Optimized administration of Prothrombin complex concentrate (PCC) vs. Standard Transfusion during/after Heart Transplantation – OPSTAHT (August 13, 2017)

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Comparative Clinical and facoeconomic Trial

Name of Product: Kcentra

Name of Active Ingredient: Human Plasma-derived Prothrombin Complex Concentrate

Title of Study: A Comparative Study of Kcentra vs. Standard Transfusion for Patients undergoing Heart Transplantation

NCT Number: NCT03341156

Study Site: University of Maryland Medical Center
University of Pittsburgh Medical Center

Objectives: Compare clinical success and costs in two treatment groups:

1. Group A: Those who will be randomized to receive Kcentra, a four factor prothrombin complex concentrate
2. Group B: Those who will be randomized to receive standard transfusion (plasma)

Methodology: A randomized, prospective, open-label, active drug controlled study in patients undergoing heart transplantation

Number of Patients: 60 (30 x 2 years)

Criteria for Inclusion: Be willing and able to provide written informed consent

Be at least 18 years of age

Patients with or without ventricular assist device (VAD) undergoing heart transplantation

Patients who have been on warfarin till at least 72 hours before cardiopulmonary bypass procedures for heart transplantation

Patients should fulfill the following parameters prior to the study intervention:
— International normalization ratio (INR) $\geq$1.5
— Body temperature > 35.0°C
— Blood pH > 7.2
— Hb > 7.0 mg/dL

Criteria for Exclusions:

$P2Y_{12}$ antagonist (clopidogrel, prasugrel, ticagrelor) administration in the 5 days preceding study surgery

Known or suspected thrombophilia such as factor V Leiden, Hereditary antithrombin III deficiency, Heparin-induced thrombocytopenia, disseminated intravascular coagulation

Ischemic or thromboembolic events within 6 weeks

Known allergy/anaphylaxis to prothrombin complex concentrate or albumin

Any indication that a potential subject did not comprehend the study restrictions, procedures, or consequences therein an informed consent cannot be convincingly given

Patients on respiratory support including extracorporeal membrane oxygenation (ECMO)

Life expectancy less than 48 hours

Test product, Dose, Mode of Administration:

Kcentra will be administered in 2 divided doses; Pre-bypass (5-10 units/kg based on body weight and preoperative INR and post-protamine (see the table for dosing); daily maximum dose not to exceed 5000 IU (50 IU/kg)

Reference therapy, Dose, Mode of Administration:

Plasma will be administered in 2 divided doses, 2 U intravenously before cardiopulmonary bypass (CPB), then up to 4-8 U of plasma added to the CPB reservoir during rewarming

Criteria for Evaluation: The primary clinical endpoint includes postoperative 24-hour chest tube drainage volume.

Secondary endpoints for evaluation:

Red Blood Cells Intraoperatively

- Total amount of red blood cells given from start of first intervention until start of 2nd intervention
- Total amount of red blood cells given after 2nd intervention (post bypass) until patient out of room time

Red Blood Cells Postoperatively

- Total amount of red blood cells given post-operatively (patient out of room time) until 24 hours after
- Total amount of red blood cells given from 25 hours postoperatively (25 hours after patient out of room time) until 30 days or hospital discharge, whichever occurs first

Postoperative INR value

- 30 minutes after the end of the last study intervention

Intraoperative and Postoperative total hemostatic blood product use

- Plasma, fresh-frozen plasma or thawed plasma
- Platelets
- Cryoprecipitate
- Recombinant activated factor VII (rFVIIa)

- Blood product use intraoperatively = OR entry to OR out of room time
- Blood product use postoperatively #1 = patient out of room time to 24 hours later
- Blood product use postoperatively #2 = 25 hours post operatively until 30 days or hospital discharge, whichever occurs first

Plasma coagulation factor levels and thrombin generation

- At baseline, post-bypass/pre-protamine, 30 minutes post-protamine, and 12-24 hours post treatment

Re-exploration for bleeding directly related to heart transplant surgery within 30 days postoperative or until hospital discharge, whichever occurs firsts

Which of these occur within 30 days post-operation or until hospital discharge if that occurs first

— Need for circulatory support (ECMO or VAD)
— Mechanical ventilation >72 hours or tracheostomy
— Renal failure requiring dialysis

Sepsis Serious infection morbidity consisted of sepsis syndrome, septic shock, or mediastinitis. In addition, the diagnosis of sepsis included organisms isolated from the cultures along with elevated temperature and white blood cell counts.

— In-hospital and 30-day mortality

- Stroke or postoperative neurological dysfunction (seizures, delirium, unconsciousness, encephalopathy)
- Gastrointestinal complication requiring bowel resection
- Peripheral vascular complication requiring surgery (thrombectomy, bypass and amputations)
- Deep vein thrombosis and pulmonary Thromboembolism

- Adverse Events

Pharmacoeconomic: Pharmacoeconomic outcomes to be evaluated include:

— Direct Costs: Acquisition costs for test agents and blood bank related charges (thawing, etc.)

— Total surgical time
— Time to hospital discharge
— Time to ICU discharge

--- Indirect costs:Extra costs related to management of volume overload and other complications related to plasma

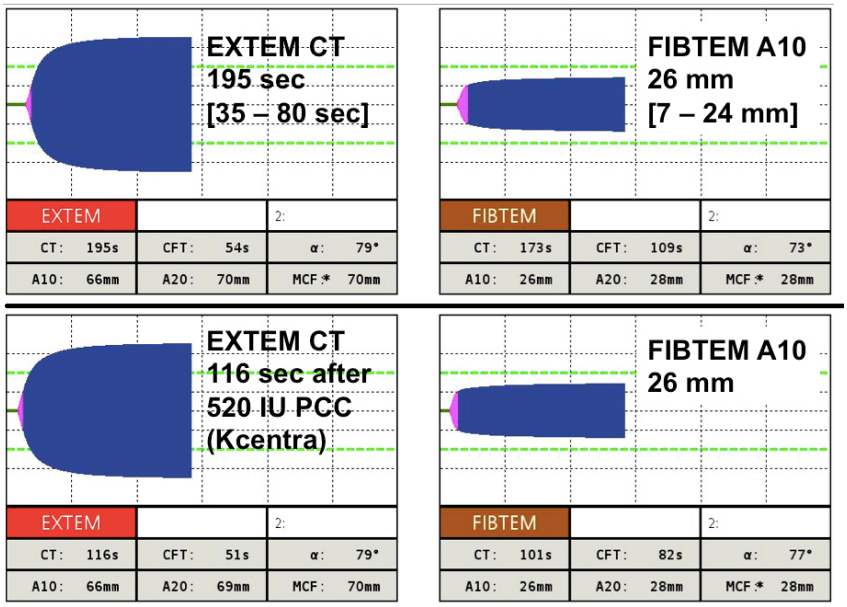
transfusion

Statistical Methods: The initial analysis will be conducted using descriptive statistics and confidence intervals. All clinical pharmaco-economic endpoints will be tabulated and statistically analyzed. Characteristics between the two treatment groups will be compared using an independent group t-test (for means) and Chi-squared test or Fisher's exact test (for percentages).

Background and Rationale

Heart transplantation is a surgical procedure at increased hemorrhagic risk because it typically involves patients on warfarin, and with prior cardiovascular surgery including a placement of ventricular assist device. Extensive surgical dissections/anastomoses, prolonged cardiopulmonary bypass (CPB) with temperature changes, and extensive hemodilution lead to moderate to severe post-operative coagulopathy.[1] The incidence of re-exploration for bleeding is as high as 20% with the standard transfusion approach, and the use of recombinant activated factor VII (rFVIIa) is not uncommon.[2,3] Plasma transfusion has been the mainstay hemostatic intervention for bleeding after CPB, but patients with compromised cardiovascular systems are prone to volume overload (12% incidence after the median 2 U of plasma).[4] There is keen interest in the use of PCC as more effective, low-volume hemostatic intervention. A number of case series, and single-center studies have indicated the potential usefulness of PCC in high-risk cardiac surgery (**Table 1**).[5-10] PCC is usually administered to fully reverse warfarin anticoagulation prior to surgical incision.[11] However, the optimal dosing scheme in cardiac surgery is unknown because of the use of heparin anticoagulation, and unpredictable pharmacokinetics during CPB. Indeed, our computational model previously indicated that a full-dose of PCC (~25 IU/kg) before CPB may be less efficacious in maintaining thrombin generation compared to the dosing schemes in which majority of PCC is given after CPB.[12] In the beginning of surgery, even 5-10 IU/kg of PCC can improve hemostasis because fibrinogen levels are usually high, and platelets are capable of supporting thrombin generation (**Fig. 1**). Conventionally, 2 U of plasma transfusion is empirically given to heart transplant patients with the intention to partially reverse warfarin. A clinical validation study to optimize PCC administration in heart transplantation is clearly needed to improve the resource utilization, and the safety of hemostatic interventions.

Figure 1. Effects of PCC on thromboelastometry



EXTEM clotting time (CT) was shortened after 520 IU of PCC in a patient with INR 3.0 undergoing heart transplantation

PCC (Kcentra, CSL Behring) is an FDA-approved, human plasma derived product for the treatment of acute bleeding episodes, and for the prevention of (surgical) bleeding in patients on warfarin anticoagulation.[11,13,14] It is a concentrated, lyophilized powder, stored at room temperature that can be reconstituted immediately prior to use. It has a 36-month shelf life and does not require ABO-matching. It contains no liquid plasma allowing for low volume infusion and quick administration. Kcentra undergoes several viral inactivation/reduction steps, and therefore, substantially increasing the cumulative virus reduction by several logs (varies by specific virus).[14] Kcentra contains a small amount of heparin and antithrombin, and is contra-indicated in patients with heparin allergy or heparin-induced thrombocytopenia.

2. Comparator Rationale

In this study, warfarin-treated patients with INR>1.5 undergoing heart transplantation will be randomized to receive (open label) either plasma (total, 6-10 U) or PCC (total, 25-35 IU/kg) in divided doses **(5-10 IU/kg before CPB and 20–25 IU/kg after CPB; rounded to the nearest vial) per dosing schedules below** (**Table 2A, 2B**). Maximum dosing weight to be used is 100 kg (i.e., anyone weighing more than 100 kg will be treated as 100 kg).

Plasma has been selected as the active comparator because it is the standard of care for the treatment of bleeding relating to heart transplantation, and other complex cardiovascular procedures. Two units of plasma will be administered in pre-bypass period. Four to eight units of plasma are administered in divided doses during and after CPB as a comparator. On-CPB administration of plasma with a hemo-concentrator is a standard practice in complex heart transplant. The risk of volume overload is very high in patients with heart failure presenting for HT. Also, plasma and blood transfusion can exacerbate right

ventricular dysfunction and early graft failure in the transplanted heart[15]. Thawed plasma that is pre-thawed fresh-frozen plasma kept at 2-25°C up to 5 days is interchangeably used with fresh-frozen plasma because vitamin K dependent factor levels are stable over 5–7 days.[16,17]

3. Known and Potential Risks and Benefits

PCC has the potential to prevent or mitigate post-operative bleeding due to acquired vitamin K dependent factor deficiencies due to warfarin and hemodilution on CPB at least as well as the current standard plasma transfusion. Because it is virally inactivated and lyophilized, PCC is potentially advantageous over plasma in terms of infectious and immunological risks. The risk associated with PCC includes a lack of efficacy (under-dosing), bleeding and allergic reaction. The proposed dose was calculated based on the computer simulation,[12] and the authors' prior clinical experiences with various PCCs.[6] Exposure to multiple units of plasma increase the risk of volume overload.[4]

4. Study Population

Male and non-pregnant female patients 18 years of age or older who are undergoing heart transplantation, who also meet the protocol inclusion/exclusion criteria will be included.
The baseline assessment of a pre-operative coagulopathy will be performed based on history and preoperative laboratory work. The enrollment cut-off for international normalization ratio (INR) is ≥1.5 because post-CPB INR values are expected to rise above 1.9 based on the literature showing 0.4-point increase after complex CPB cases.[18]
All patients suspected of having or with a known history of thrombophilia, hereditary AT III deficiency, recent thromboembolic events, or life expectancy less than 48 hours will be excluded from the study.

5. Primary Objective

The objective of this trial is to demonstrate the clinical efficacy and economic utility of using PCC (Kcentra) for the mitigation of post-operative bleeding due to vitamin K dependent factor deficiency secondary to warfarin and hemodilution on CPB in patients in lieu of plasma.

6. Sample Size

The total sample size was determined from the estimated 12-hour chest tube loss after complex cardiac surgery for PCC therapy (750 ml) versus standard therapy (1000 ml) with a standard deviation of 300 ml.[6] A sample size of at least n=23 per group would allow us to detect a difference between the two treatment groups of 250 ml of blood loss with 80% power for a superiority trial assuming α=0.05. We plan to recruit 60 patients allowing for drop-outs.

7. Adverse Events (AE)

An AE is any untoward medical occurrence in a subject administered the trial product(s), which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of trial product(s), whether or not considered related to the trial product(s). An increase in severity or

frequency of a sign or symptom of a concomitant disease in a given subject would also be reported as an AE. AEs can also be recognized from changes in the subject's physical examinations from baseline. In general such changes should be considered as AEs and need to be reported subsequent to the following scrutiny:
1) If the change from baseline is considered by the investigator to be part of the normal daily fluctuations of an underlying disease process, this shall not be reported as an AE
2) If the change from baseline is considered by the investigator to be an untoward medical occurrence different from the standard of care, this medical occurrence shall be reported as an AE.

Should there be any question regarding these classifications, the matter should be discussed with the institutional review board (IRB) and DSMB (**Appendix 2**). Any AE observed by the investigator or reported by the subject will be assessed according to the instructions below. All AEs, including any new illnesses or worsening of existing illnesses, must be documented and reported to the IRB and DSMB. The period of observation for all AEs extends from the time the subject gives informed consent to the final examination procedures on Day 30. SAEs will be reported up through the Day 30 follow-up (Table 1). AEs are divided into the categories "serious" and "nonserious". This determines the procedure
An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is according to investigator's judgment another medically important condition

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasms requiring intensive treatment in an emergency room or at home, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
"Life-threatening" means that the subject was at immediate risk of death from the AE as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death. "Requires inpatient hospitalization" should be defined as hospital admission required for treatment of the AE. Hospital admission for scheduled elective surgery would not be a SAE. AEs, which do not fall into these categories are defined as nonserious. Expected AEs are determined by this protocol and the current Investigator's Brochure, a copy of which will be delivered to each investigator. Regardless of the classification of an AE as serious or nonserious (see above), its severity must be assessed as mild, moderate or severe, according to medical criteria alone:

- **Mild**-Does not interfere with routine activities
- **Moderate**-Interferes somewhat with routine activities

- **Severe**-Impossible to perform routine activities

It should be noted that a severe AE need not be serious in nature and that an SAE need not, by definition, be severe. Subjects will be instructed by the investigator to report the occurrence of any AE. The following algorithm will be used to assess the causality of all AEs:

- **Not related** The event can readily be explained by factors not involving the trial product(s), and a temporal relationship with the trial product(s) does not exist
- **Possibly related** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the trial product(s), but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
- **Probably related** The temporal relationship between the administration of the trial product(s) is compelling, and the event cannot be explained by the subject's medical condition or other therapies
- **Related** The event follows a reasonable temporal sequence from administration of the IMP, follows a known or suspected response pattern to the trial product(s), is confirmed by improvement upon stopping the trial product(s) and reappears upon repeated exposure.

All AEs, regardless of severity, will be followed-up by the investigator until satisfactory resolution. All subjects experiencing AEs - whether considered associated with the use of the trial product(s) or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an "AE/SAE" page in the CRF and in the subject's medical records.
In the event the investigator considers an AE to be serious enough to require specific knowledge of the identity of the study substance, the investigator may, only if necessary for the subject's care, break the blind for that subject only.
Withdrawal from the clinical study and therapeutic measures shall be at the discretion of the investigator. A full explanation for the discontinuation from the clinical study will be made on the appropriate CRF.

7.1 Events (AEs/SAEs) that are specific to coagulation therapy
The below listed events are often accompanying coagulation therapy and shall therefore be assessed as 'expected'.

Allergic reaction towards coagulation therapy/medication may be observed immediately after administration of coagulation therapy (platelets, plasma, cryoprecipitate or PCC).
Systemic thromboembolism may be observed immediately after administration of coagulation therapy (platelets, plasma, cryoprecipitate or PCC).

Specific thrombosis / Embolism without underlying disease including myocardial infarction, apoplexy, or peripheral embolism within intra-operative or post-operative

course may occur secondary to the use of coagulation therapy (platelets, plasma, cryoprecipitate or PCC).

Transfusion Related Acute Lung Injury (TRALI) is associated with the administration of blood and blood products.

Transfusion-related acute left or right ventricular volume overload is closely related to the administration of RBCs and/or coagulation therapy (platelets, plasma, and cryoprecipitate).

Non-surgical hemorrhage and Surgical re-exploration is defined as Post-operative hemorrhage not related to surgical intervention and therefore related to coagulopathy.

7.2 Events (AEs/SAEs) that are specific to the common underlying disease, the surgery process, and hospitalization in the ICU

The below listed events are often accompanying aortic replacement surgery and their causality shall therefore be assessed as "may be related".

Problems of renal function

Problems of intestinal or liver functions

Infections (either local or systemic, i.e. sepsis with multi organ failure)

Post-pump syndrome is a generalized, inflammatory syndrome with volume loss caused by increased capillary permeability; subsequent to the surgical trauma or intra-operative employment of the CPB without detectable accompanying infection.

Impaired lung function or lung failure is caused by artificial ventilation, intra-operative mechanical damage especially of the left lung, and caused by infections due to ICU hospitalization.

Common, acute left or right ventricular load is based on large intra- and post-operative volume changes through crystalloid (Ringer or normal saline) or colloid solution.

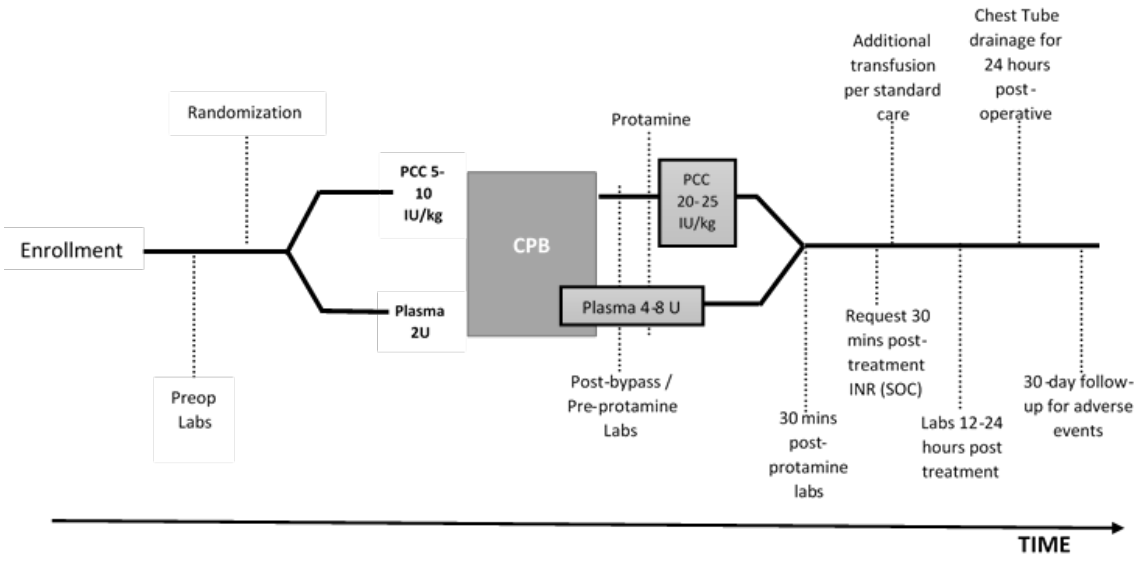
Surgical bleeding may occur due to an incomplete anastomosis, or a disruption of surgical sutures.

9. Study Design and Methodology

This study will be a randomized (1:1; PCC vs. plasma), open-label trial of hemostatic therapies during heart transplantation. The goal is to enroll 60 patients. Informed consent will be obtained from patients meeting the inclusion and exclusion criteria before the

initiation of any study specific procedures. Eligible patients will be randomized to receive either PCC or plasma transfusion. The efficacy of interventions will be evaluated after 30 minutes of protamine administration. After the heart transplantation, thrombocytopenia and/or hypofibrinogenemia may worsen bleeding associated with vitamin K dependent factor deficiencies. Transfusion of platelets and/or cryoprecipitate is permitted if abnormal laboratory values are observed during the rewarming phase of CPB; platelet count <100 x 10^3/µl, and fibrinogen <200 mg/dl, respectively; **Appendix 1**). Maximum dose of PCC is per dosing schedule (**Table 2B**) in the operating room. **If there is evidence of refractory bleeding, 2–4U of plasma will be given to PCC group patients as a rescue therapy in the operating room. In patients assigned to plasma treatment, refractory bleeding after 10 units of plasma may be treated with PCC (20 IU/kg). If the patients continue to bleed with prolonged INR in the intensive care unit, a single rescue dose of PCC may be given to both groups at 5–10 IU/kg as long as it is within a total daily maximum dose of 50 IU/kg (or 5000 IU for those weighing over 100 kg). Thereafter, any hemostatic intervention in the presence of microvascular bleeding is up to the care team in the intensive care unit per institutional standard practice.**

10. Schematic Diagram of Trial Design



11. Randomization

Randomization will occur once the patient has been confirmed to meet all study inclusion and exclusion criteria, including laboratory criteria. When blood products are ordered for the case the patient in the study will be given either PCC or plasma by the blood bank staff investigator. Randomization will be monitored to ensure that distribution of patients between the two groups is approximately equal. Each patient will receive either PCC or plasma in an open-label ratio. Treatment groups will be studied concurrently.

12. Withdrawal Criteria

Investigator can discontinue any patient at any time if medically necessary. Prior to discontinuing a patient in the study for medical reasons, the Investigator(s) should discuss the situation with the DSMB unless delay in discontinuing the patient from the study would likely result in harm to the patient. It will be documented whether or not each patient completed the clinical study. If, for any patient, study treatment or observations were discontinued, the reason will be recorded and the Sponsor should be notified promptly.

Reasons that a patient may discontinue from the study include:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Unsatisfactory therapeutic effect
- Protocol violation
- Withdrawal of consent by patient
- Any event or issue deemed appropriate by the Investigator(s)
- Discontinuation of the study by the Sponsor

It is imperative to obtain complete follow-up data for all patients whether or not they receive the study drug or have discontinued study drug. Every attempt should be made to collect follow-up information except for those patients who specifically withdraw consent to release of such information. All procedures and laboratory specimens or tests requested for evaluation following administration of the study drug should be carried out when possible whether or not a patient continues to receive treatment according to the protocol.

13. Trial Products

Kcentra (PCC): each vial will be administered as a 20 ml intravenous injection once before CPB, and upon the weaning from cardiopulmonary bypass, and prior to the administration of protamine.

Directions for Reconstitution:

Do not use Kcentra beyond the expiration date. Kcentra contains no preservative. Use aseptic technique when preparing and reconstituting Kcentra.

Reconstitute Kcentra at room temperature as follows:

1. Remove the cap from the product vial to expose the central portion of the rubber stopper.
2. Clean the surface of the rubber stopper with an antiseptic solution and allow it to dry.
3. Using an appropriate transfer device or syringe, transfer 20 mL of Sterile Water for Injection into the product vial.
4. Gently swirl the product vial to ensure the product is fully dissolved. Do not shake the vial.

After reconstitution, the Kcentra solution should be colorless and clear to slightly opalescent. Inspect visually for particulate matter and discoloration prior to administration. Do not use if the solution is cloudy or contains particulates. Do not freeze Kcentra solution. Discard partially used vials. Kcentra is stable for 24 hours after reconstitution when stored at 20-25ºC and should be administered within this time period. Do not mix Kcentra with other medicinal products or intravenous solutions, and should be administered through a separate injection site. Use aseptic technique when administering Kcentra. Administer Kcentra at room temperature by slow intravenous injection at a rate not exceeding 8.4 ml per minute.[14]

14. Treatment Compliance

The treatment, dosage and period of administration for each study medication given must be documented. A monitor will review patient source documents and drug accountability records to assess treatment compliance on a one time basis.

15. Pre-treatment Period (Day -1)

The Pre-treatment period occurs 24 hours prior to study drug initiation and consists of confirming patient eligibility, obtaining informed consent, and collecting pre-treatment (baseline) assessments.

Written informed consent will be obtained for this study by the Principal Investigator, Sub-Investigator or delegated clinician, from all patients before the performance of any protocol-specific procedure.

The following procedures must be performed within 24 hours prior to randomization:

a) Perform patient screening and confirm inclusion/exclusion criteria
b) Obtain informed consent
c) Complete medical history (as per normal clinical practice)
d) Laboratory tests (hematocrit, platelet count, PT, PTT, POC-PT, coagulation factor and inhibitor levels (e.g., factor II, antithrombin), thromboelastometry or thromboelastography, endogenous thrombin generation)
e) Urine or serum pregnancy test (women of child-bearing potential only)

16. Randomization

Randomization should only occur once the patient has given written informed consent and patient eligibility is confirmed (all inclusion and exclusion criteria must be met).

17. Treatment Period

A complete schedule of events is included (**Table 3**). The treatment period is for the time it takes to infuse platelets, PCC or plasma, and reverse heparin.

18. Follow-up Period

The follow up period will be up to 30 days after infusion of products. At post-bypass/pre-protamine, 30 minutes post-protamine and 12-24 hours after the trial product infusion, the laboratory tests will be repeated for hematocrit, platelet count, PT, PTT, Fibrinogen, Factor V, Factor VII, Factor VIII, Factor IX, Factor X, Antithrombin III, Protein C,Protein S and Prothrombin. During the intensive care unit (ICU) stay, the standard of care will be provided by the care team independent from the Investigator(s). Postoperative transfusion will be directed by the standard protocol to use platelets, FFP, and cryoprecipitate, respectively in the presence of abnormal laboratory values (platelet count < 100 x 10^3/µl, INR > 1.5, and/or fibrinogen < 200 mg/dl) and clinical bleeding (>200 ml/h blood loss). Rescue dose of PCC can be given in the postoperative period if there is prolonged INR associated with clinical bleeding but total daily dose in both groups will not exceed 5000 IU (50IU/kg). A medical chart review will be performed to assess LOS in ICU and hospital, the need for subsequent surgical reexploration(s) due to bleeding, and observed adverse events related to transfusion, and use of topical agents in the operating room.

19. References

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