Management of Acute Pulmonary Hypertensive Crisis in Children with Known Pulmonary Arterial Hypertension

Study Protocol

NCT05439460

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Scientific protocol

1) **Name of study:** Management of acute pulmonary hypertensive crisis in children with pulmonary arterial hypertension (PAH)

2) **PI and other key investigators or key study personnel:**

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3) **Specific source of institutional funding:**

Internal or Departmental funding

4) **List of sources from which you are seeking funds (or have sought funding) for this project:**

Once we have pilot data we will apply for external funding.

5) **Specific Aims and basic hypothesis including an explicit primary hypothesis or goal**

From this prospective study we will demonstrate that

1) Phenylephrine can be safely used to treat PH crisis
2) Arginine vasopressin may be better since it decreases pulmonary artery pressure while increasing systemic blood pressure
3) Epinephrine, the drug most commonly used for resuscitation, will be the least effective in managing PH crisis.

6) **General background (2 page maximum including published preclinical and animal data supporting basic hypothesis, if relevant).**

PAH increases perioperative morbidity and mortality in children [1-4]. Acute exacerbations of PAH, commonly referred to as PH crisis, must be recognized early and managed expeditiously to avoid cardiac arrest and death. Results of resuscitation following arrest are poor in this population therefore rapid recognition and management are essential. PAH crisis may present as systemic hypotension with or without EKG changes of ischemia and associated increase in mean PA pressure. The goal of resuscitation in this situation must be to increase aortic pressure and cardiac-output so right heart coronary filling and output are maintained. However there is no consensus on what is the optimal therapy to achieve this. While administration of pulmonary vasodilators, systemic or inhaled, may be effective and the patient may already be on such therapy, these agents may not provide rapid additional decreases in pulmonary vasculature required to support the failing right ventricle.

Although vasopressors have been widely used to resuscitate the right ventricle, this

practice is controversial. Vasopressors such as nor-epinephrine, phenylephrine, isuprel and dobutamine have been advocated in managing PH patients in the intensive care units. However, there is no consensus on the optimal agent or dosing regimens.

Epinephrine, the vasopressor a part of most ACLS protocols, has instant appeal for reasons of cost and ease of availability. The theoretical reasons to avoid catecholamines such as epinephrine or nor epinephrine, would be the increase in heart rate (Beta agonist effect), which would further reduce coronary filling and worsen myocardial ischemia, despite the increase in SVR caused by systemic vasoconstriction (alpha receptor mediated effect). In patients with PAH, depending on its severity, coronary artery filling of both ventricles occurs mostly during diastole and increases in HR could reduce the coronary flow. There are no trials of epinephrine in acute PH crisis. However norepinephrine has been used successfully in an observational study of newborns with PPHN (Persistent Pulmonary Hypertension of Newborn), with improvements in echo derived measures of LV output, LV pressure, and a decrease in pulmonary/systemic pressure ratio. Additional neonatal animal data and data in adult humans also support the use of norepinephrine in PPHN and PHN respectively. There are no systematic trials in pediatric patients with chronic PHN, with acute exacerbations. Phenylephrine is a pure alpha agonist and increases the both SVR and PVR without increases in HR. However the increase in SVR with resultant improved coronary perfusion and despite the increase in PVR, the ratio of SVR/PVR favors improved interventricular interaction. Studies of phenylephrine showing benefits or not are in adults with PHN[10, 11].

Arginine vasopressin is a systemic vasopressor used in vasodilatory shock and cardiopulmonary resuscitation in both adults and children. It has been used widely for managing acute gastrointestinal bleeds in both adults and children ([6,9]). This would appear to be an ideal agent as it is not a catecholamine hence has no stimulating effects on heart and produces systemic vasoconstriction. In addition, it has pulmonary vasodilatory effects ([6]). AVP causes endothelial dependent vasodilatation by binding to endothelial V1 receptor. Recent case reports discuss the use of AVP or a synthetic analogue in children with PAH in the perioperative setting and in septic shock ([9-review]).

Traditionally at LPCH, we have used phenylephrine for hypotension and management of PAH crisis. Annually about 40 children undergo cardiac catheterization for diagnosis or follow up of PAH. From a 12 month review of anesthesia data, we noted a 1% use of phenylephrine (0.5-1 µg/kg bolus administered one or more times) to manage systemic hypotension and or PAH during the procedure. In 4 patients with PAH undergoing cardiac catheterization, detail records were available to assess hemodynamic information. Of the 3, there was no change in PVR/SVR in one 1 (equivocal), in another the ratio increased (not a benefit) and in the other 2 the ratio decreased (benefit). In all 4, cardiac indexes were maintained after phenylephrine. We also noted from this data that the effects of phenylephrine were not detectable beyond 5 minutes and pressures returned to baseline. In addition anecdotal evidence from our institution on the use of phenylephrine in the operating room in children with PAH undergoing non-cardiac procedures to treat acute PH crisis exists.

7**)** **Preliminary unpublished data (1 page maximum)**

In 4 patients with PAH we had complete hemodynamic data when phenylephrine was required. In 2 of the 4 the PVR/SVR change was beneficial; with no change in 1 and in another a small increase in PVR/SVR. We have no experience with AVP in this population in the cath lab. Epinephrine has never been our drug of choice, although an anecdotal report of significant tachycardia with a 5μg/kg dose was recorded.

8) Experimental design and data analysis, including inclusion and exclusion criteria, statistical basis for the number of subjects to be enrolled, the statistical plan for analyzing at least the primary hypothesis, matrix showing procedure plan for each study visit, data safety monitoring plan (4 pages maximum)

Study protocol: This is an open label study which will be done in 3 phases, allowing us to assess safety and efficacy of treatment as the study progresses.

Phase 1: Following baseline hemodynamic catheter measurements, baseline transthoracic echo will be obtained to assess the position of interventricular septum. Following these measurements a 1 μg/kg bolus of phenylephrine will be given and hemodynamic data continuously recorded for up to 5 minutes after the bolus. We expect that phenylephrine will increase both mean pulmonary (MPAP) and systemic arterial pressure (MSAP) but the MSAP increase will exceed MPAP increase, favoring coronary arterial blood flow to the right ventricle. Further if cardiac index is unchanged then the increase in SVR will be greater than increase in PVR such that the ventricular septal shift toward the right will favor improved LV output. In addition to making hemodynamic catheter measurements, transthoracic echocardiography will be repeated 2 minutes following bolus.

End Points of the study: Table 2 outlines the hemodynamic measurements that will be made at baseline and at 2 minutes after end of bolus. Adverse events will be described as a 20% increase in mean PAP or a 20% increase in PVRI, or a 20% decrease in CI or MVO2. After studying 10 consequential patients with phenylephrine we will then start the next phase of the study.

Phase 2: epinephrine bolus as 1μ/kg will be administered and measurements repeated. There will be 10 patients in this category. The dose chosen is based on the current "dwindle" dose used in the ICU's to treat sudden hypotension. The full code dose of 10μg/kg will be excessive in this population. As we have anecdotal report of tachycardia even with 5μg/kg IV in this population.

Phase 3: These will be patients with a known diagnosis of PAH undergoing cardiac catheterization. This is a dose escalation study of arginine vasopressin as a treatment to alter the SVRI/ PVRI ratio in patients with PAH. Baseline data will be collected as in phase 1. Following baseline data collection, a single dose of AVP will be administered. Dose of AVP used in children with septic shock is 0.01-0.03 units/kg and the duration of effect is 30 minutes. For the purposes of this study we will use of 0.01 units/kg as the dose. This dose might have no significant effect on any of the measured hemodynamics. If this pattern is consistent in 5 patients then we will increase the dose to 0.02units/kg and reassess the hemodynamics in an

additional 5 patients. If this dose also does not alter hemodynamics and there are adverse events then we will increase the dose to 0.03 units/kg in additional 5 patients No further dose escalation is planned. Dr Pearl, chairman of Anesthesia has anecdotal reports administering 1 unit of AVP to adults in PAH crisis with significant improvement. Our initial dose of 0.01 u/kg may be insufficient as children have a larger volume of distribution. However we have never systematically studied this medication in this group and are conservative.

Inclusion criteria: Patients 1-18 years of age with diagnosis of PAH either by previous cardiac catheterization or by echocardiography.

Exclusion criteria: PAH patients with intracardiac shunts; failure to obtain consent; emergency cases done at night or weekends where staff may not be available for following the protocol

For the current study a power analysis was not performed. Annually about 50 cardiac catheterization are performed in children with PH. About 20% have intra-cardiac shunts and we expect 10% refusal rate for consent. We expect to draw from the remaining 70% to get pilot data. With this preliminary data we plan to compute the statistical power. This question has not been studied systematically in children and we are confident that preliminary results will be valuable for planning future studies and funding.

Table 1: Demographic data:

Name	Age
Gender	Height
Weight	BSA
Diagnosis	Current Medications
Date of Procedure	

Table 2: Data Collection during the study

Drug Name and Dose:		
Parameter	Baseline	Post treatment
HR (beats/min)		
ECG		
Systemic Systolic pressure (SSAP)		
Diastolic (SDBP)		
Mean (SMAP)		
Pulmonary Systolic		
Pulmonary Diastolic		
Pulmonary Mean (MPAP)		
RVEDP		
RAP		
PCWP		
CI		
MVO2		
SaO2		

Calculated PVRI/SVRI		
Transthoracic Echo (septal position)		

Data Safety Monitoring Plan:

Protocol Director will be the monitoring entity. In addition to height, weight, age and gender the following will be collected: Heart rate, blood pressure: systolic, diastolic, mean; ECG, mixed venous oxygen saturation, arterial blood gas, pulmonary artery pressure: systolic, diastolic and mean, pulmonary capillary wedge pressure. If there are allergic reactions to any of the medications that will be noted under adverse events and the events reviewed carefully. This will help us determine if any changes need to be made to the protocol.

Unanticipated events will be reported within 10 days to the IRB.

Study data will be assessed at the end of each phase. If any of the medications result in hemodynamic responses that are unfavorable to the patient, such as decrease in systemic blood pressure but increased pulmonary artery pressure we will stop to review data and decide whether we need to change what we are doing.

9) **Significance (1 paragraph or less)**

Pulmonary arterial hypertension (PAH) is a disease where the blood pressure in the pulmonary arteries (PAP) are high[4]. PAH increases the risk of adverse events, including risk of death, during and or after procedure. The severity of baseline PAH correlates with the incidence of major complications, such that those with PAP higher than their systemic blood pressure (SBP) had a 8 fold increased risk of complications. These children present for procedures where an acute exacerbation of their chronic illness-termed PH crisis, can occur, often resulting in death if not detected and managed expeditiously. Unfortunately there is little data and no consensus in the pediatric literature on how PH crisis should be managed. Over the last 10 years we have developed considerable expertise in managing children with PAH and preventing and treating their acute crisis, using a medication called phenylephrine. This medication is routinely used to increase the blood pressure in patients (adults and children) with hypotension. Our theory has been that by increasing SBP, we can increase the blood flow to the coronary arteries and prevent the right ventricle from failing acutely. The latter can result in catastrophic hypotension, heart arrhythmias and death. There is no consensus or protocol guiding the management of the acute crisis. This purpose of this study is to close that gap.

10) **Key references:**

1. Williams GD, Maan H, Ramamoorthy C, Kamra K, Bratton SL, Bair E, Kuan CC, Hammer GB, Feinstein JA: Perioperative complications in children with pulmonary hypertension undergoing general anesthesia with ketamine. Paediatric anaesthesia 2010; 20: 28-37

2. Carmosino MJ, Friesen RH, Doran A, Ivy DD: Perioperative complications in children with pulmonary hypertension undergoing noncardiac surgery or cardiac catheterization. Anesthesia and analgesia 2007; 104: 521-7
3. Ramamoorthy C, Haberkern CM, Bhananker SM, Domino KB, Posner KL, Campos JS, Morray JP: Anesthesia-related cardiac arrest in children with heart disease: data from the Pediatric Perioperative Cardiac Arrest (POCA) registry. Anesthesia and analgesia 2010; 110: 1376-82
4. Friesen RH, Williams GD: Anesthetic management of children with pulmonary arterial hypertension. Paediatric anaesthesia 2008; 18: 208-16

5. Abman SH: Pulmonary hypertension in children: a historical overview. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2010; 11: S4-9
6 Evora P, Pearson P, Schaff H: Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. Chest 1993; 103: 1241-1245
7 Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ: Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. Critical care 2010; 14: R169
8 Taylor MB, Laussen PC: Fundamentals of management of acute postoperative pulmonary hypertension. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2010; 11: S27-9
9 Wolf A: Vasopressin in paediatric practice. Paediatric anaesthesia 2008; 18: 579-81
10 Zamanian RT, Haddad F, Doyle RL, Weinacker AB: Management strategies for patients with pulmonary hypertension in the intensive care unit*. Critical care medicine 2007; 35: 2037-2050
11 Kleinman ME, de Caen AR, Chameides L, Atkins DL, Berg RA, Berg MD, Bhanji F, Biarent D, Bingham R, Coovadia AH, Hazinski MF, Hickey RW, Nadkarni VM, Reis AG, Rodriguez-Nunez A, Tibballs J, Zaritsky AL, Zideman D: Part 10: Pediatric basic and advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 2010; 122: S466-515