Title: Comparison of Fibrinogen Concentrate and Cryoprecipitate in Pediatric Cardiac Surgery Patients

NCT04376762

Document Date: 8/5/2020

PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

INSTRUCTIONS

- This should include a referenced systematic evidenced-based review when possible.
- If this study involves qualitative research explain the major constructs of your study.
- Do not state in this section what you plan to do in this study. This information should be entered later under "What will be done in this protocol?"
- Do not include the bibliography in this section.
- For studies submitted under the Expedited review criteria, this section need not be more than a few paragraphs.
- For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/ procedures/data points.
- If this is a FIVE YEAR UPDATE make sure the information throughout the protocol includes the most current information.

Answer/Response: Postoperative bleeding in children undergoing cardiac surgery is a common complication that is associated with increased morbidity and mortality. While life saving during acute bleeding, the transfusion of red blood cells (RBC) and other blood-derived coagulation factors may be associated with serious postoperative complications such as infections, acute kidney injury, thromboembolic events, immunomodulation, volume overload (transfusion-associated cardiovascular overload, TACO) and lung injury (transfusion-related acute lung injury, TRALI) that can result in significant morbidity and mortality. Therefore, a significant effort is being invested in patient blood management strategies that will incorporate point-of-care-based transfusion algorithms and the use of novel coagulation concentrates in an attempt to reduce postoperative bleeding and need for allogeneic blood product transfusions after cardiac surgery[1].

Acquired fibrinogen deficiency is believed to be one of the key factors contributing to coagulopathy after cardiopulmonary bypass (CPB). Fibrinogen is the most abundant clotting factor in the human circulation and it plays a crucial role in hemostasis by promoting platelet aggregation and clot polymerization. However, it is also the first factor to be depleted during cardiac surgery, as there is no extra-vascular storage of fibrinogen[2]. During cardiopulmonary bypass, fibrinogen levels may fall to 40-50% from baseline[3] as a result of acute bleeding, hemodilution due to priming of the CPB circuit, consumption due to activation of the coagulation cascade and increased breakdown (hyperfibrinolysis). Thus, in post-CPB bleeding patients with low fibrinogen levels, replenishment of fibrinogen may be indicated to achieve adequate hemostasis[4].

Until recently, the only option for fibrinogen supplementation in the USA for patients with hypofibrinogenemia (either congenital or acquired) was the transfusion of cryoprecipitate. As such, the standard of care fibrinogen replenishment in bleeding

surgical patients with acquired fibrinogen deficiency is cryoprecipitate transfusion. Recently, however, the use of purified human fibrinogen concentrate (FC) has been approved in the USA and in Canada and its use in bleeding cardiac surgery patients has significantly increased[5] and is recommended by transfusion guidelines in cardiac surgery patients [6,7]. As such, UVA Medical Center has recently approved the use of fibrinogen concentrate as an alternative to cryoprecipitate in bleeding adult and pediatric surgical patients (including cardiac surgery patients).

FC is a lyophilized, nano-filtered and pathogen reduced and inactivated human fibrinogen concentrate with a constant content of 900-1300 mg/vial (final concentration 20g/L). While cryoprecipitate is still in use in North America, it is not available in Europe (except for the UK) due to safety concerns, as it does not undergo pathogen reduction and inactivation. FC has several important potential advantages over cryoprecipitate including: standardized fibrinogen content, higher purity, faster preparation without need for blood bank processing or cross-matching (which also eliminates the risk of human-related transfusion errors), improved safety via pathogen reduction, avoidance of transfusion related acute lung injury (TRALI) and significantly decreased volume of transfusion (which may be particularly important in children with congenital heart diseases as they may be intolerant to excessive volume overload). Yet, cryoprecipitate may be a better hemostatic agent as it also contains factors VIII and XIII, fibronectin, von Willebrand factor and platelet microparticles, all of which are important for normal hemostasis in bleeding patients. Hence it is not known whether FC will provide hemostatic efficacy similar to cryoprecipitate in bleeding pediatric cardiac surgery patients.

Initial studies evaluating the use of FC in cardiac surgery patients reported conflicting results[8-11]. Surprisingly, several studies failed to report a benefit with the use of FC mainly due to enrollment of patients who did not have low fibrinogen levels [8,12]. A recent large randomized controlled study in adult cardiac surgery patients, however, demonstrated non-inferiority of FC compared to cryoprecipitate in bleeding cardiac surgery adult patients with low fibrinogen levels (and as a matter of fact FC was found to be superior over cryoprecipitate in regard to several outcome measures)[5]. Hence it seems that FC may be a better alternative for fibrinogen supplementation in bleeding cardiac surgery patients compared to cryoprecipitate.

Despite the growing data about the potential advantages of the use of FC in adult cardiac surgery patients, it is not yet known, however, whether the use of FC in pediatric cardiac surgery patients may offer similar advantages. A recent prospective randomized study by Downey et al[13] compared the use of FC to cryoprecipitate in pediatric patients undergoing cardiac surgery. Although there was no difference in postoperative bleeding between the study groups, children in the FC group received significantly less allogeneic blood products compared to patients who received cryoprecipitate. Some of the patients, however, also received prothrombin complex concentrate – a potent mixture of vitamin K–dependent clotting factors, which may complicate the interpretation of the results. Furthermore, the standard of care at the UVA Medical Center, as well as in other pediatric cardiac surgery institutions, is to prime the cardiopulmonary bypass pump only with RBCs without adding FFP (which is different than in the Downey paper). This results in a much more significant hemodilution that may lead to a higher risk of postoperative bleeding.

Taken together, there is a growing body of evidence supporting the use of fibrinogen concentrate as an alternative for cryoprecipitate in adult cardiac surgery patients, however, there is insufficient data in the literature to determine whether FC may be a comparable (or even a superior) alternative to cryoprecipitate for fibrinogen supplementation after pediatric cardiac surgery. Therefore, we propose a single-institution, prospective randomized pilot study to compare the use of FC (Fibryga, Octapharma USA, Hoboken, NJ, USA) to cryoprecipitate in pediatric cardiac surgery patients with postoperative bleeding and low fibrinogen levels. If FC is found to offer similar hemostatic efficacy as cryoprecipitate it may be a much better alternative for fibrinogen supplementation in bleeding pediatric cardiac surgery patients given its higher safety profile.

Objectives/Hypothesis

INSTRUCTIONS:
If this study involves biomedical research clearly state the objectives and hypotheses and clearly define the primary and any secondary outcome measures. If this study involves qualitative research clearly state your research hypothesis or question.

This section should not include information already included in other sections such as background information or information from the procedures section.

Answer/Response: Our hypothesis is that fibrinogen concentrate will be as effective as cryoprecipitate in achieving adequate hemostasis after separation from CPB in pediatric cardiac surgery patients.

Study Design: Biomedical

1. Will controls be used?
Answer/Response: Yes

►IF YES, explain the kind of controls to be used.
Answer/Response: active comparator

2. What is the study design?

Example: case series, case control study, cohort study, randomized control study, single-blind, double-blind, met-analysis, systematic reviews, other. You may also view the IRB-HSR Learning Shot on this topic to help you answer this question. (http://www.virginia.edu/vpr/irb/learningshots/Writing_protocol_June09/player.html

Answer/Response: this will be a single-center, prospective, randomized, active-control study in pediatric (age < 24 months) patients undergoing elective cardiac surgery with CPB in-whom fibrinogen supplementation after separation from CPB is indicated, based on the presence of clinically-significant bleeding and documentation of low fibrinogen level on viscoelastic point-of-care testing (MCF < 10 mm on the FIBTEM assay of ROTEM)

3. Does the study involve a placebo?

Answer/Response: No

►IF YES, provide a justification for the use of a placebo

Answer/Response:

Human Participants

Ages: __under 24 months of age__

Sex: **__male or female__**

Race: **__any__**

Subjects- see below

INSTRUCTIONS: For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.

1. Provide target # of subjects (at all sites) needed to complete protocol.

INSTRUCTIONS: If this is NOT a database protocol, this number should be the same as the number of subjects needed to obtain statistically significant results.

Answer/Response: 30 total with 15 in each arm

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

Answer/Response: 5%

3. How many subjects will be enrolled at all sites?

INSTRUCTIONS: This number must be the same or higher than the # from question # 1 in order to account for the # of screen failures, dropouts, withdrawals described in question # 2.

Answer/Response: 32

4. How many subjects will sign a consent form under this UVa protocol?

INSTRUCTIONS: If the protocol does not have a consent form- the number listed here should reflect such things as the number of subjects from whom specimens will be obtained, the number of charts to be reviewed etc.

Answer/Response: 32

Inclusion/Exclusion Criteria

INSTRUCTIONS:

- The inclusion and exclusion criteria should be written in bullet format.
- *This item applicable if the study will require consent (verbal or written).* Unless there is a scientific reason for not recruiting a certain type of vulnerable population(e.g. not

enrolling fetuses, neonates or children in a study regarding Alzheimer's) list the following vulnerable populations under either Inclusion or Exclusion criteria below: pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non- English speaking subjects .

- If you will not enroll subjects who do not speak English because certain procedures cannot be carried out if the subject does not speak English (e.g. a survey is not validated in other languages) insert the following as an Inclusion Criteria: Willingness and ability to comply with scheduled visits and study procedures.
- If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
- The stop date must be prior to the version date of this protocol.
- *Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion

Answer/Response:

- pediatric (age < 24 months) patients undergoing elective cardiac surgery with CPB in-whom fibrinogen supplementation after separation from CPB is indicated, based on the presence of clinically-significant bleeding and documentation of low fibrinogen level on viscoelastic point-of-care testing (MCF < 10 mm on the FIBTEM assay of ROTEM).

2. List the criteria for exclusion

Answer/Response:

- refusal to participate in the study,
- known severe allergic reaction/anaphylaxis to fibrinogen concentrate,
- administration of FC or cryoprecipitate in the 24 hours prior to surgery and
- baseline fibrinogen level higher than 300 mg/dL (to avoid the risk of increasing the fibrinogen level above the normal upper level of 400 mg/dL)

3. List any restrictions on use of other drugs or treatments.

Answer/Response: None

Statistical Considerations

1. Is stratification/randomization involved?

Answer/Response: Yes

►IF YES, describe the stratification/ randomization scheme.

INSTRUCTIONS:
The stratification factors and/or the randomization plan should be identified. If there is no randomization component or important patient characteristics that will be used in treatment allocation or data analysis, a statement to this effect should be included.

Stratification factors: These are pretreatment patient characteristics which could be balanced across treatment arms by design or may be used to determine starting dose or treatment allocation.

If randomization is going to be used, the details of the randomization plan should be described.

The description should include:
--the method and timing of randomization
--the type of randomization scheme that will be used in the study
--whether or not the randomization masked/blinded/if so, then to whom is it masked/blinded
--who has access to the randomization scheme

Answer/Response:

- Once the need for fibrinogen supplementation is confirmed after separation from CPB, patients will be randomized into one of two treatment groups (n=15 in each group):
  1. Cryoprecipitate group (dose: 10 ml/kg; active control group) or
  2. Fibrinogen Concentrate group (dose: 70 mg/kg; intervention group).
- 1:1 randomization unblinded using a computer generated randomization list

►IF YES, who will generate the randomization scheme?

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
_____ UVa Investigational Drug Service (IDS)
__x___ Other*:* Specify Answer/Response: computer generated by the CRC

2. What are the statistical considerations for the protocol?

The objectives section and the statistical section should correspond, and any objective for which analysis is unfeasible should be deleted. Also, the estimates and non-statistical assumptions of the statistical section should be supported by discussion in the background section.

The answer to this question should include:
--Study Design/Endpoints
--Recap of study objectives and endpoint definitions. An assessment of how study objectives will be assessed by identifying & defining which endpoints will be used to assess each component of the study objectives.
--The study design should include contingencies for early stopping, interim analyses, stratification factors (If applicable), and any characteristics to be incorporated in analyses.
--The power/precision of the study to address the major study endpoint(s), the assumptions involved in the determination of power/precision.

--If statistical hypothesis testing is included then specify the null and alternative hypotheses, the test statistic, and the type I and II error rates
--If precision of an estimate, then provide a definition for precision
--If other, then specify

Answer/Response: Baseline clinical and demographic characteristics, follow-up measures, and clinical outcomes will be compared on an intention-to-treat basis according to the randomized study group assignment. Continuous variables will be compared using the Student *t* test for normally distributed variables or the Mann-Whitney *U* test or Wilcoxon matched-pairs signed-rank test for non-normally distributed variables. Categorical variables will be compared using the Pearson χ^2 test or Fisher exact test as appropriate. We estimate that 30 patients would be needed (15 in each study arm) to determine that an exposure to 2 additional allogeneic blood products will be statistically significant (C.I. 95%) providing 80% power with a type I error probability $\alpha = 0.05$ (including 20% dropouts/withdrawals from the study)

3. Provide a justification for the sample size used in this protocol.

Include sample size calculations or statistical power estimation. If not applicable, please provide explanation.
Also include the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate, adjustments for drop-outs etc. and study duration.

Answer/Response: This is a pilot study and no power analysis was performed. We anticipate enrollment in 2 years.

4. What is your plan for primary variable analysis?

Include primary outcome(s)/predictor variable(s), statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation.

Answer/Response:
Outcomes: the primary outcome of the study will be any allogeneic blood transfusion within the first 24 hours after administration of the FC or cryoprecipitate.

5. What is your plan for secondary variable analysis?

Include the following:
--Secondary outcome(s)/predictor variables, statistical methods/models/tests to be employed, or descriptive summaries as appropriate. If not applicable, please provide explanation.
--For phase III studies, the power/precision of the study to address the secondary objective(s).

Answer/Response: Secondary outcomes will include: administration of individual blood products (RBC, platelets, FFP, cryoprecipitate) over the initial postoperative 48 hours and up to 7 days after surgery, bleeding over the first postoperative 48 hours (intraoperatively = cell saver volume; postoperatively = chest drain/s output), the need for surgical re-exploration for hemostasis over the first postoperative 48 hours, the use of recombinant factor VIIa as rescue for refractory bleeding in the first 48 postoperative hours, length of ICU stay, hospital length of stay, thromboembolic complications over the first seven postoperative days and a 30-day composite of AKI, stroke, severe myocardial dysfunction or myocardial infarction, sepsis and

mortality (or until discharge whichever is earlier).

6. Have you been working with a statistician in designing this protocol?

Consultation with a professional statistician is highly recommended to ensure good science of the study and facilitate the review process.

Answer/Response: Yes

IF YES, what is their name?
Answer/Response: Jennie Z Ma

7. Will data from multiple sites be combined during analysis?
Answer/Response: No

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?
Answer/Response:

IF YES, will randomization be done at each site or among sites?
Answer/Response:

7(b). Has the sample size calculation considered the variation among sites?
Answer/Response:

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?
Answer/Response:

7(d). Is there a common protocol used in all sites?
Answer/Response:

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?
Answer/Response:

Study Procedures-Biomedical Research

1. What will be done in this protocol?

INSTRUCTIONS:
This should include everything that will be done as part of this protocol. Do not repeat information that is included in other sections such as Background or Hypothesis sections.
This section should include an indication of which research interventions if any offer a prospect for direct benefit and which interventions (invasive measurements, collection of blood, tissue, data, surveys, etc.) are being done solely to answer a research question and generate generalizable knowledge. If the interventions done solely for research purposes are associated with greater than minimal risk they need to be justified.

Describe and justify any control and experimental arm and include method, dose, and duration of drug administration. Reference any claim of clinical equipoise if applicable.

If you are obtaining specimens or data, provide information regarding the type of specimen/data, amount of specimen needed and how the specimen/data will be obtained and what analysis will be done with the specimen/data.

Special note for studies with waiver of consent/waiver of documentation of consent: Include a statement regarding how subjects will be recruited. For other studies this information is captured in Recruitment does not need to be duplicated in this section.

Answer/Response:
The parent/ legal guardian will be consented at a clinic or hospital visit prior to surgery by study staff and will include the Peds Cardiac NP they are familiar with when possible. Subjects will be monitored for 48 hours for the need for fibrinogen supplementation

Once the need for fibrinogen supplementation is confirmed in the OR or PICU, subjects will be randomized into one of two treatment groups (n=15 in each group):

1. Cryoprecipitate group (dose: 10 ml/kg; active control group) or
2. Fibrinogen Concentrate group (dose: 70 mg/kg; intervention group) single dose.

Administration of the study drug is via transfusion.

There will be no placebo group since withholding treatment is neither consistent with standard of care nor acceptable ethically.

No other aspects of care will be modified.

In the event that a second round of fibrinogen supplementation is required (bleeding with documented hypofibrinogenemia) participants will receive either FC or cryoprecipitate based on their initial randomization. If any additional fibrinogen supplementation is then needed (after the first 2 supplementation doses), cryoprecipitate will be administered to all subjects per standard of care (including those who received FC).

Data to be obtained:
1. Demographic/preoperative data: collected from the medical record
- age in days/months (all patients to be younger than 24 months)
- gender
- weight
- preoperative diagnosis
- surgery type & date (Norwood, arterial switch, truncus arteriosus, Glenn, Fontan, TAPVR, AV canal, tetralogy of Fallot, etc)
- preoperative standard of care labs PT/aPTT/INR/hgb level/ hematocrit/ platelet count/

fibrinogen level (if exists)/ creatinine

2. Intra-operative Data: collected from the medical record
- CPB time & aortic cross clamp time
- use of hypothermic circulatory arrest (ice packs placed on the head)
- was post-CPB ultrafiltration performed?
- Platelet count prior to separation from CPB
- was ATIII administered? (thrombate)
- Transfusion requirements: PRBC/Cell Saver/FFP/PLT/ cryo - to be collected as number of units per each product, not volume. (for PLT - was it pooled PLT or single donor apheresis, if possible)
- was rFVIIa given (factor seven, novoseven). Please pay attention - the fact that rFVIIa was ordered DOES NOT mean that was actually administered as we order factor VII for ALL big cases (to have available in the OR) but not necessarily administer it
- Need for ECMO
- Was the chest left open? (always in ECMO, but open chest does not necessarily mean ECMO)

ROTEM (clotting labs) will be drawn for research purposes after admission and after administration of the study treatment: Extem (CT/A10/A20/MCF); Fibtem (A10/A20/MCF) and fibrinogen. The blood drawn for this will be obtained through an existing line, put into place as part of the subject's usual care.

3. Postoperative Data (PICU, up to 48 hours after surgery) collected from the medical record
- admission PT/aPTT/INR/platelet count/ fibrinogen level/ hgb level/HCT level (could be obtained from initial ABG)
- Bleeding (Chest drain/s output)
- Need for additional transfusion (PRBC/cell saver/FFP/platelets/cryoprecipitate). Will need to know, if possible, whether transfused from same unit that was already exposed to in the OR or new unit (= new exposure)
- Factor VIIa administration
- re-exploration? (= starting ECMO in the PICU)
- delayed chest closure? (will answer whether went to PICU with chest open)

2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.

Example: If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
Instructions: Answer NA if this study does not involve a study treatment.

Answer/Response: There is no transition from study treatment.

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
   (e.g. study team will administer study drug/ study interventions, study drug inventory of dispensed and returned drug, diary etc.)
   Answer/Response: Study team/ anesthesiologist / PICU staff will administer study drug and document administration in EPIC

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
   (e.g. subject returns more than 20% of the study drug, subject misses 20% of study visits)
   Answer/Response: Not applicable

Bibliography

INSTRUCTIONS: Provide a current bibliography supporting the hypothesis, background and methodology including references to papers and abstracts that have resulted from previous work by the investigator and references to the work of others.

1. Faraoni D, Meier J, New HV, Van der Linden PJ, Hunt BJ. Patient Blood Management for Neonates and Children Undergoing Cardiac Surgery: 2019 NATA Guidelines. J Cardiothorac Vasc Anesth 2019;33:3249-63.
2. Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion 2014;54:1389-405.
3. Edmunds LH, Jr. Managing fibrinolysis without aprotinin. Ann Thorac Surg 2010;89:324-31.
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5. Callum J, Farkouh ME, Scales DC, et al. Effect of Fibrinogen Concentrate vs Cryoprecipitate on Blood Component Transfusion After Cardiac Surgery: The FIBRES Randomized Clinical Trial. JAMA 2019:1-11.
6. Raphael J, Mazer CD, Subramani S, et al. Society of Cardiovascular Anesthesiologists Clinical Practice Improvement Advisory for Management of Perioperative Bleeding and Hemostasis in Cardiac Surgery Patients. Anesth Analg 2019;129:1209-21.
7. Erdoes G, Koster A, Meesters MI, et al. The role of fibrinogen and fibrinogen concentrate in cardiac surgery: an international consensus statement from the Haemostasis and Transfusion Scientific Subcommittee of the European Association of Cardiothoracic Anaesthesiology. Anaesthesia 2019;74:1589-600.
8. Rahe-Meyer N, Levy JH, Mazer CD, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. Br J Anaesth 2016;117:41-51.

9. Ranucci M, Baryshnikova E, Crapelli GB, et al. Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. J Am Heart Assoc 2015;4:e002066.
10. Rahe-Meyer N, Solomon C, Hanke A, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. Anesthesiology 2013;118:40-50.
11. Rahe-Meyer N. Fibrinogen concentrate in the treatment of severe bleeding after aortic aneurysm graft surgery. Thromb Res 2011;128 Suppl 1:S17-9.
12. Bilecen S, de Groot JA, Kalkman CJ, et al. Effect of Fibrinogen Concentrate on Intraoperative Blood Loss Among Patients With Intraoperative Bleeding During High-Risk Cardiac Surgery: A Randomized Clinical Trial. JAMA 2017;317:738-47.
13. Downey LA, Andrews J, Hedlin H, et al. Fibrinogen Concentrate as an Alternative to Cryoprecipitate in a Postcardiopulmonary Transfusion Algorithm in Infants Undergoing Cardiac Surgery: A Prospective Randomized Controlled Trial. Anesth Analg 2020;130:740-51.