

Acute Normovolemic Hemodilution (ANH) in Complex Cardiac Surgery

NCT#05049590

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Specific Aims: Indicate the purpose of the research, specifying the problems and/or hypotheses to be addressed.

1. We hypothesize that ANH will reduce allogeneic (unrelated donor) red blood cell units transfused in complex cardiac surgery.
2. We hypothesize that ANH will reduce platelet transfusions in complex cardiac surgery.
3. We hypothesize that ANH may reduce the incidence of acute kidney injury (sudden kidney failure/damage) in complex cardiac surgery.

Background and Significance: Postoperative bleeding in cardiac surgery is a frequent complication, and cardiac surgery utilizes 15-20% of the national blood supply. Packed red blood cells (pRBCs) are associated with worse short and long term outcomes. For each unit transfused, there is an additive risk of mortality and cardiac adverse events. Despite current guidelines and numerous approaches to bleeding reduction, >50% of the patients undergoing cardiac surgery receive transfusions. Acute normovolemic hemodilution (ANH), a blood conservation technique that removes whole blood from a patient immediately prior to surgery, could be a valuable method to reduce transfusion in complex cardiac surgery. ANH has been studied in simple cardiac surgery, such as coronary artery bypass grafting, however it has not been studied in complex cardiac surgery, such as aortic surgery and adult congenital heart disease. ANH has been demonstrated to reduce pRBC transfusion in lower risk cardiac surgery without any significant complications. Complex heart surgery utilizes more blood products. This study could identify the benefits of ANH in a higher risk surgical group.

Research Design and Methods: This is a prospective, randomized study for adult patients undergoing complex heart surgery as defined by redo sternotomy, aortic surgery, or adult congenital heart disease. The primary outcome of the study is units of pRBCs transfused between the ANH group compared to the control group.

Adult patients undergoing complex heart surgery will be randomized to 1 of 2 groups using block randomization: the intervention arm receiving acute normovolemic hemodilution (ANH) or the control arm receiving standard of care. Patients will be screened prior to their date of surgery to determine their eligibility for study participation. Please see the below listed inclusion and exclusion criteria. Eligible patients will be contacted via telephone prior to their date of surgery and given relevant information about the study. On the day of surgery, patients will be consented by study co-PIs and co-investigators for study participation. As day of surgery hemoglobin/hematocrit is critical to the final determination for study participation, patients will be randomized to control or intervention arms after the first intraoperative arterial blood gas (ABG) is obtained. It is the current standard of care at UCLA to obtain an ABG prior to surgical incision.

Anesthetic Management: All patients will undergo general anesthesia with standard monitors. Our standard monitors for cardiac surgery include peripheral intravenous access, invasive arterial monitoring, central line access with pulmonary artery catheter, transesophageal echocardiography and near-infrared spectroscopy for cerebral oximetry. Fluid management and selection of inotropic or vasopressor support will be guided per current practice and is within the purview of the attending anesthesiologist and cardiothoracic surgeon.

It is the current practice to obtain an intraoperative arterial blood gas after placing the invasive arterial line and the hemoglobin/hematocrit obtained from this ABG is used to determine the postdilutional hematocrit. The following equations will be used to calculate the estimated postdilutional hematocrit pre- and post-ANH.

$$\text{Estimated pre-ANH postdilutional Hct} = \frac{(\text{Hct} * \text{Wt} * \text{BV})}{(\text{BV} * \text{Wt}) + \text{Prime vol} + \text{Anes vol}}$$

$$\text{Estimated post-ANH postdilutional Hct} = \frac{(\text{Hct} * \text{Wt} * \text{BV}) - (\text{Hct} * \text{ANH vol})}{(\text{BV} * \text{Wt}) + \text{Prime vol} + \text{Anes vol} + \text{ANH vol}}$$

Hematocrit (Hct) is reported as a proportion (0.xx). Weight (Wt) is reported in kilograms. Blood volume (BV) is reported as cc/kg and is estimated using the following weight based ranges: 85cc/kg (0-10kg), 80cc/kg (11-20kg), 75cc/kg (21-30kg), 70cc/kg (31-40kg) and 65cc/kg (>40kg). Anesthesia volume (Anes vol) is the estimated volume in cc given by anesthesiology providers prior to bypass which is typically 400-500cc. ANH volume (cc) is the volume of whole blood that is removed and replaced with an equivalent volume of crystalloid or colloid. The prime volume is 1200cc (small adult CPB circuit) for patients less than 70kg and 1400 cc (adult CPB circuit) for patients greater than 70kg.

Patients with pre-ANH or post-ANH postdilutional Hct lower than 22-24 will not be eligible for inclusion in the ANH arm of the study. With respect to ANH volume, a total of 8-10cc/kg of whole blood will be removed with a maximum volume of 700cc.

For the Study Group: Using sterile techniques, ANH is performed by removing 8-10cc/kg of whole blood with a maximum of 700cc, from the patient through a Arrowg+ard Blue percutaneous sheath introducer (9Fr) or Arrowg+ard Blue multi-access catheter (distal end 9Fr) in the operating room prior to incision. Whole blood will be collected in standard citrate phosphate dextrose adenine bags (Fresenius Kabi AG Fenwal Blood-Pack Units) and stored at room temperature. Each bag contains 63ml of citrate phosphate dextrose adenine (anticoagulant) solution. Each bag can collect and process up to 450ml of whole blood. Hemodynamics are assessed during whole blood removal to ensure adequate stability. ANH will be discontinued if the patient becomes hemodynamically unstable (i.e. significant hypotension greater than 20% reduction from pre-ANH, unstable arrhythmia, evidence of myocardial ischemia or evidence of worsening myocardial function). After whole blood removal, the patient is hydrated to maintain isoolemia with an equivalent volume of crystalloid and/or colloid given, and the blood is stored in the operating room at room temperature. After cardiopulmonary bypass (CPB) is complete, the whole blood is returned to the patient. Whole blood stored at room temperature will be transfused within 8 hours of initial collection. After 8 hours, ANH whole blood will be considered expired and will be transfused back to the patient prior to expiration and not discarded. Laboratory coagulation and ROTEM studies (assess blood clotting) will be resent after the ANH blood is returned to the patient. Transfusion requirement will be continuously reassessed based upon laboratory values and surgical assessment of clinical bleeding.

For the Control Group: Blood conservation will not be performed in the OR. Coagulation labs (i.e. platelet count, fibrinogen level and ROTEM studies) are sent while the patient is on bypass. After separation from bypass, coagulation laboratory studies and clinical bleeding are assessed in collaboration with the surgeon. Based on laboratory values and surgical assessment, allogenic transfusions (donor/recipient not the same person) occur in a targeted fashion (i.e. clinical bleeding with platelet count less than 150 x10E3/uL and a ROTEM results indicative of inadequate clot strength will result in platelet transfusion). Transfusion requirements are continuously reassessed based upon updated laboratory values and surgical assessment of clinical bleeding.

The current standard of care for hemostasis and transfusion will be the same for both study and control groups. Under the discretion of the anesthesiology and surgical teams, patients receive antifibrinolytic therapy and cell salvage is routinely employed throughout the case. Techniques

to limit hemodilution include the use of retrograde autologous priming prior to initiation of cardiopulmonary bypass and the use of ultrafiltration on bypass to remove excess fluids as tolerated. With respect to intraoperative practices, transfusion triggers are as follows. On cardiopulmonary bypass, pRBC will be administered to maintain a Hct greater than 20-24, approximately a Hgb between 6.7-8g/dl. Post-cardiopulmonary bypass, pRBC will be administered to maintain Hct greater than 21. Fresh frozen plasma will be administered if ROTEM or PT/INR indicate a deficiency in clotting factors (EXTEM CT greater than 80, HEPTM CT > 200 or INR > 1.6). Cryoprecipitate will be administered for fibrinogen less than 100g/dL or FIBTEM A20 less than 7. Platelets will be administered for platelet count less than 100 x10E3/ μ L or ROTEM MCF/A20 less than 50mm. See table 1 for additional information about transfusion triggers.

Data will also be collected and recorded from the medical record.

Risks/Benefits: The benefits of ANH include reduced risk of adverse reaction to allogeneic blood, and improved clotting since the patient's blood has normal clotting factors and platelets. In addition, patients in the study group may receive fewer pRBC transfusions.

Potential benefits to society include: ANH may improve outcomes for all patients coming for complex cardiac surgery. It may decrease blood utilization which is also important from a societal standpoint.

ANH is simple and low cost without any evidence of risk to the patient. There are no patient costs and no additional labs between the groups.

Indicate how much time will be required of the subjects, per visit or contact, and in total for the study: No additional time will be required of the subjects. The ANH will be done after the patient is asleep in the operating room. No additional follow-up is needed.

Statistics and Data Analysis: Describe the proposed statistical procedures or descriptive analyses for the study. If applicable, indicate how the sample size was determined.

Data will be analyzed on an intention-to-treat basis. Normally distributed variables will be presented as mean and standard deviation (SD) and compared with the unpaired two tailed *t* test. Proportions will be analyzed with the chi-square test. Logistic regression will identify variables associated with postoperative outcomes.

Sample size: Previous studies have demonstrated that in simple cardiac surgery, ANH can reduce the incidence of pRBC transfusion from approximately 60% to 30%. With an alpha error of 0.05 and a power of 80%, we would need to enroll 112 total patient to detect a statistically significant difference between the groups.

Number of participants: 112

Inclusion/Exclusion Criteria (based on recent Shander et. al. 2020 consensus recommendations):

Inclusion criteria:

- Patients greater than 18yo presenting for elective complex cardiac surgery requiring cardiopulmonary bypass
- Surgical procedures to include:

- Redo surgery
- Adult congenital heart disease surgery (ACHD)
- Aortic surgery including aortic surgery requiring deep hypothermic circulatory arrest

Exclusion criteria:

- Low-risk cardiac surgery
- Cardiac surgery not requiring cardiopulmonary bypass
- baseline anemia (Hct < 39/Hgb < 13 for men and Hct < 36/Hgb < 12 for women)
- post-dilution Hct < 21-24 (basis for this is increased risk of AKI on CPB with Hct 21-22)
- preop treatment for anemia
- high-risk ischemia lesions (critical left main, multi-vessel disease, active/recent chest pain, unstable angina, presence of a balloon pump, recent history of MI either NSTEMI/STEMI, regional wall motion abnormalities on echo)
- Low left ventricular systolic function (LVEF < 35-40%)
- decompensated heart failure
- HOCM patients with significant LVOT gradients
- history of recent blood transfusion
- history of recent GI bleed
- patient refusal to participate in the study
- severe AS with reduced LVEF
- pulmonary hypertension
- underlying significant liver disease impairing synthetic function (elevated PT/INR or PTT) at baseline
- clotting disorders, inherited or acquired or iatrogenic coagulopathy (i.e. thrombocytopenia, pancytopenia)
- baseline CKD stage 3/above or ESRD +/- hemodialysis
- hemodynamically unstable patients including sepsis/recently treated sepsis
- active or current infection or endocarditis
- preop ECMO or high suspicion for postop ECMO
- Emergent cases

List of data elements:

Demographics and data variables:

- Age
- Gender
- Preop labs (creatinine, CBC, coags, LFTs)
- Preop meds including anti-coagulants and aspirin as well as discontinuation prior to surgery
- Comorbidities
- Preop cardiac diagnosis
- Preop planned procedure
- Preop LVEF, RV function, and valvular assessment
- Usage of fibrinolytics, factor 7, PCC, or ddAVP by anesthesia and perfusion
- CPB times and x-clamp time
- Preop, intraop and postop inotropes/pressors

Primary endpoint: total transfusion of allogenic pRBC units administered 24/48/72 hours post-CPB

Secondary endpoint:

- total transfusion of allogenic platelet units administered 24/48/72 hours post-CPB
- total transfusion of allogenic cryoprecipitate units administered 24/48/72 hours post-CPB
- total transfusion of allogenic fresh frozen plasma units administered 24/48/72 hours post-CPB
- vasopressor score
- postop AKI
- bleeding severity (chest tube output, etc.)
- pre/post ANH coagulation studies (plt, fibrinogen, PT/INR, PTT, Hgb/Hct)
- pre/post ANH ROTEM studies (ideally a post-ANH ROTEM would be great)
- markers of perfusion on bypass (NIRS/SvO₂, lactate)
- changes in delirium
- post-op infection/sepsis

	Absolute indication	Physician discretion
pRBC		
Hemoglobin	6-7g/dL or £10g/dL if patient has cyanotic congenital heart disease	>7g/dL (acyanotic) or >10g/dL (cyanotic) <u>OR</u> active bleeding
Platelet		
Platelet count	£100 x10E3/ μ L	100-150 x10E3/ μ L
HEPTEM/EXTEM MCF	£50mm	50-70mm
EXTEM A20	£50mm	50-70mm
H/o antiplatelet therapy	Any platelet count with ongoing bleeding	
Cryoprecipitate		
Fibrinogen	£100mg/dL	100-150mg/dL
FIBTEM A10	£7mm	7-10mm
FIBTEM MCF	£7mm	7-10mm
Fresh frozen plasma		
INR	³1.6	<1.6
EXTEM CT	>80sec	40-80sec
HEPTEM CT	>200sec	120-200
Clotting factor deficiency	Treat as indicated	
Desmopressin	History of vWF deficiency or renal disease or as indicated	
Activated Factor 7	Ongoing bleeding despite appropriate transfusion to manage coagulopathy	
Prothrombin concentrate complex	Ongoing bleeding despite appropriate transfusion to manage coagulopathy	