcomes to determine if FC can decrease transfusion related risks such as increased mechanical ventilation, prolonged ICU/hospital stays, infection risks, and thrombosis.

Sample Size/Statistical Analysis

The primary aim of this study is to determine if fibrinogen concentrate can decrease allogenic donor transfusions in infants undergoing cardiac surgery with cardiopulmonary bypass in patients when compared with the current standard of care, cryoprecipitate. Therefore, we analyzed our blood product transfusion data from CHOA in infants requiring CPB. We counted the number of units of packed red blood cells (PRBCs), fresh frozen plasma (FFP), cryoprecipitate, and platelets the patient received. Each unit was counted as one donor exposure. On average, the patients had nine donor exposures. We propose replacing two units of cryoprecipitate with fibrinogen concentrate will result in a 20% reduction in donor exposures. In order to achieve a power of 0.9, we plan to enroll 15 patients in each arm, for 30 patients at this institution.

The Quantitative Statistical Unit at Stanford University will provide assistance with data management, conducting data analyses, and interpreting statistical results. Continuous variables will be compared by analysis of variance and will be presented as mean $\pm$ standard variation if normally distributed or by median (IQ range) if non-normally distributed. Nominal variables will be compared by chi-squared analysis or Fisher's exact test. Significance will be defined as a p-value less than or equal to 0.05.

Adverse Events Reporting

Monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs) is an important aspect of data collection. The study subjects will be reviewed on a case-by-case basis. The principal investigator will determine the seriousness of each adverse event and whether or not the event was related to the study.

After enrollment, the principal investigator or designee will collect the adverse experiences from the medical record. Serious adverse Events (life-threatening, requiring intervention) will be reported to the IRB within the guidelines set by the IRB.

The risk of Fibrinogen concentrate administration is low, but adverse events include headache, fever, chills, allergic reaction, or thrombosis. The risks are comparable to the administration of cryoprecipitate.

Data Safety Monitoring Plan

A potential risk of this study is related to drug reactions including fever, chills, headache, allergic reactions, or thrombosis. This medication has been used extensively in Europe and as part of transfusion algorithms around the United States. Based on this data and the need to minimized transfusions in the infant population undergoing cardiac surgery with CPB, the FDA has granted an IND exemption for use of this medication in this randomized, control trial.

The study subjects will be reviewed on a case-by-case basis by the PIs at each institution and quarterly at a committee of experienced cardiac anesthesiologists not involved in the study for review of each study subject for potential adverse events and whether or not the event was related to the study.

A second risk of this study is patient confidentiality since protected health information is included in the study data. This risk will be minimized by only recording information absolutely necessary to fulfill the study's objectives. Information directly identifying patients will be excluded (names, addresses, telephone numbers, social security numbers, email addresses, and account numbers). A unique study number will identify the study subjects. The study information will be collected and stored in a password-protected database. Consents, along with the code linking a subject's identity to an assigned number, will be locked in the office of the principal investigator or designee.

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