Official title: Prospective Randomized Pilot Study Comparing Bivalirudin Versus Heparin in Neonatal and Pediatric Extracorporeal Membrane Oxygenation

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Protocol for Investigator Initiated Studies

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1. Introduction and Purpose:
Anticoagulation is essential during extracorporeal membrane oxygenation (ECMO) to prevent catastrophic circuit clotting. Use of unfractionated heparin (UFH) as the standard of care during ECMO was adapted from the knowledge gained from cardiopulmonary bypass. Unfortunately, UFH has several limitations during ECMO. Bivalirudin, a direct thrombin inhibitor, is an alternative and potentially superior anticoagulant for patients on ECMO. Previous studies of bivalirudin use during ECMO have shown that compared to UFH, bivalirudin is safe and may decrease bleeding, decrease blood product transfusion, and decrease ECMO cost [1-4]. Improving anticoagulation during ECMO is critically important as the most common complications during ECMO are secondary to bleeding and clotting [5].

We hypothesize that neonatal and pediatric ECMO patients receiving bivalirudin will spend more time at goal anticoagulation and will experience less hemorrhagic and thrombotic complications when compared to patients receiving unfractionated heparin.

Aim 1: Compare the efficacy of bivalirudin versus UFH during neonatal and pediatric ECMO.
Aim 2: Define the incidence of hemorrhagic and thrombotic complications in patients receiving bivalirudin during ECMO.
Aim 3: Determine the optimal dosing for bivalirudin for effective anticoagulation on ECMO.

The primary outcome of the study will be to compare the percentage of time spent at goal anticoagulation for patients receiving UFH versus patients receiving bivalirudin. Secondary outcomes will include incidence of major bleeding events as defined by the International Society of Thrombosis and Hemostasis including fatal bleeding, intracranial hemorrhage, retroperitoneal hemorrhage, extrasurgical or unexpected surgical site bleeding that causes a decrease of hemoglobin of > 2 g/dL or leads to transfusion of two or more red blood cell transfusions within a 24 hour period, and surgical site bleeding that requires surgical intervention [6, 7]. We will compare the need for blood product transfusion of packed red blood cells, platelets, fresh frozen plasma, cryoprecipitate, and antithrombin III (thrombate) between those who received UFH versus those who received bivalirudin. Lastly, we will describe the median dose needed for bivalirudin in all patients and for those with renal insufficiency and renal failure.

2. Background:
Extracorporeal membrane oxygenation (ECMO) is a lifesaving therapy for patients with respiratory and/or cardiac failure. Approximately 1500 to 2000 neonatal and pediatric patients are placed onto extracorporeal membrane oxygenation (ECMO) each year for respiratory failure [8]. At Children's Medical Center, we place approximately 40 neonatal and pediatric patients onto ECMO each year. Despite advancements in ECMO circuit technology such as heparin coated tubing, smaller oxygenators, and improved cannula, hemorrhage and thrombosis are the most common complications during ECMO [8, 9]. Approximately 4-11% of neonatal and pediatric ECMO patients suffer an intracranial hemorrhage and 30% have some form of thrombosis [10, 11]. Hemostatic complications during ECMO are associated

with increased morbidity and mortality [5, 11]. In order to prevent catastrophic circuit clotting, anticoagulation is essential.

As mentioned previously, UFH is currently the standard anticoagulant for ECMO but it has several important limitations. UFH requires antithrombin for maximum therapeutic effect but neonates and critically ill patients are known to be deficient in antithrombin. Besides binding to antithrombin, UFH binds to the ECMO circuit and other plasma proteins altering its pharmacokinetics. The tests used to monitor UFH's clinical effectiveness such as aPTT, ACT and anti-factor Xa are all imperfect tests and have been shown to have variable correlation to themselves and to UFH during ECMO [12-16]. There are no randomized studies that have investigated superiority of UFH over other anticoagulants during ECMO. In addition, there is no universally accepted test or combination of tests to monitor the functional effect of UFH during ECMO.

Bivalirudin is a specific and reversible direct thrombin inhibitor. Bivalirudin binds to both bound free and clot-bound thrombin and unlike UFH it does not require antithrombin. In addition, bivalirudin also has a short half-life of 25 minutes and has low to negligible immunogenic potential. Bivalirudin is currently FDA approved for patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA), percutaneous coronary intervention (PCI) with use of glycoprotein IIb/IIA inhibitor, and patients with heparin induced thrombocytopenia undergoing PCI [17]. Bivalirudin is currently used off label for pediatrics.
Bivalirudin has been used off label in children for deep venous thrombosis prophylaxis and treatment, cardiopulmonary bypass, cardiac catherization and ECMO [17]. An open label study conducted by the manufacture of 110 neonatal and pediatric patients identified the dosing regimen, plasma concentration, and safety profile of bivalirudin. Bleeding occurred in 2 of 110 patients (1.8%) and thrombosis occurred in 8 of 110 patients (7.5%) [18]. At our institution, 6 non-ECMO neonatal and pediatric patients have been initiated on bivalirudin for concern of or confirmed heparin induced thrombocytopenia. In the six patients there were no thrombotic or hemorrhagic complications.

Pediatric ECMO studies using bivalirudin have thus far shown benefit and confirmed safety of bivalirudin but are limited to single case reports, one small case series, and one small retrospective study. Nagle et al described 12 neonatal and pediatric ECMO patients on bivalirudin and found no major bleeding events [1]. The study also defined the maintenance dose need to achieve goal aPTT. A combined pediatric and adult retrospective review compared 21 total patients using bivalirudin to UFH and found that patients receiving bivalirudin had decreased bleeding, decreased blood product transfusion, and decreased pediatric ECMO cost compared to patients receiving UFH [2]. An adult case-control study of 10 patients receiving UFH compared to 10 patients receiving bivalirudin, found that patients receiving bivalirudin had less variation of aPTT and a trend towards decreased number of changes of bivalirudin dose compared to patients receiving UFH [3]. No difference was seen in bleeding or thrombotic complications between the two groups [3]. To our knowledge, there is no prospective study comparing bivalirudin to UFH for pediatric or adult ECMO.

3. Concise Summary of Project:
We will prospectively enroll 30 neonatal and pediatric ECMO patients in the Pediatric Intensive Care Unit and Pediatric Cardiovascular Intensive Care Unit at Children's Medical Center, Dallas campus. The patients will be randomized into two arms; one arm will receive unfractionated heparin and the other arm will receive bivalirudin. There will be 15 patients in each arm for a total of 30 patients. We estimate that we will need to consent 50 patients to achieve our goal of 30 enrolled patients. Enrollment and completion of this study will require approximately two years.

After consent is obtained, patients will be randomized into either the unfractionated heparin group or bivalirudin group. The UFH group will be given UFH as is currently standard of care at Children's Medical Center. A bolus of UFH will be given on initiation and the UFH infusion will be titrated throughout the entire ECMO run based on combination testing of anti-factor Xa, aPTT, and thromboelastogram (TEG).

The bivalirudin group will receive an UFH bolus during cannulation and UFH infusion until consent obtained (maximum time of 24 hours) and then transitioned immediately from UFH infusion to bivalirudin infusion. Once initiated, the bivalirudin infusion will be titrated based on aPTT.

Bivalirudin's trade name is ANGIOMAX® and is manufactured by The Medicines Company. Bivalirudin directly inhibits thrombin by binding to the free and clot-bound thrombin. It stored in a single-dose vial with 250 millograms of bivalirudin to be reconstituted with sterile water. After reconstitution it may be stored at 2-8°C for up to 24 hours. It is excreted predominantly through proteolysis with 20% cleared renally. Patients with renal insufficiency or failure required a decrease in infusion rate based on creatinine clearance.

ECMO circuit tubing will be collected at time of circuit tubing change or at the end of ECMO. Normally, the used circuit tubing system is discarded in the appropriate biohazard waste container. For this study, will analyze the circuit tubing after it has been removed from the patient. After removal, the circuits will be drained and filled with normal saline (to prevent further clotting) by one of the ECMO team members or one of our study team members. The steps involved are detailed in the paragraphs bellow and will be covered by study finances and not billed to the patient in any way.

The cannula with the circuit tubing system attached is cut away from the patient per standard of care and the circuit is drained of blood. The A-V loop (arterial venous) is created using a T-connector (1/4 x 3/8 inch size) and connected to the circuit. A 1 liter bag of normal saline is run through the circuit until the fluid looks clear with the exception of clots, or fibrin strands, already adhering to the tubing. The bridge ports are then capped and the circuit is placed in a biohazard bag.

After removal of the circuit from the patient, the blood will be appropriately drained into a biohazard bag. The circuit will be filled with normal saline and stored in a biohazard bag. The circuit and the biohazard bag will be labeled with the patient study ID and date. There will be no patient identifiers on the circuit, biohazard bag, or shipment label. The biohazard bag will then be stored in a dedicated storage area that is locked with badge-access entrance only. The circuits will be shipped in the red biohazard bags, in a standard FedEx cardboard box (flushed circuits are non-infectious), with the appropriate shipping label for shipment to Biotechnology Building (IBB) at the Georgia Institute of Technology. The individual responsible for receiving the study circuits is Susan Hastings.

For the primary outcome, all aPTT and anti-factor Xa values (for the UFH group only) will be recorded during the ECMO run. Hemorrhagic complications will be defined using the International Society of Thrombosis and Hemostasis major bleeding criteria. Blood product transfusion will recorded in ml/kilogram/ECMO day. Thrombosis will be defined as need for circuit change and clot burden in the ECMO circuit. A clot burden score will be performed on each patient every 6 hours. ECMO cost will include cost of the circuit, cost of blood products including antithrombin, cost of circuit change, and cost of anticoagulant.

Patients in the UFH arm may cross over into the bivalirudin arm if they develop heparin induced thrombocytopenia or heparin resistance defined as UFH dose of > 70 u/kg/hour with inability to obtain goal Xa or aPTT. Bivalirudin patients may cross over into the UFH arm if they are unable to achieve adequate anticoagulation and have continued development of thrombosis in the circuit or the patient or if the patient develops an intracardiac thrombus. The primary team or parent/guardian can withdraw the patient from the study for any reason at any time.

4. Study Procedures:

Unfractionated heparin group:

Patients in this group will receive UFH anticoagulation as is current standard of care at Children's. During cannulation a bolus dose of 50-100 units/kg of intravenous UFH will be given. A continuous UFH infusion based on age will be initiated once ACT is < 300 seconds. Infants less than one year will receive a starting dose of 28 units/kg/hour and children > 1 year will receive a starting dose of 20 units/kg/hour per current Children's protocol.

The UFH infusion will be titrated based on targeted anti-factor Xa, aPTT, and thromboelastogram. Labs will be drawn per current standard of care as noted below.

aPTT and anti-factor Xa levels:
From time of cannulation until goal anticoagulation achieved: every 4-6 hrs
Once achieved goal: every 6 hours
Heparin dose change: 4 hours after change

Other labs:
Daily TEG, PT/INR, d-dimer, fibrinogen, antithrombin, triglycerides, plasma free hemoglobin
Every 12 hour complete blood count
Every one hour ACT

Bivalirudin group:

Patients in the bivalirudin group will initially receive UFH to allow for time for consent and randomization. During cannulation, an intravenous UFH bolus of 50-100 units/kg will be given. A continuous UFH infusion based on age will be initiated once ACT is < 300 seconds. Infants less than one year will receive a starting dose of 28 units/kg/hour and children > 1 year will receive a starting dose of 20 units/kg/hour. Once consent is obtained, the patients will be immediately transitioned from UFH to bivalirudin. The initial bivalirudin dose will be 0.15mg/kg/hr.

The bivalirudin infusion will be titrated via the nomogram below based on aPTT. Goal aPTT will be 1.5-2.5 times baseline. For patients with a normal aPTT prior to cannulation this translates to aPTT between 60-80 seconds.

Measured aPTT	Bivalirudin dose adjustment
< 45 seconds or < 16 seconds below target aPTT	Increase by 0.04 mg/kg/hr
45-59 seconds or 1-15 seconds below target aPTT	Increase by 0.02 mg/kg/hr
60-80 seconds or 1.5-2.5 times baseline aPTT	No change
81-95 seconds or 1-15 seconds above target aPTT	Decrease by 0.02 mg/kg/hr
>95 seconds or > 16 seconds above target aPTT	Decrease by 0.04 mg/kg/hr

For patients with renal insufficiency or failure, the initial bivalirudin dose will be adjusted based on creatinine clearance according to the nomogram below.

Creatinine Clearance (CrCl)	Initial infusion rate
> 60 ml/minute	0.15 mg/kg/hr
30-60 ml/minute	0.08 mg/kg/hr
< 30 ml/minute	0.05 mg/kg/hr
Dialysis dependent	0.02mg/kg/hr

aPTT labs:
From time of cannulation until goal anticoagulation achieved: every 2 hours
Once achieved goal: every 6 hours
Bivalirudin dose change: 2 hours after change

Other labs:
Daily TEG, PT/INR, d-dimer, fibrinogen, antithrombin, triglycerides, plasma free hemoglobin
Every 12 hour complete blood count
Every hour ACT

Blood product transfusion:
For both arms of the study patients, transfusion parameters will include: 15 ml/kg (maximum of 1 unit) of platelets for platelet count < 100 x 10^9, 1 unit/kg of cryoprecipitate for fibrinogen < 100 mg/dL, and 15 ml/kg (maximum of 1 unit) of packed red blood cells for hemoglobin < 8 -10 g/dL.

Cross over:
Patients in the UFH arm may cross over into the bivalirudin arm if they develop heparin induced thrombocytopenia or heparin resistance defined as UFH dose of > 70 u/kg/hour with inability to obtain goal Xa or aPTT. Bivalirudin patients may cross over into the UFH arm if they are unable to achieve adequate anticoagulation and have continued development of thrombosis in the circuit or the patient or if the patient develops an intracardiac thrombus.

Randomization:
Patients will be randomized 50/50 into the bivalirudin group or the heparin group. Each group will have 15 patients for a total of 30 patients. Randomization will occur via a sealed envelope assignment.

Research related costs:

Thrombin generation assay will be performed on day one and on day three for patients in both arms. The patients will not be responsible for the cost of the test. In addition, per current standard of care at Children's echocardiograms will be performed at time of cannulation and as needed to evaluate cardiac function and/or cannula position. If an echocardiogram is performed on patients in the bivalirudin arm to evaluate for intracardiac thrombus, the patient will not be responsible for the charge.

Patients will be responsible for all standard ECMO related costs including blood product transfusion and anticoagulant. The average wholesale price of bivalirudin for a 250mg vial is $609. On average one vial per day will be used per patient. The average wholesale price of unfractionated heparin for a 250ml bag is $20. The entire bag or portion of bag will be used per day per each patient. Therefore, the patients in the bivalirudin arm may incur a higher cost.

Data will be collected on the patients from time of ECMO cannulation to time of hospital discharge. Blood draws for the both groups of patients will follow current CMC protocol for ECMO except that bivalirudin patients will not get anti-factor Xa testing. The only additional test will be a thrombin generation assays. Thrombin generation assays will require an extra 5.4 ml total of blood. In addition, blood samples for dilute thrombin time, ecarin chromogenic assay, bivalirudin level and aPTT will be frozen and stored for future analysis after study completion. Samples will be drawn daily, and obtained from leftover SOC coagulation labs drawn per protocol so no additional blood sampling will be required. Patients will not be responsible for the cost of this analysis.

5. Sub-Study Procedures:
None

6. Criteria for Inclusion of Subjects:
All patients aged 0 days to less than 18 years that require venovenous or venoarterial ECMO in the Pediatric Intensive Care Unit and Pediatric Cardiovascular Intensive Care Unit at Children's Medical Center, Dallas campus.

7. Criteria for Exclusion of Subjects:
Exclusion criteria will include:

1) Patients with known or suspected heparin induced thrombocytopenia prior to consent
2) Patients with aPTT > 2 times normal with AST and or ALT > 500
3) Patients with plan to decannulate from ECMO within 48 hours
4) Known or suspected pregnant women
5) Previous enrollment in this study
6) Primary language spoken that is not English or Spanish
7) Patients with congenital diaphragmatic hernia since this small subgroup of patients are receiving surgical repair while on ECMO and if they were in the Bivalirudin group would need to have the Bivalirudin suspended during and after the surgical procedure. Since the study team is not aware of any published data to suggest how long to hold Bivalirudin for this particular operation, this population is excluded due to safety concerns.

8. Sources of Research Material:
The electronic medical records of each enrolled patient will be accessed to obtain demographic data, laboratory values, echocardiogram reports, imaging reports, blood product transfusion requirements, and disposition. All study documents containing patient information will remain password protected. Only study personnel will have access to the study records.

9. Recruitment Methods and Consenting Process:
Patients will be identified by the Children's Medical Center ECMO team. It is possible that potential subjects will be patients of the investigators. In that case where possible another member of the study team will approach the parent or guardians for consent. Parents or guardians will be approached by the study team within 24 hours of the start of ECMO.

If the patient is between 10 to 17 years old, we will obtain assent once sedation is removed and the patient is clinically able to give assent.

10. Potential Risks:
Bivalirudin is rapidly cleaved by proteotlytic enzymes creating a short half-life of 25 minutes. There is a theoretical increased risk of intracardiac thrombus development if the patient has stagnant blood flow due to poor cardiac output [19]. Daily echocardiograms will be performed to rule out intracardiac thrombus if there is clinical concern for stagnation of intracardiac blood flow including pulse pressure ≤ 10mmHg on arterial line or non-palpable pulses. Echocardiograms on patients in the bivalirudin arm that are performed to evaluate for intracardiac thrombus will not be charged to the patient. If the patient develops an intracardiac thrombus the patient will be changed to heparin infusion.

As noted previously, there is a potential risk of increased cost for the patient's in the bivalirudin group as bivalirudin is more expensive than heparin. A retrospective study comparing bivalirudin versus heparin noted that pediatric patients who received bivalirudin actually had decreased overall ECMO cost due to decreased number of blood product transfusions as compared to patients receiving UFH [2]. Like all anticoagulants, bivalirudin may cause unintended bleeding.

11. Subject Safety and Data Monitoring:
Per current ECMO protocol all patients will be monitored closely for bleeding including intracranial hemorrhage. Neonates (patients aged 0 days to 28 days) will receive a head ultrasound every day for the first 3 days and thereafter per clinical discretion per current standard of care at CMC. All patients will receive a MRI after decannulation and prior to hospital discharge per current standard of care at CMC.

See DSMP for further information regarding data safety and monitoring.

12. Procedures to Maintain Confidentiality:
Data will be stored in a password protected excel file with access granted only to study personnel.

13. Potential Benefits:
This study has the potential to have a tremendous impact on the anticoagulation practice for all future neonatal and pediatric ECMO patients. Pending the results of this pilot study, we plan to develop and implement a multicenter study randomized control trial to confirm the benefits of bivalirudin. Improving ECMO anticoagulation is essential as the most common complications on ECMO are due to hemorrhage or thrombosis. Besides potentially devastating intracranial hemorrhage, ECMO patients are at risk for stroke, surgical site bleeding, cannula site bleeding, and exposure to multiple blood products. Improving anticoagulation could decrease these complications and significantly improve the outcomes of these critically ill children.

14. Biostatistics:

Based on prior data from Ranucci et al in adult ECMO patients a sample size of approximately 10 in each arm (total 20 patients) will be sufficient to obtain statistical significance for the primary outcome. In this study we will use a variety of methods including tests of differences in means and medians, ANOVAS, correlations between changes of doses and changes in aPTT and multivariate ANOVAS and logistic regressions to analyze the impact of these treatments on a variety of patient outcomes such as time to goal aPTT, time in goal range of aPTT, ACT levels and changes , incidence of bleeding and clotting events, number of changes in dosage and other events, variations in aPTT level during treatment, time on ECMO, time in the ICU, ventilator days and mortality outcomes. Duration models will be used where appropriate.

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