Children's Hospital and Health System™

INSTITUTIONAL REVIEW BOARD SUMMARY

IRBNet 885148 / NCT03088345
Document Date: 05/10/2018

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STUDY TITLE: Use of Arginine Vasopressin in Early Postoperative Management after Fontan Palliation

A. PURPOSE OF THE STUDY

The treatments for preventing and managing low cardiac output syndrome after congenital heart surgery with cardiopulmonary bypass include manipulations of vascular volume and infusions of phosphodiesterase inhibitors (milrinone) and catecholamines (epinephrine and norepinephrine) for inotropic and vasoactive effects, all of which have associated risks which can contribute to morbidity and mortality. Vasopressin, a vasoactive drug with efficacy in septic shock, has also been utilized to improve postoperative hemodynamics after cardiac surgery in children. It is a common institutional practice to use vasopressin in this patient population, but usually after escalation through two or three other vasoactive drugs. There have been several studies in pediatrics and adults which suggest that vasopressin is not inferior to other vasoconstrictor therapies, and advantageous when looking at specific end points. [1-5] We propose to randomize the use of vasopressin to use at an earlier point in our typical post-operative medication strategy. The proposed study is a double blinded, randomized, placebo control study of vasopressin infusion immediately after the completion Fontan operation. The goal is to identify a vasoactive treatment strategy that improves hemodynamics with lower catecholamine infusion burden, reduces volume of fluid resuscitation, and reduces in-hospital resource utilization

B. HYPOTHESIS / SPECIFIC AIMS

Specific Aim 1:
To assess the hemodynamic profile of patients undergoing Fontan palliation as characterized by vasoactive inotropic score (VIS), fluid balance, organ perfusion pressure, transpulmonary pressure gradient (CVP minus LAP), arterio-cerebral and arterio-somatic saturation difference between the two groups (Vasopressin [VP] and non-vasopressin [non-VP] groups) during the first 48-hours following cardiopulmonary bypass.

Hypothesis
The group receiving vasopressin will have a more favorable hemodynamic profile as measured by lower vasoactive inotropic score and better surrogate determinants of oxygen economy.

Rationale:
The vasoactive inotropic score has been shown to be a strong predictor of morbidity and mortality by characterizing the degree of support following cardiopulmonary bypass. [6,7] A significant difference in VIS, fluid balance and other markers of hemodynamic state between the two groups will have a significant impact on post-operative management after Fontan completion.

Catecholamine infusions such as epinephrine and norepinephrine are standard therapy for post-operative cardiac patients, but they come with the risk of arrhythmias and increased myocardial oxygen demand. In the post-operative Fontan patient, inotropic agents can improve systolic function but may worsen diastolic function by impairing ventricular relaxation. Vasodilators are indicated when ventricular dysfunction is present, but organ perfusion pressure is threatened in the Fontan patient by higher venous pressures, and thus vasodilator treatment must be used with caution. Vasopressin acts by increasing systemic vascular resistance and in turn increasing mean arterial pressure. This differs from catecholamine infusions in that it does not have a direct effect on cardiac contractility, therefore it does not have as much effect on myocardial oxygen demand or arrhythmia potential. Vasopressin infusions have been used in a number of clinical settings, including septic shock and cardiogenic shock, in both adults and children. [4,8-11] The systemic vasoconstriction and pulmonary vasodilation effects of vasopressin are unique among vasoactive agents and this vasoactive profile has major theoretic advantage in the Fontan patient. A recent retrospective study reported that post-operative Fontan patients receiving vasopressin infusion had improved outcomes including less chest tube output, less positive fluid balance in the early postoperative period and a shorter hospital length of stay when compared to historical controls. [12]

<u>Specific Aim-2</u>:
To assess the difference in incidence of oliguria, hyponatremia, and organ dysfunction between the two groups (VP and non-VP).

Hypothesis
Low dose VP will not negatively effect sodium levels, urine output, renal function or transaminases.

Rationale
Vasopressin is a neurohypopphyseal hormone naturally occurring in the body (endogenous). It is synthesized in the hypothalamus and released in posterior pituitary in response to reductions in plasma volume with the primary aim of vasoconstriction/increased systemic vascular resistance for improved regulation of blood pressure or increases in plasma osmolarity to retain water in the body. When higher-dose exogenous vasopressin is administered for vasoconstriction, it can also cause hyponatremia, oliguria, and transaminitis from decreased renal and mesenteric blood flow [13,14]. This is of particular interest in patients after completion Fontan due to predictable increases in intra-abdominal venous pressures that further potentiate risk to the kidneys and liver.

<u>Specific Aim 3</u>
To compare the secondary outcomes including post-operative fluid resuscitation, chest tube drainage and duration, and hospital length of stay (LOS) between the two groups (VP and non-VP).

Hypothesis
The VP group will have lower resource utilization that are directly related to volume of fluid resuscitation during the first 24 hours after Fontan completion, resulting in decreased chest tube drainage and duration, which results in shorter hospital LOS.

Rationale
The Fontan procedure is performed in patients with single ventricle anatomy undergoing stepwise surgical palliation, typically as a planned third step between the ages 2-6 years. Although operative mortality is less than 5%, [15-17] these patients have significant physiologic vulnerability, with longer hospital stay and higher risk of morbidities, resulting in significant resource utilization for institutions and patients/families. After the Fontan procedure, cardiac output is more vulnerable to changes in venous preload and pulmonary vascular resistance because there is no high-compliance cardiac pump (functional right atrium and ventricle) in the pulmonary circulation Because the single (functionally left) ventricle does all work of both systemic and pulmonary circulations, systemic blood flow is more vulnerable to changes in systemic venous pressure pulmonary vascular resistance. The most readily reversible cause of low cardiac output syndrome after the Fontan operation is hypovolemia. Aggressive fluid resuscitation in the post-operative period can have adverse consequences, in particular in the setting of ongoing capillary leak, and third spacing of fluid. This characteristic is the typical inflammatory effects of post-CPB period and in particular the postoperative Fontan patients who have an increase in their venous pressure. The adverse effects of fluid resuscitation to maintain cardiac output can include worsening lung function, edema and positive fluid balance. These effects can result in prolonged ventilator support, development of pleural effusions, requirement for aggressive diuresis and longer hospitalization. These potential deleterious effects are more pronounced in patients with Fontan anatomy, because higher venous pressure can worsen pulmonary vascular resistance and initiate a spiral of CVP elevation and worsening pulmonary function. Thus strategies that maintain cardiac output with less fluid administration would be helpful.

The mechanisms related to the development of pleural effusions in the post-Fontan patients have been well described and include an inflammatory response to CPB, generalized capillary leak resulting from changes in hydrostatic pressures from the increase in venous pressure that results from the increase in pulmonary blood flow attendant to the inferior vena cava connection to the pulmonary arteries, and the activation of the renin-angiotensin pathway resulting in reabsorption of water and other electrolytes. Pleural effusions are typically the most frequent postoperative problem requiring prolonged hospitalizations following the Fontan procedure with replacement of electrolytes, intravascular volume, protein, clotting factors and anticipating resolution with diuretic therapy or requiring more definitive treatment with chest tube placement, or even sometimes additional procedures including pleurodesis or thoracic duct ligation.

Vasopressin is a neurohypopysial hormone that most notably increases systemic vascular resistance without directly affecting cardiac contractility. In addition to vasopressin's ability to increase mean arterial pressures by directly increasing systemic vascular resistance, vasopressin has also been described to decrease capillary leakage by tightening endothelial intercellular junctions and reducing capillary hydrostatic pressure. Vasopressin has also been described as a coronary and pulmonary vasodilator by promotion of endothelial nitric oxide release in animal models. [18,19] The specific effects on systemic and pulmonary vascular resistance make vasopressin a physiologically-rational agent to

manage the specific circulatory vulnerabilities of the Fontan patient. The clinical consequences of this physiologic improvement would be beneficial effects in the early postoperative fluid balance, chest tube output and overall resource utilization.

Specific Aim-4
To measure vasopressin levels pre-cardiopulmonary bypass (CPB) and immediately post-CPB (prior to initiating study drug)

Hypothesis
Patients receiving the placebo will have lower vasopressin levels, which will be associated with higher post-operative catecholamine support and higher volume of fluid resuscitation during the first post-operative day.

Rationale
Vasopressin is an alternative vasoactive therapy that improves postoperative hemodynamics and decreases dependence on traditional therapies such as fluid resuscitation and catecholamine infusions in neonatal and pediatric CHD patients. Landry and colleagues first reported a beneficial use of AVP in critically ill adult patients with septic shock in whom maximal inotropic and vasopressor therapy failed to maintain blood pressure. These patients also demonstrated a deficiency of vasopressin that was probably secondary to a defect in baroreflex-mediated release of the hormone. [10] This prompted a randomized adult trial of vasopressin in patients undergoing a left ventricular assist device (LVAD) placement where they noted significant reduction in need for catecholamine infusion after initiation of exogenous vasopressin in patients with vasodilatory shock. [8] Since then, vasopressin levels and the use of vasopressin infusion has been described in a number of studies in various disease states. Increase plasma levels of AVP have been observed post-CPB in adult patients undergoing coronary artery bypass grafting. [20] And Morrison et. al. also reported an increase in AVP levels in all children after CPB. [21] However, a large pediatric prospective observational study reported some children undergoing CPB had relatively low AVP levels at baseline, which remained low after CPB and determined that these patients are likely optimal candidates for exogenous vasopressin infusions for hemodynamic instability. [22] In our study proposal, we look to prospectively identify the effect of exogenous vasopressin on AVP levels and hemodynamics in the postoperative Fontan population.

C. BACKGROUND, SIGNIFICANCE, AND RATIONALE

Neonatal and pediatric interventions associated with congenital heart disease (CHD) continue to produce improved outcomes. There are no established guidelines for managing patients after congenital heart surgery due to lesion-specific unique challenges in the post-operative period. Volume resuscitation and catecholamine infusions are the traditional treatment methods to maintain adequate perfusion. However, these two treatment modalities are associated with increased risk of worsening lung function and prolonged ventilator support with aggressive fluid resuscitation, increased myocardial oxygen demand, and precipitation of arrhythmias. Given the multifactorial etiology of postoperative low cardiac output syndrome, it is often unclear which catecholamine infusion is optimal to improve circulatory function. Vasopressin, an alternative vasoactive therapy commonly utilized in shock, has been utilized to improve postoperative hemodynamics in neonatal and pediatric patient populations and has recently gained more attention.

The use of arginine vasopressin infusion in infants and children after cardiac surgery was first reported in 1999 in a case series of 11 patients with vasodilatory shock in the postoperative period. [4] This case series reported initiation of vasopressin for hypotension refractory to traditional treatment methods and reported a significant rise in hemodynamics with improved blood pressure in all patients as well as weaning inotropic support in 10/11 patients. Since this study there have been conflicting reports regarding vasopressin levels and the use of vasopressin to improve hemodynamics. Results from a study published in 2008 evaluated vasopressin levels in 39 patients with CHD in the pre and post-operative periods and concluded that children do not have deficient levels of vasopressin following surgery with cardiopulmonary bypass (CPB). In addition, lower levels were not associated with hypotension. [21] A larger study in 2010 of 121 patients who had congenital heart surgery with CPB described results suggestive of clinically important hypotension associated with low vasopressin levels. [22] Several other publications have reported improved blood pressure and decreased catecholamine usage in patients with CHD. [14,23,24] Two of these reports have focused on vasopressin use in infants with single ventricle physiology. [23,24] In all of these reported case series the vasopressin infusion has been initiated in the post-operative period as a rescue therapy. None of the studies have advocated for initiation of vasopressin immediately post-operatively and prior to a time period of hemodynamic instability, except for one retrospective chart review by Alten et al. [25] This study from 2012 initiated vasopressin in the operating room after CPB in 19 neonates undergoing either an arterial switch for d-transposition of the great arteries or the Norwood palliation procedure for hypoplastic left heart syndrome. [25] In this study, all neonates in whom vasopressin was initiated in the operating room received significantly lower amounts of volume replacement and catecholamine support in the immediate post-operative period. They also described lower heart rate, lower incidence of arrhythmias, shorter duration of mechanical ventilation and shorter intensive care unit stay when compared to lesion-matched control group. More recently in 2016, a single center retrospectively reviewed their experience with vasopressin and patients undergoing Fontan operations over a 10 year period and it's effects on chest tube output. They determined that patients receiving vasopressin perioperatively had less chest tube output and shorter duration of chest tube drainage in addition to shorter hospital length of stay and improved fluid balance as compared to historical controls. [12]

There is a gap in the literature describing improved outcomes with a specific targeted vasoactive and inotropic therapy regimen to use in the post-operative Fontan procedure patients. Our proposed novel study will further provide evidence for outcome based post-operative medical interventions. The proposed study is a double blinded, randomized control study of vasopressin infusion versus placebo in the first 24-hours after Fontan completion. The aim of this study is to evaluate the impact of vasopressin on the early postoperative course in a relatively homogenous population, with specific attention to catecholamine use, hemodynamics, pleural drainage, extracardiac organ function (kidney and liver) and length of stay. Furthermore, we plan to evaluate vasopressin levels between the two groups.

D. DESIGN AND METHODS

This is a double-blinded, randomized, placebo-controlled, study of vasopressin use in patients following Fontan palliation. All patients undergoing Fontan palliation at CHW will be screened for eligibility into this study using the following inclusion and exclusion criteria:

Inclusion

1. Planned completion of Fontan palliation
2. English or Spanish speaking.
3. Completed Informed consent

Exclusion

1. Previous attempt at completion Fontan with subsequent takedown
2. Planned concomitant atrioventricular valvuloplasty or neoaortic valve or arch reconstruction at time of completion Fontan.
3. History of renal failure requiring renal replacement therapy
4. Absence of informed consent
5. Concurrent enrollment in other interventional studies

Patients who meet all inclusion and no exclusion criteria will be approached for consent prior to surgery, most often during their pre-operative visit to the cardiology clinic. Consent procedures will be explained in more detail in Section N.

Randomization

Patients whose families give permission for them to participate will be identified by the study team immediately prior to admission for surgery. At this time, an order will be placed by the PI for the study drug/placebo, which will trigger initiation of the randomization procedure by the investigational pharmacist. After randomization, study drug or placebo will be prepared by the pharmacist as per the subject's study group assignment.

Blinding

Blinding of the study drug/placebo will be done in the pharmacy. The prepared placebo will look no different than prepared study drug. The infusion pump will note the drug as "Fontan Vasopressin Study" as reference. The study team will remain blinded throughout enrollment, data collection, and data analysis for all study subjects. Data will be unblinded for the purpose of safety reviews and available only to the members of the DSMB.

E. TOTAL NUMBER OF HUMAN RESEARCH PARTICIPANTS PROPOSED FOR THIS STUDY AT THIS SITE AND GLOBALLY. WHAT ARE THESE NUMBERS BASED ON?

Based on 2015 census, we anticipate about 25 patients per year will meet our inclusion/exclusion criteria. From previous studies at CHW 80-90% of families for patients with congenital heart disease will agree to participate in studies involving blood draws and drug trials. We anticipate being able to enroll 20 patients, with approximately 10 in each randomization arm. Enrollment numbers are based on available subjects. As this is a pilot study to we wish to determine feasibility of a larger, better powered study to show true efficacy of using VP as a first-line treatment for hemodynamic instability after Fontan palliation.

F. DRUGS OR PROCEDURES

Study Drug Administration

On the day of surgery, the subject's operative plan and anesthetic management will proceed per current institutional practices. The investigational pharmacist will deliver study drug/placebo to the OR during the course of the subject's surgery. Following the modified ultrafiltration period (MUF) the anesthesiologist will start the study drug/placebo infusion. The subject will receive low dose vasopressin or placebo started at 0.3mU/kg/min and will not be titrated. Total infused volume will be calculated using the subject's pre-surgical dosing weight.

After study drug initiation the attending provider will treat the patient per standard of care. If the subject requires vasoconstrictor therapy, open label vasopressin or any other appropriate medications will be added at the discretion of the attending physician.

The study drug/placebo infusion will be maintained at this rate for 20 hours when it will be weaned off at 0.1 mU/kg/min every hour over 3 hours. The subject's care team will monitor and titrate the study drug/placebo wean so it is tolerated clinically by the subject.

Throughout the active study period, postoperative care will be provided per usual practice with goal-directed interventions with vasoactive medications and fluid based on standard monitoring including invasive pressure (venous and arterial) monitoring and use of two-site near infrared spectroscopy.

Vasopressin is used in our standard practice; we are proposing that we randomize the vasoactive medication to an earlier point in our standard protocol. The study does not constrain use of other intraoperative or postoperative pharmacology such as milrinone, epinephrine and norepinephrine from being used.

Study Sample Collection

During the course of the study, non-SOC arginine vasopressin (AVP) levels will be drawn on all subjects consented for this study at 5 different time points. As well, non-SOC cystatin levels will be drawn at 2 time points as a marker of renal function pre and post operatively. A maximum of 3 ml and minimum of 2 ml of blood will be drawn at each time point. A maximum of 7 ml of blood will be drawn in one 24 hour period. All samples drawn for the study will be sent to the CHW lab for analysis and processed per their standard procedures for AVP and cystatin levels. Results of the AVP lab will not be entered into the subject's medical record in order to maintain the blind. Cystatin levels will be included in the subject's EMR.

All samples will be preferentially collected from an indwelling venous or arterial line. This will be done as close as possible to the target time. In a minority of cases, if no catheter is available the sample will be collected at the same time as an already scheduled clinical blood draw. This should be done as close as possible to the target time. Of note, the sample collection times in the CICU correspond with the timing of standard of care labs being collected in post-operative Fontan patients. We anticipate being able to draw the majority of study labs simultaneously with standard of care to reduce the number of times a subject's line is accessed. The following time points will be used for AVP sample collection:

	Pre-CPB	Post-CPB/ Pre Study Infusion	4 hrs. post CICU	20 hrs. post CICU/pre-weaning	48 hrs. post CICU
AVP	✓	✓	✓	✓	✓
Cystatin	✓			✓	
Total Volume	3 ml	2 ml	2 ml	3 ml	2 ml

Data Collection
For all subjects enrolled in the study, data will be extracted from the EMR. Specific data points can be found on the data collection form attached to this IRB submission.

G. RISK CATEGORY:

Patients enrolled in Study Drug Cohort: (2) 45 CFR 46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

Patients enrolled in the placebo group: (3) 45 CFR 46.406 - Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition.

H. RISKS AND THE PRECAUTIONS, WHICH WILL BE TAKEN TO MINIMIZE RISK EXPOSURE

Study Drug Administration
The standard risks and side effects of exogenous vasopressin infusion are minimal and rarely occur at the lower-dose infusion at which we will be running. However known side effects, which can be seen include: hyponatremia, decreased urine output, nausea, tremors, vertigo, diaphoresis, and thrombocytopenia. Other side effects that are rare, but more serious include anaphylaxis, clinical evidence of regional ischemia. The standard treatment for the less serious side effects would be symptomatic. The standard treatments for addressing the more serious side effects would be to titrate down or discontinuing infusion.

Sample Collection
Procedures for venipuncture and obtaining blood samples from indwelling catheters are routine in pediatric intensive care units and all care will be taken to ensure protecting the child from the potential risks. Ideally, samples will be collected through an indwelling catheter, or concurrently with a clinically ordered blood draw to minimize the number of needle sticks per patient. As with all blood draws, there is a chance the patient may experience slight pain, bleeding or bruising at the venipuncture sight. There is also a slight chance of fainting or infection as a result of the venipuncture, but no greater risk than with a routine blood draw.

Data Collection
Data will be extracted from the subject's medical record by the investigators and research coordinators working on this project. Files will be maintained on paper and electronically for the study. Any paper records maintained will be stored in a locked file cabinet in the critical care research office. A list linking the patient's identity, along with other collected PHI, to an assigned study subject number will be maintained separately from the clinical data that is extracted from the medical records.

Records maintained electronically will be stored in a MCW-maintained REDCap database; access to this database will be limited only to study staff who will enter and analyze data. PHI will be maintained in the same database, but will be electronically marked so that data export can easily be done in an anonymized manner.

I. PROVISION FOR THE PROTECTION OF PRIVACY OF SUBJECTS AND TO MAINTAIN THE CONFIDENTIALITY OF DATA

Please indicate which encryption tools you are using to secure your research data.

___ Credent Mobile Guardian (RS, PD)
___ GuardianEdge Hard Disk and GuardianEdge Removable Storage Encryption (HD, RS, PD)
___ IronKey encrypted flash drives (RS)
___ McAfee Endpoint Encryption (HD, RS)
___ Microsoft Bitlocker (HD, RS when used with Windows 7 and FIPS compliant algorithms are enabled)
___ PGP Whole Disk Encryption and PGP Portable (HD, RS)
___ SafeNet Protect Disk and SafeNet Protect File (HD, RS)
___ Seagate Secure Self-Encrypting Drives (HD when encryption option is enabled)
✓ Symantec Endpoint Encryption (HD, RS, PD)
___ WinMagic SecureDoc encryption (HD) (for MCW owned computers)
___ Other (*add description*)

Does not apply because:
___ Data is de-identified – no PHI collected (*please provide detailed information on data elements in your protocol application)*
___ Data is stored on paper only
___ Data is stored on CHW secured shared drives.
✓ Data is stored on MCW secured shared drives.

Only research personnel will have access to any information gathered. Identifying information will be kept in the research office at MCW in a locked area only accessible by study staff. The key connecting the subject's identity to the sample will be kept separate from other collected information.

As of June 30th, 2018 Dr. Bigelow will be leaving CHW and completing a fellowship at Cincinnati Children's Hospital and Medical Center in Ohio. She will remain as a collaborator on this study after her departure, but she will only have access to data that has been entered into the study REDCap database. Her access will be updated to include only deidentified data.

J. PROVISIONS FOR MONITORING DATA TO ENSURE THE SAFETY OF SUBJECTS; AND ADDITIONAL SAFEGUARDS TO PROTECT THE RIGHTS AND WELFARE OF SUBJECTS WHO ARE LIKELY TO BE VULNERABLE

During the active phase of this study, research team members will monitor subjects in real time for potential serious adverse events (SAEs) related and unrelated to study drug/placebo administration. We will monitor subjects for known risks during active study drug administration (risks listed in section H). The study team will work closely with the care team for this subject to ensure accurate collection

of this information. The majority of the active study period will take place in the CICU where 24 hour cardiac intensivist coverage is standard of care for all post-operative Fontan patients.

Any SAEs that do occur will be reported to the IRB per their reporting guidelines.

If at any time the attending physician feels that the study drug/placebo infusion needs to be halted for the safety of the patient this can be done at their discretion. Study team contact information will at the bedside of all subjects to promote open communication between the study and care teams. All cardiac intensivists that are

All data collected will be provided to the Data Monitoring Committee (DMC) that has been created for this study. Details on the review done by the DMC are in Section M.

K. ANTICIPATED BENEFITS ASSOCIATED WITH THE PROTOCOL TO HUMAN RESEARCH PARTICIPANTS AND SOCIETY

The benefits of this study are unknown. The research team believes that initiating low dose vasopressin in the immediate post-operative period will reduce the need for inotropic support which could minimize fluid resuscitation and arrhythmias in the post-operative period. There is a chance this may decrease chest tube output meaning decreased duration of CT placement and likely decreased hospital length of stay in addition to less hospital resource utilization, however, all of this is only speculative. This study will hopefully lead to a better understanding of the postoperative period for these patients and improved treatment protocols in the future.

L. STOPPING POINTS THAT WOULD NOT ALLOW THE STUDY TO CONTINUE AS PROPOSED

Known side effects (listed below) of vasopressin, if present, will act as potential stopping points for the study infusion. However, if these side effects are noted in the subject it is at the discretion of the CICU attending to determine if the study infusion will be stopped or other catecholamine infusions will be stopped in an effort to reverse the noted side effects. If the CICU attending determines it is necessary to stop the study drug/placebo infusion earlier than the protocol dictates, data and blood sampling collection will continue per protocol.

- Hypertension that is not otherwise corrected or explained by weaning of inotropic agents or other vasoactive medications
- Low Urine Output which will be categorized by urine output <0.3mL/kg/hr for 4 hours not otherwise correctable by standard treatments
- Clinical evidence of regional ischemia

Additional stopping points are outlined in Section M.

M. IS THERE A DATA SAFETY MONITORING BOARD (DSMB) IN PLACE? WHO ARE IT'S MEMBERS? HOW OFTEN DO THEY MEET?

A DMC is in place for this study, made up of the following individuals:

- Rebecca Russell, MD, pediatric critical care physician

- Viktor Hraska, MD, pediatric cardiothoracic surgeon
- Eckehard Stuth, MD, pediatric anesthesiologist

Prior to the first subject being enrolled, DMC members will be provided with the study protocol, and all data collection tools to familiarize them with the study.

A full review of DMC review will be completed after the first subject randomized to the vasopressin arm has been completed. If any subjects were randomized to the placebo arm during this time the data from these individuals will be reviewed as well. A final interim review of enrolled subjects will take place after the tenth subject has been randomized and all study data collection has been completed.

In the event that the DMC find a serious adverse event deemed related to study-drug administration, enrollment will be temporarily halted until further review of this event is completed. In this study serious adverse events are considered anaphylaxis, hyponatremia < 120mEq/dL, evidence of regional ischemia or any other unanticipated event listed in the CTCAE (version 4) of grade 4 or higher that the PI has determined to likely be related to study drug administration. After the DMC has reviewed the data, it will determine if the study will

1. Stop due to patient safety concerns (either temporarily or permanently)
2. Continue enrollment as is
3. Continue enrollment with protocol modifications
4. Discontinue enrollment due to futility.

N. DESCRIBE HOW THE CONSENT AND ASSENT PROCESS WILL TAKE PLACE. INCLUDE A LIST OF APPROPRIATELY TRAINED PERSONNEL WHO WILL BE INVOLVED

Once patients are identified, guardians will be approached by research personnel for the enrollment and consent process. Information about the study and any associated risks and benefits will be presented to the parent(s)/guardian by a study investigator during the preoperative evaluation about one week prior to surgery. Families will be able to consent at this time, or take documentation home for further review. If the family does not consent during the pre-operative visit the study team will meet with the family prior to the start of the subject's procedure to determine their willingness to participate.

The Principal investigator, all of the listed sub-investigators, and the research coordinators listed as part of the study team will be able to obtain consent for the study. To ensure a robust consent conversation one coordinator and one of the PI/Sub-I members will be present for each consent conversation. In the case that the subject is admitted to the CICU at the time of consent, study team members who are part of the subject's CICU care team will not participate in the consent conversation. We do not anticipate obtaining assent for this study as the Fontan procedure is not typically done on patients over 5 years old.

O. PROCEDURES TO BE EMPLOYED IN ANALYZING DATA AND THE ANTICIPATED SIGNIFICANCE OF THE PROPOSED STUDY

We propose that postoperative low dose vasopressin (VP) infusion initiated after separation from cardiopulmonary bypass will be associated with improved hemodynamic profile and overall lower resource utilization.

Data will be compared using a t-test for continuous normally distributed data. For skewed data, such as LOS, data will be compared using a Mann Whitney U. Categorical data will be analyzed using a Chi-square test. If the expected value of any cell is less than five then a Fishers Exact test will be used. Dichotomous outcome variables will be analyzed using logistic regression and potential confounders will be controlled for. All tests will be conducted as two-tailed tests with a significance level of 0.05.

P. FINANCIAL RELATIONSHIPS

There is no cost to the patient, their guardians, or their insurance company for participation in this study. Investigators have no financial relationships to disclose. Some funding from this study has been obtained from CHW to be used to offset the cost of lab testing.

Q. ADVERTISEMENTS / FLIERS

No advertisements or fliers will be used for recruitment in this study.

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