Cover page

PROTOCOL TITLE: Use of Vasopressin Following the Fontan Operation: Both Pilot and Multicenter Studies.

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PRINCIPAL INVESTIGATORS:

Phase 1- Pilot Study: Nathanya Baez Hernandez, MD Resident V, Medical Education-Pediatrics Advocate Children's Hospital Oak Lawn IL
4440 W 95th St. Oak Lawn, IL 60453
Nathanya.baezhernandez@advocatehealth.com

Phase 2- Multicenter Study: Jamie Penk, MD
Advocate Children's Hospital Oak Lawn IL
4440 W. 95th St. Oak Lawn, IL 60453
Jamie.penk@advocatehealth.com

SUB-INVESTIGATORS: Robert Horvath Csongradi
Children's Hospital and Clinics of Minnesota, Minneapolis
2525 Chicago Ave South. Minneapolis, MN 55404
RHorvath@chc-pa.org

Parag Jain, MD
Texas Children's Hospital
6621 Fannin St. Houston, TX 77030
drparagjain@gmail.com

Mohammed Absi, MD
Le Bonheur Children's Hospital
51 N Dunlap St #100. Memphis, TN 38105
mabsi74@yahoo.com

Kiona Y Allen, MD
Ann and Robert H Lurie Children's Hospital of Chicago
225 E. Chicago Ave. Chicago, IL 60611

Kallen@luriechildrens.org

Richard Fernandez, MD
Nationwide Children's Hospital
700 Children's Dr. Columbus, OH 43205
Richard.Fernandez@nationwidechildrens.org

Ilias Iliopoulos, MD
Cincinnati Children's Hospital Medical Center
3333 Burnet Ave. Cincinnati, OH 45229
ilias.iliopoulos@cchmc.org

Cheryl Lefaiver, PhD, RN, CCRP
Advocate Children's Hospital Oak Lawn IL
cheryl.lefaiver@advocatehealth.com

Julie Connolly, BSN, RN
Advocate Children's Hospital Oak Lawn IL
julie.connolly@advocatehealth.com

RESEARCH FACILITIES: Advocate Children's Hospital-Oak Lawn
4440 W. 95th Street, Oak Lawn, IL 60453

Children's Hospital and Clinics of Minnesota, Minneapolis MN
2525 Chicago Ave South. Minneapolis, MN 55404

Texas Children's Hospital, Houston TX
6621 Fannin St. Houston, TX 77030

Le Bonheur Children's Hospital, Memphis, Tennessee
51 N Dunlap St #100. Memphis, TN 38105

Nationwide Children's Hospital, Columbus OH
700 Children's Dr. Columbus, OH 43205

Cincinnati Children's Hospital Medical Center, Cincinnati, OH
3333 Burnet Ave. Cincinnati, OH 45229

Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL
225 E. Chicago Ave. Chicago, IL 60611

IRB: Advocate Health Care Institutional Review Board
3075 Highland Parkway
Downers Grove, IL 60515

1) **Protocol Title:** Use of Vasopressin Following the Fontan Operation: Both Pilot and Multicenter Studies

2) IRB Review History

N/A; first time submission

3) Objectives

1. To evaluate the effects of vasopressin on chest tube output and duration following the Fontan operation

   Hypothesis 1: Vasopressin at a dose of 0.3-0.5 mU/kg/min will reduce chest tube output and duration relative to placebo in patients following the Fontan operation.

2. To evaluate if the use of vasopressin following the Fontan operation will influence total length of hospital stay

   Hypothesis 2: Vasopressin at a dose of 0.3-0.5 mU/kg/min will reduce total hospital stay relative to placebo in children following the Fontan operation.

3. To evaluate low dose vasopressin for safety in this population

   Hypothesis 3: There will be no significant difference in adverse events between the vasopressin and placebo groups.

4) Background

The Fontan operation is the third and final procedure in palliation of patients with single ventricle physiology. Several modifications have been adopted since its establishment in 1971 (1,2).

Advances in surgical technique and post-operative care have significantly decreased morbidity and mortality following the Fontan operation; however, prolonged pleural drainage remains one of the most serious complications associated with considerable morbidity and significant resource utilization. Pleural effusions after the Fontan operation increase risk of infection, prolong hospital stay, and may necessitate a pleurodesis procedure.

The presence of significant prolonged pleural effusions after the Fontan operation has been reported to occur in up to 45% of patients (3). Fu et al. reported results from a retrospective study of 95 consecutive patients after Fontan performed between July 1996 and July 2007. They found post-operative persistent pleural effusion lasting more than 15 days in 38.9 % of the patients (37 out of 95). The median length of hospital stay was 14 days. The multivariate analysis found that lack of a fenestration, low preoperative oxygen saturation, and post-operative infections were independent risks factors for prolonged pleural drainage. Long cardiopulmonary bypass (CBP) time, non-fenestration, small conduit size, and low pre-operative saturation were independent risk factors for excessive volume of pleural drainage (>25ml/kg/day) (4).

Another retrospective report of 100 extracardiac Fontan procedures showed that 37% had pleural drainage lasting greater than two weeks, and this was associated with lower pre-operative oxygen saturations, prolonged cardiopulmonary bypass (CPB) time, post-operative infection and smaller conduit size (5). In addition, results from the multicenter, Single Ventricle Reconstruction Trial found that 18% of the patients had pleural drainage that persisted for more than 7 days (6).

Factors found to be related to reduced pleural effusions and shorter hospitalizations in some studies were the creation of a fenestration, partial exclusion of the hepatic veins during completion of the Fontan procedure, and an extracardiac Fontan operation (7, 8). However, as noted above, despite these interventions, there are still a significant number of patients with prolonged pleural effusions.

One potential medical intervention to address the above stated problem is the use of vasopressin. Vasopressin may target several mechanisms that lead to prolonged chest tube drainage. It acts on the cardiovascular system by increasing peripheral vasoconstriction. This decreases the hydrostatic pressure transmitted to the capillary bed and therefore leads to less extravasation of fluid. This vasoconstriction also improves blood pressure without the need for further fluid administration. Perhaps more importantly, vasopressin decreases capillary leakage by tightening endothelial intercellular junctions. These results were also seen in an ovine induced severe sepsis model when vasopressin and selective V1a-agonistPhe2-Orn8-Vasotocin (POV) analog were found to attenuate vascular dysfunction and fluid accumulation. Alveolar neutrophil migration and plasma levels of nitric oxide were reduced, resulting in higher mean arterial pressures and reduced vascular leakage in the treated group as compared to controls (9).

Vasopressin in states of vasodilatory shock at doses ranging from 0.1-8 mU/kg/min has been reported. At this dose range, vasopressin increased the mean arterial pressure, promoted diuresis and decreased vasopressors requirements (10, 11, 12)

Data on vasopressin use in children is sparse, but growing. In a retrospective study, Jerath et al. evaluated the clinical impact of vasopressin infusion on hemodynamics, liver and renal function in pediatric patients. A total of 117 patients, of which 85 were cardiac, received vasopressin for vasodilatory shock. The median dose of vasopressin was 0.1mU/kg/min for cardiac patients and 0.2 mU/kg/min in non-cardiac patients. The median infusion time was 24 hours in cardiac

patients and 18 hours in non-cardiac patients. Both cardiac and non-cardiac patients showed a significant decrease in inotrope requirement, without any change in central venous saturation or lactate during infusion. Higher doses of vasopressin were associated with increased urea and creatinine and decreased urine output in both groups, but these effects were reversible (13).

Rosenzweig et al. reported the outcomes of vasopressin use at a dose of 0.3 to 2 mU/kg/min in 11critically ill infants and children (age 3 days to 15 years; median 35 days) with vasodilatory shock after cardiac surgery. Three of the patients had single ventricle physiology. The mean duration of therapy was 71 ±46 hours (range 6-144 hours). Vasopressin was initiated immediately after CPB in 5 patients, within 12 hours following the surgery in another five and in one child on the second post-operative day. The use of other inotropes declined significantly in 9 patients and remained unchanged in the other two. All 9 children with vasodilatory shock survived their intensive care unit stay. The 2 patients who received AVP in the setting of poor cardiac function died, despite transient improvement in blood pressure. Urine output, perfusion and electrolytes remained unchanged. There were no episodes of peripheral vasoconstriction or cyanosis that required discontinuation of vasopressin (14).

Lechner et al. reported a retrospective study on the effects of vasopressin treatment in neonates with catecholamine-resistant systemic vasodilatation after cardiopulmonary bypass. They evaluated 172 neonates who underwent open-heart surgery of which 17 developed vasopressor-resistant hypotension and were treated with vasopressin. Thirteen of these had Stage 1 palliation of a single ventricle (Norwood procedure), two underwent the Ross procedure, and two had the arterial switch operation. All patients received multiple inotropes and vasopressors prior to vasopressin administration. Vasopressin was administered at a dose of 0.1 mU/kg/min to a maximum of 0.3 mU/kg/min. The use of vasopressin resulted in a significant increase in blood pressure and decreased other vasopressors requirement. No peripheral vasoconstriction or ischemic lesions were observed (15).

In a retrospective study, Alten et al. reported use of a low dose vasopressin infusion initiated in the operating room in neonates following the Norwood procedure or arterial switch operation. Nineteen patients that received low dose vasopressin (0.3 mU/kg/min) were compared to 18 historical controls that did not received vasopressin. Mean fluid resuscitation in the first 24 hours and median maximum inotrope score was lower in the vasopressin group compared to the control group. The vasopressin group reached median net negative cumulative fluid balance sooner (55 hours vs. 76 hours) when compared to the group that did not receive vasopressin (16).

In the specific population we plan to study, Kumar reported the results of 62 consecutive patients who underwent the Fontan operation. Forty patients who received vasopressin at a dose of 0.3-0.5mU/kg/min as part of the perioperative management following Fontan operation were compared to 22 historical controls that did not. Chest tube output and duration were significantly decreased in the group that received vasopressin with a median of 22 ml/kg versus 68 ml/kg. The median duration of chest tube drainage was 6 days less in the group that received vasopressin.

Median hospital length of stay was reduced from 16 to 9 days (17). This was a retrospective study, but the results were dramatic and not readily explained by any other practice change.

Vasopressin use after the Fontan surgery is a promising intervention. A retrospective analysis showed dramatic reduction in length of stay and pleural drainage. A prospective, multicenter randomized controlled trial is needed to confirm these findings and make this treatment strategy available to the high risk children with congenital heart disease undergoing this surgery.

5) Inclusion and Exclusion Criteria

Inclusion criteria:

- 1.5-7 years old
- Undergoing the Fontan operation at ACH-OL

Exclusion criteria:

- Patients with a planned fenestrated Fontan
- Patients undergoing revision surgery for a prior failed Fontan procedure
- Evidence of renal insufficiency prior to surgery defined by creatinine >1 mg/dl
- Planned arch reconstruction at the time of the Fontan procedure

Withdrawal criteria:

Subjects that meet any of the following criteria will be withdrawn from the study:

- Evidence of significant renal injury after surgery defined by:
  - Doubling creatinine level from baseline and
  - Absolute creatinine level >1.5 ml/dL
- Prolonged positive pressure ventilation greater than 96 hours post operatively
- Use of open label vasopressin
- Subjects that require extracorporeal membrane oxygenation (ECMO) support

6) Study Wide Number of Subjects

Pilot Study:

A total of 10 subjects will be enrolled in a pilot study at ACH-OL. This number was selected to test feasibility and complete the pilot study within a 1 year period.

Multicenter Study:

A total of 84 subjects will be enrolled, with 42 subjects in each treatment arm: Vasopressin vs placebo (normal saline). See Section 12 for sample size and estimation rationale.

7) Study-Wide Recruitment Methods

Pilot study:

The study will be conducted in the operating room and Pediatric Surgical Heart Unit (PSHU) at ACH-OL. A total of 10 patients will be recruited. Potential subjects will be identified and contacted prior to surgery by our local study coordinator. Consent will be obtained at the pre-operative visit. Five patients will be randomly assigned to receive vasopressin while five will receive placebo (normal saline).

Multicenter study:

The study will be conducted in the cardiac operating room and the cardiovascular intensive care unit (CVICU) at 7 pediatric cardiovascular programs in the United States.

A total of 84 patients (12 per site) will be recruited. Potential subjects will be identified and contacted prior to surgery by the local study personnel at each site. The site principal investigator (PI) or other study personnel will obtain the consent during the pre-operative visit. Six patients at each site will be randomly assigned to receive vasopressin while six will receive placebo (normal saline). Seven sites were chosen in order to allow for completion of the multicenter study within a year and to test vasopressin across a range of clinical management strategies. This approach will provide more certainty that results can be generalized across all centers.

8) Study Timelines

Pilot study:

- January 2017 to October 2017: Recruitment, enrollment and data collection
- November 2017 to December 2017: Data analysis

Multicenter study:

- January 2018 to December 2018: Recruitment, enrollment and data collection

- January 2019 to March 2019: Data analysis

9) Study Endpoints

Primary Endpoints:

- Total chest tube output (cc/kg) post Fontan procedure
- Duration (days) that chest tubes remain in place (removed when less than 2cc/kg/day)

Secondary Endpoints:

- Post-operative fluid balance by day (cc/kg)
- Total length of hospital stay (days)

10) Procedures Involved

Design

The study is designed as a randomized, double blinded placebo control clinical trial to evaluate the use of vasopressin following the Fontan operation. The study will consist of two phases:

Phase 1 will be a single center pilot study and will be conducted at Advocate Children's Hospital, Oak Lawn IL. Ten patients will be enrolled and randomized in double blind fashion with five patients as control group and five receiving vasopressin. The same protocol will be used for both phases of the study. For the pilot study vasopressin levels will be obtained prior to initiation of vasopressin and subsequently on post-operative day 1. Electrolytes and albumin level will be monitored with complete metabolic panel (CMP) which will be obtained prior to surgery, on post-operative Day 1 and Day 3. Safety and effect size will be evaluated after this pilot study.

Phase 2 will consist of a multicenter study conducted in the cardiac operating rooms and cardiac intensive care unit (CVICU) of 7 pediatric cardiovascular programs in the United States. We will enroll 12 subjects undergoing the Fontan operation from each participating institution and randomization will be stratified by site. Six patients will be randomly assigned to receive vasopressin while six will receive placebo.

Sample:

Pilot study

A total of 10 patients undergoing the Fontan procedure will be included and randomized to one of the two treatment groups.

Group 1 will include 5 subjects who will receive vasopressin for 48 hours following the Fontan operation. Group 2 will include 5 subjects who will receive placebo (normal saline) and will serve as a control group.

Multicenter Trial

A total of 84 patients undergoing the Fontan operation will be included in the study and randomized to one of the two treatment groups.

Group 1 will include 42 subjects who will receive the treatment drug (vasopressin) for 48 hours following the Fontan operation. Group 2 will include 42 subjects who will receive placebo (normal saline) and will serve as a control group.

Drug administration protocol

For subjects in the experimental group, vasopressin at a dose of 0.3 mU/kg/min will be started while coming off cardiopulmonary bypass. The dose of vasopressin will be titrated in the CVICU to a maximum of 0.5 mU/kg/min according to clinical assessment. The drip will eventually be titrated down to 0.3 mU/kg/min for at least 2 hours and from that dose will be discontinued 48 hours after arrival in the CVICU.

Subjects in the placebo group will receive normal saline which will be titrated according to clinical assessment at the same 'dose' of the vasopressin group. The treating physician will be blinded.

All other clinical interventions will be at the discretion of the treating physician at each participating institution. For the multicenter trial each site is to provide their usual standard of care. The standard care at each site will be described prior to initiation of the Phase 2 study and deviations from this will be reported to the PI and recorded.

Research procedures

The subjects will be randomized by the pharmacist on site to either group of the study. Only the pharmacist will be aware of the randomization process and study drug. Randomization forms will be generated at the primary center. Identical forms will be sent to each institution so that the pharmacy team at each center will execute randomization in the same manner.

Group 1 will receive vasopressin and group 2 will receive normal saline.

Post-surgical care

Postoperative clinical interventions will be at the discretion of each participating institution per their routine care. Each site will describe their initial post-operative management strategy and this will remain consistent throughout the study. If deviation from normal treatment occurs, these will be reported. This will allow a variety of treatment strategies with vasopressin as the only difference in each center.

Data collection (see schedule of events below)

During phase one of the study (pilot study) vasopressin levels will be obtained prior to initiation of vasopressin in the operating room after coming off cardiopulmonary bypass.

Clinical data to be collected will include

- Age
- Gender
- Race
- Weight pre-operatively within one week of surgery
- Cardiac diagnosis
- History of chylothorax
- Right ventricle as systemic ventricle
- Presence of genetic syndrome
- Heterotaxy
- Pre-operative oxygen saturation (from catheterization report)
- Pre-operative creatinine (within two months of Fontan)
- Pre-operative hemoglobin (within two months of Fontan)
- Pre-operative mean pulmonary artery pressure (from the catheterization report)
- End diastolic pressure (from catheterization report)
- Degree of atrioventricular valve regurgitation (from most recent echocardiogram)
- Ventricular function (from most recent echocardiogram)
- CVP (Arrival to ICU, 6, 12, 18, 24, and 48 hours)
- Procedures performed (type of Fontan, maze, atrioventricular valve surgery, etc)
- Lateral tunnel versus extracardiac Fontan
- Conduit size

- Use of cardioplegia
- Cardiopulmonary bypass time
- Blood products used post operatively
- Vasopressin levels post operatively (Phase 1 only)
- Evidence of post-operative infection defined as culture positive infection treated with antibiotics by the clinical team
- Hourly vasoactive Inotrope score for 48 hours
- Vasopressin dose hourly for 48 hours
- Hourly systolic and diastolic blood pressure
- Maximum post-operative creatinine
- Sodium and albumin level pre-operatively, post operative day 1 and day 3 (pilot only)
- Platelet count pre-operatively and on POD 2 (pilot only)
- Inhaled nitric oxide use post-operatively
- Sildenafil use post-operatively
- Time until extubation
- Unscheduled re-intubation
- Total fluid in and out per day
- Daily chest tube output (cc/kg/day)
- Duration of chest tube output (day of surgery will be Day 0)
- Presence of chylous effusion after surgery defined as pleural triglyceride level greater than 110 mg/dL
- Presence of acute kidney injury (peak creatinine) (AKI grade 1 or higher)
- Length of stay in ICU
- Length of hospital stay
- Length of hospital stay to the day when only anticoagulation treatment is preventing discharge (defined by treating clinical team)
- Readmission within two weeks of discharge

Schedule of Events

	Screening						End Study
Visit description	Pre-operative	Time 1 Off CPB – before vasopressin (POD0)	Time 2 POD1	Time 3 POD2	Time 4 POD3	POD 5 through discharge	Discharge date
Informed Consent	x						
Demographic information	x						
Laboratory tests							
CBC	pilot			Pilot			
CMP	pilot		pilot		Pilot*		
Vasopressin		Pilot*		Pilot*			
Clinical course							
Chest tube output			x	x	x	x	x
Chest tube duration			x	x	x	x	x
Hospital stay							x
Safety adverse event reporting							
Complications			x	x	x	x	x

"pilot" represents tests that will be measured during the pilot study only to determine safety profile and determine if necessary for the multicenter trial

*=Not part of routine care and will be covered with the grant funds

11) Data and Specimen Banking

All data will be entered and stored electronically in REDCap database. This is a cloud-based database application that is centrally secured and can be accessed by authorized personnel at participating centers.

12) Data Management

Sample Size Estimation

Sample size estimation for the Phase 2 multicenter clinical trial was calculated based on the previously reported difference of 6 days between groups for the outcome of duration of chest tube in days (17). We used a more conservative difference between groups than that previously reported to accommodate the anticipated non-normal data and allow us to control for possible variation among clinical sites. Group sample sizes of 42 (study group) and 42 (control group) achieve 80% power to reject the null hypothesis of equal means when the population mean difference is 1.6 with standard deviations of 0.5 group 1 and 3.5 for group 2, and with an alpha of 0.05 using a two-sided two-sample unequal-variance t-test.

After the collection of the proposed pilot data (n=10), a power calculation will be conducted and a revised sample size estimation will be tested to confirm the estimated sample of 84 for the multi-site clinical trial.

Data management and storage

All information gathered during this study will be kept confidential. Study data will be managed using REDCap[18] electronic data capture tools hosted by Advocate Health Care. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The data will be accessible to only the study investigators and REDCap administrators. Subjects will be assigned case numbers. Data being extracted from the REDCap database will include only the case numbers and be de-identified via the electronic removal of PHI prior to data download. After data collection is complete and records have been verified, identifiers will be permanently removed from the data set.

Data access will be grouped according to site so that each site will only have access to their data. The principal investigator will have access to all data stored in the database.

Data analysis

Data analysis will include descriptive statistics of all variables of interest for each group to examine data for normality and statistical assumptions. Descriptive statistics will also be used to test for differences between clinical sites. Appropriate inferential statistics (e.g. independent t-test or Mann Whitney U) will be used to test for differences between groups for chest tube duration, output and hospital length of stay. Statistical tests will be performed as two-sided tests and will be adjusted to the multi-centric design of the study. If differences are detected between clinical sites, analysis of covariance will be used to

control for the clinical site. A 2-tailed significance level of $p<0.05$ will be used to evaluate all comparisons.

Data storage

All information gathered during this study will be kept confidential. Subjects will be assigned case numbers and data collection forms will not include any patient names. A subject log with case numbers and patient names will be maintained in a locked cabinet at each study site. No PHI will be stored in the electronic REDCap database and all data extracted from the file will be de-identified. The data will be accessible to only the study investigators and REDCap administrators. .

13) Provisions to Monitor the Data to Ensure the Safety of Subjects

Monitoring Plan

The individual responsible for data safety and monitoring will be Dr. Jamie Penk (principal investigator - PI). Quality control will include regular data verification and protocol compliance checks by Dr. Jamie Penk. In order to ensure trials at other sites are conducting appropriately monthly phone calls will be conducted.

Collection and reporting of SAEs and AEs

Throughout the study, each site investigator will monitor study participants for adverse events. Dr. Penk will review all adverse events (AEs) and serious adverse events (SAEs) individually and in aggregate on a biweekly basis until the end of the study trial (hospital discharge). Adverse events still ongoing after study drug discontinuation will be followed until 30 days after study drug discontinuation or until resolution or stabilization or until the event is otherwise explained. AEs and SAEs will be reported to the site IRB and to the study sponsor, Dr. Penk. The PI will be notified of any adverse events within 24 hours of identification. Dr. Penk will report all AEs and SAEs to the Advocate Health Care IRB and the FDA according to the AE reporting guidelines listed below. Any events will be communicated via email to the research teams at each participating study site.

For this study, the following standard AE definitions will be used:

Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease, that did not exist at the time of the subject's entry into the study and that is temporally associated with the use of the study medication, regardless of whether it is considered related to the study medication.

The following risks have been reported during the infusion of Vasopressin. These risks will be monitored individually through a review of the hospital chart on a

weekly basis and with a physical examination of the subject, if indicated. Adverse events will be reported in aggregate within the IND application annual report.

- Hyponatremia (sodium level less than 130mEq/L)
- Vomiting (recorded at number of times per day, pilot only)
- Decreased platelet count (less than 50,000)
- Limb necrosis
- Grade one acute kidney injury (creatinine 1.5 x baseline and increase of at least >0.3mg/dl)

Suspected adverse reaction: A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

Adverse Reaction: An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected Adverse Event: An adverse event or suspected adverse reaction is considered "unexpected" if it is not consistent with the risk information described in this plan.

The following risks are examples of unexpected adverse events suspected to be related to the study drug that would require reporting in this study.

- Extended Ventilatory support (Positive Pressure Ventilation > 4 days post-operative)
- Extracorporeal membrane oxygenation (ECMO) support

Serious Adverse Event: An adverse event or suspected adverse reaction is considered "serious" if, in the view of the Sponsor-Investigator it results in any of the following outcomes:

- Death
- Life threatening adverse event
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical

judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

AEs will be monitored throughout the time that a subject is in the trial (hospital length of stay). AEs will be assessed through a review of the hospital chart on a weekly basis and with a physical examination of the subject, if indicated.

REPORTING OF ADVERSE EVENTS

Events determined by the PI to involve injury or to be unanticipated problems involving risk will be reported by the PI to the IRB within 5 days per HRP 213. Adverse events that are determined by the PI not to involve injury or to be an anticipated risk of the Fontan procedure during the infusion of vasopressin will be reported per IRB policy at the time of continuing review.

An IND safety report will be reported to the FDA by the PI when an event meets all three of the definitions for *suspected adverse reaction, serious* and *unexpected*. All FDA reporting will be consistent with 21 CFR 312.32 (c).

- Unexpected serious suspected adverse reactions will be reported to FDA as soon as possible but no later than within 15 calendar days following the Sponsor-Investigator initial receipt of the information.
- Unexpected fatal or life-threatening suspected adverse reactions will be reported to FDA as soon as possible but no later than 7 calendar days following the Sponsor-Investigator initial receipt of the information.

AEs will be graded by the investigator according to the following scale:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. This includes transient laboratory test alterations.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities. This includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An event that prevents normal everyday activities. If prolongation of hospitalization is required for treatment it becomes an SAE. (An AE that is severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as mild, moderate or severe.)

The study will use the following **AE attribution scale**:

Unrelated: The AE is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered

to the subject (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Not likely related: The event was most likely produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject, and does not follow a known response pattern to the study drug.

Possibly related: The event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study drug; but it could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably related: The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug; and it cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Vasopressin treatment discontinuation due to adverse events.

Vasopressin treatment will be stopped if any of the following occur:

- Evidence of renal injury after surgery defined by creatinine doubling and with an absolute number > 1.5mg/dL through the second post-operative day.
- Prolonged need for positive pressure ventilation greater than 4 days
- Subjects that require extracorporeal membrane oxygenation support

Data Analysis Plans and Interim Reports

An independent Data Safety Monitoring Board (DSMB) will perform a statistical review of the study data and will have access to fully patient data if necessary, to ensure patient safety. The DSMB will be comprised of 3 individuals who are not involved in the conduction of the study, representing pediatric cardiology or pediatric intensive care and research. The DSMB will be empowered to recommend, based on safety considerations, modifications to the protocol or early termination of the study.

The board will function independently of the investigators. The following data will be monitored by the DSMB in an unblinded* manner:

Number and type of adverse events and serious adverse events in each group

Primary Endpoints:

- Chest tube output quantity in cc/kg

- Duration that chest tubes remain in place (remove when less than 2cc/kg/day).

Secondary Endpoints:

- Length of hospital stay
- Mortality

The DSMB will review data at the end of the single site pilot study (n=10) and during the multi-site study after enrollment of 30 and 55 subjects have been enrolled.

*The randomization code will be kept strictly confidential. This code will be provided to the DSMB by the pharmacist at each participating institution to ensure patient safety.

The DSMB will prepare and submit a report to the PI after each review. This report will be submitted to the IRB and FDA at continuing review and annual review.

14) Withdrawal of Subjects

Subjects that meet any of the following criteria will be withdrawn from the study:

- Evidence of renal injury after surgery defined by:
  - Doubling creatinine level from baseline AND
  - Absolute creatinine level >1.5 ml/dL
- Prolonged positive pressure ventilation greater than 96 hours post operatively
- Use of open label vasopressin
- Subjects that require extracorporeal membrane oxygenation (ECMO) support

When subjects are withdrawn, we will continue to collect the same data as described above. This will allow for an 'intention to treat' analysis.

15) Risks to Subjects

Risks to the patients involved in this study are related to adverse effects of the vasopressin.

Vasopressin risks are dose dependent and in this study we will be using low dose of this medication. Major side effects from vasopressin include but are not limited to hyponatremia, limb ischemia, localized blanching, peripheral vasoconstriction, water

intoxication, mesenteric ischemia, nausea, vomiting, decreased platelets count, renal insufficiency.

Off label vasopressin has been used for the treatment of gastrointestinal hemorrhage, vasodilatory shock, following complex heart surgery (Norwood, arterial switch operation), refractory, persistent pulmonary hypertension of the newborn. A retrospective study reported the use of vasopressin following the Fontan operation at a dose of 0.3-0.5mU/kg/min with no significant side effects.

All subjects in this study will be monitored in the ICU after surgery and monitored for adverse events as described in section 13. Appropriate medical care will be provided for any adverse events.

16) Potential Benefits to Subjects

There are no guaranteed benefits to any subjects in this study. The results of this study will be used to evaluate the potential benefits of vasopressin in reducing pleural effusions following the Fontan operation. Subjects in the treatment group may benefit from decreased pleural effusions and a shorter length of stay if the hypothesis is correct.

17) Vulnerable Populations

This research involves children as a vulnerable population. With that in mind, we have reviewed Checklist HRP-416 and feel that this study meets the criteria for research involving children under 21 CFR §50.51/45 CFR §46.404;

Utilization of vasopressin in children and side effects are described in section 15. Being in this study would put the children at no greater risk than other children where this medication has been used previously.

All subjects in this study will be monitored in the ICU after surgery and monitored for adverse events as described in section 13.

18) Multi-Site Research

This study will be performed at 7 different pediatric cardiovascular programs in the United States. The participating institutions sites are Advocate Children's Hospital Oak Lawn, IL; Children's Hospital and Clinics of Minnesota, Minneapolis MN; Texas Children's Hospital, Houston TX; Le Bonheur Children's Hospital, Memphis, Tennessee; Nationwide Children's Hospital, Columbus OH; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL;

Each site has a sub-investigator and research coordinator to consent patients and monitor results. IRB approval will be sought at Advocate Children's Hospital first and subsequently by each of the remaining six sites. Data will be shared via RedCap database as described in section 11.

19) Community-Based Participatory Research

Not applicable

20) Sharing of Results with Subjects

Parents will be aware of duration of chest tube drainage and other clinical outcomes. Parents will not be informed of which treatment arm their child is in.

21) Setting

Identification and recruitment of potential subjects will be conducted at Advocate Children's Hospital Oak Lawn, Il; Children's Hospital and Clinics of Minnesota, Minneapolis MN; Texas Children's Hospital, Houston TX; Le Bonheur Children's Hospital, Memphis, Tennessee; Nationwide Children's Hospital; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL.

Administration of medications and monitoring of patients will start in the operating room when patients are coming off cardiopulmonary bypass and will be continued in the pediatric intensive care unit of the above participating institutions.

22) Resources Available

Dr. Penk, the PI, has extensive experience treating patients with congenital heart disease post-operatively. He has completed a cardiology fellowship at Lurie Children's Hospital and a critical care fellowship at Children's National Medical Center. He has over three years experience as an attending in the cardiac intensive care unit at Advocate Children's Hospital. Dr. Penk has experience carrying out and designing scientific studies. Prior publications include several retrospective studies of patients with congenital and acquired heart disease. Dr. Penk also served as the PI for a prospective, randomized, double blinded trial of pain and sedation strategies. This study also required safety monitoring and reporting and administration of medication in a blinded fashion. Outcomes were studies in the cardiac intensive care unit, similar to the proposed study.

Nathanya Baez Hernandez, MD (Co-Investigator) is a pediatric cardiology fellow at Advocate Children's Hospital-Oak Lawn. She is involved in the design and conduction of this study. She is the first author for the phase one of the study (pilot study).

Six other sub-investigator from the six participating sites will be involved in this research project (please refer to page 1 for their names and institutional affiliations).

Cheryl Lefaiver, PhD, RN, CCRP, Manager, Patient Centered Outcomes Research will be a collaborator on this project and will assist with data management and statistical analysis.

Julie Connolly, BSN, RN, CCRN (sub-investigator and regulatory coordinator) is a Pediatric Senior RN Research Coordinator for Advocate Center for Pediatric Research at Advocate Children's Hospital-Oak Lawn. She will serve as coordinator for this study.

23) Prior Approvals

Not applicable

24) Recruitment Methods

Patients will be identified via the surgical schedule. All patients undergoing the Fontan operation will be evaluated for eligibility.

25) Local Number of Subjects

For the pilot study, 10 patients will be included. For the multicenter study, 12 patients will be enrolled from each site. This will represent a total of 22 patients from the Advocate Children's Hospital site (pilot and multicenter phases).

26) Confidentiality

All information gathered during this study will be kept confidential. Data collection forms and the database that include the patient name and other protected health information will be seen only by the principal investigator and research team at each site. All information and data gathered in this study will be placed in a password-protected computer with restricted access by only the investigative team. The results of this study may be published in scientific journals or be presented at professional meetings, but no individuals will be identified. A federal regulatory agency and the Institutional Review Board may inspect the research-related records for this study.

27) Provisions to Protect the Privacy Interests of Subjects

See Protocol Section 12 and 26

28) Compensation for Research-Related Injury

If the subject needs any medical care because of taking part in this research study, that care will

be made available. No funds have been set aside by Advocate health Care as compensation for

research related injury or associated costs

29) Economic Burden to Subjects

The patient is not responsible for any extra costs related to the research. Every intervention except the vasopressin use is included as part of the standard of care. Grant support will be obtained to fund research coordinator support, IRB costs, pharmacy costs for vasopressin and randomization and for biostatistics support.

30) Waiver of Consent Process

No applicable. Written parental informed consent will be obtained from each child's parent or legal guardian prior to surgery.

31) Consent Process

Written parental permission/informed consent will be obtained from each child's parent or legal guardian prior to surgery. We will follow procedures outlined in SOP HRP-090 to obtain informed consent/parental permission.

The consent will be sent to the parents of the identified subject via mail in advance for their review. Also, if the parents agree to consider participating in the research study, the principal investigator or one of the sub investigators will call them to explain the research study and the consent in detail and answer any questions they may have in regards to the research study. The consent will be finally discussed with parents during their preoperative visit to cardiovascular surgical clinic and/or prior to the surgery. The consent process will be constantly reviewed by the principal investigator to ensure that the consent is being obtained in an appropriate manner.

The informed consent process will take place at the same time the consent for surgery is obtained. The consent for surgery is usually obtained 1-2 days before surgery date. Consent will be obtained and explained only by personnel who have been approved for obtaining the consent (principal investigator, sub investigator, advanced cardiovascular nurse practitioner). Approximately 15 to 30 minutes will be assigned for discussing the research study and potential related risks to the subject. The person obtaining the research consent will clearly distinguish its difference from the surgical consent. If the parents want to think about the research study, they will have sufficient time to decide whether to enroll or not. All questions will be answered prior to obtaining consent.

Non-English Speaking Subjects

There is a potential that a patient with Spanish speaking parents will be invited to participate in this study. In this case, the Spanish short form will be used for consent with the English consent presented orally in Spanish with the assistance of an interpreter.

Subjects who are not yet adults (infants, children, teenagers)

All subjects involved in the study are < 8 years of age. The consent form will be obtained from at least one parent before any study procedures are performed, though both parents will be encouraged to discuss the child's participation.

32) Process to Document Consent in Writing

We will be following procedures outlined in SOP HRP-091. The consent for the research study will be documented together with the consent for surgery as a note in the medical record of the patient.

33) Drugs or Devices

Vasopressin is already available and has been used off label in children with vasodilatory shock, diabetes insipidus, gastrointestinal bleeding, following complex heart surgery (Norwood, arterial switch operation), refractory, persistent pulmonary hypertension of the newborn. At least one institution uses vasopressin successfully as part of their standard of care in patients following the Fontan operation (Kumar et al).

An application for an investigational new drug (IND) was submitted to the Food and Drug Administration and approved. The IND number is 132609.

34) Glossary of acronyms

ADH: Antidiuretic hormone

CPB: Cardiopulmonary bypass

CVICU: Cardiovascular intensive care unit

CMP: Comprehensive metabolic panel

CBC: Complete blood count

REDCap: Research Electronic data Capture

DSMB: Data Safety Monitoring Board

ACH-OL: Advocate Children's Hospital-Oak Lawn

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