

**Cincinnati Children's Hospital Medical Center
Division of Cardiology**

Protocol Title: Early Renal Replacement Therapy vs. Furosemide for Neonates with Oliguria after Cardiopulmonary Bypass

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1. ABSTRACT

Background: Acute kidney injury (AKI) is a common postoperative complication after heart surgery with cardiopulmonary bypass (CPB). Multiple studies have demonstrated that patients with AKI have worse clinical outcomes, such as longer ventilation times and increased length of stay, which is thought to be secondary to associated oliguria and subsequent fluid overload. Studies suggest that early renal replacement therapy (RRT) via peritoneal dialysis (PD) may prevent fluid overload and therefore be a superior management to diuretic (i.e. furosemide) administration. However, there is no published evidence to suggest superiority or laboratory data available to guide decision making.

Objective: Our primary objective is to determine if early institution of PD improves clinical outcomes compared to administration of furosemide in post-operative cardiac infants with acute kidney injury. We hypothesize that early initiation of PD will improve clinical outcomes. We will determine if these clinical outcomes will be better among good responders to furosemide compared to poor responders. We will determine if postoperative NGAL concentrations are predictive of poor response to furosemide.

Design / Methods: The study will be a single-center randomized clinical trial among neonates undergoing cardiac surgery with CPB with planned placement of a PD catheter due to risk of AKI. If patients demonstrate oliguria within the first postoperative day, they will be randomized to early PD or trial of furosemide. Clinical and laboratory data will be collected and compared between groups.

2. PURPOSE OF STUDY

Primary Aim:

The primary aim is to determine if infants with oliguria after CPB will have better clinical outcomes when initiated on early PD rather than trialed on furosemide. Oliguria is defined as urine output of < 1 ml/kg/hr for a 4 hour (cumulative) period within the first 24 hours after surgery. Clinical outcomes include: fluid balance, time to negative fluid balance, length of hospital and CICU stays, duration of mechanical ventilation, and in-hospital mortality rate.

Fluid balance is defined as the net difference of postoperative inputs and outputs during the past 24hrs calculated at 6am on postoperative day (POD) 1 and 2. Time to negative fluid balance is defined as the time (increments of 8hr shifts) when all outputs exceed all inputs within the postoperative period. The day of surgery will be considered POD0.

The primary outcome is the percentage of patients who have a negative daily fluid balance during the 24hrs from 6am on POD1 to 6am on POD2. The secondary outcomes are the fluid balance at 6am on POD1 and POD2, time to negative fluid balance, length of hospital and CICU stay, duration of mechanical ventilation, and in-hospital mortality rate.

Our primary hypothesis is that compared to those who are first trialed on furosemide, infants with postoperative oliguria who are initiated on early PD will have higher incidence of negative fluid balance.

Our secondary hypotheses are:

Compared to those who are first trialed on furosemide, infants with postoperative oliguria who are initiated on early PD will have:

- 1) less time to negative fluid balance;*
- 2) shorter hospital stay;*
- 3) shorter CICU stay;*
- 4) shorter duration of mechanical ventilation;*
- 5) lower in-hospital mortality rate;*

Secondary Aims:

Secondary aim 1 is to determine if clinical outcomes will differ between patients who are good responders to furosemide and those who are poor responders to furosemide. Patients who are randomized to furosemide treatment after oliguria will be included in the analysis. Outcomes will include percentage of patients with negative fluid balance on POD2, time to negative fluid balance, length of hospital and CICU stay, duration of mechanical ventilation, and in-hospital mortality rate.

We hypothesize that when compared to infants who are good responders to furosemide, those who are poor responders will have worse clinical outcomes including:

- 1) incidence of negative fluid balance during the 24hrs from 6am on POD1 to 6am on POD2*
- 2) time to negative fluid balance;*
- 3) duration of hospital stay;*
- 4) duration of CICU stays;*
- 5) duration of mechanical ventilation;*
- 6) in-hospital mortality rate;*

Secondary aim 2 is to determine if urine and plasma NGAL are predictive of poor responsiveness to furosemide (need for RRT) in patients with oliguria following CPB. Patients who are randomized to furosemide treatment after oliguria will be included in the analysis. Poor response to furosemide is defined as less than 1ml/kg/hr over the subsequent 16 hours after initiation of treatment post oliguria.

We hypothesize that urine and plasma NGAL at 2 hours post initiation of CPB are significant predictors of subsequent poor responsiveness to furosemide with higher NGAL concentration corresponding to higher risk of poor responsiveness to furosemide.

Secondary aim 3 is to determine if infants with oliguria post-CPB will have improved markers of well-being when initiated on early PD rather than trialed on furosemide. The following outcomes will be collected and compared between the two treatment groups.

1) Respiratory indices: A modified oxygenation index will be derived by the product of Mean Airway Pressure and FiO_2 ($\text{MAP} \times \text{FiO}_2$) to represent respiratory status at 24 and 48 hours after the initiation of CPB. Lower oxygenation indices demonstrate less need for respiratory support and thus improved status.

We hypothesize that infants who are initiated on early PD will have lower respiratory indices at 24 and 48 hours after the initiation of CPB, than those trialed on furosemide.

2) Electrolyte derangements: Each patient will be given a score to account for the number of electrolyte abnormalities on the AM renal panel (collected at 4am) and whether medications are given to correct the electrolyte abnormalities, on the second, third, fourth and fifth postoperative morning.

One point will be given for each of the following check list.

- i) hypokalemia (potassium (K) $<$ 3)
- ii) hypochloremia (chloride (Cl) $<$ 90)
- iii) metabolic alkalosis (bicarbonate (bicarb) $>$ 30)
- iv) azotemia (blood urea nitrogen (BUN) $>$ 30)
- v) One or more dose of potassium chloride (KCL) was given over the previous 24 hours
- vi) One or more dose of arginine hydrochloride (arginine) was given over the previous 24 hours

The total “Electrolyte Derangement” score for each patient is the sum of points up to a maximum of 6. Lower scores correlate with lower electrolyte abnormalities and represent better outcome.

We hypothesize that infants who are initiated on early PD will have lower “Electrolyte Derangement” scores on the second, third, fourth and fifth postoperative morning.

3) Doses of potassium chloride (KCl) and arginine chloride for the correction of electrolyte abnormalities: Total doses given over first 5 days postoperative will be counted. Administration of KCL and arginine will be at the discretion of the attending CICU physician.

We hypothesize that infants who are initiated on early PD will require fewer doses of KCL and arginine for the correction of electrolyte abnormalities.

4) NGAL levels: NGAL level is a measure of AKI with higher concentrations relating to worse outcomes. Urine and plasma NGAL will be measured at 2, 6, 12, 24 and 48 hours after the initiation of CPB. Both urine and plasma NGAL concentration levels will be quantified by two methods: the area under the curve (AUC) of the 48-hour concentration curve and the proportion of patients with NGAL $<$ 50 ng/ml at 12 and 24 hours after the initiation of CPB.

We hypothesize that for both urine and plasma NGAL, infants who are initiated on early PD will demonstrate lower 48-hour AUC and greater proportion of infants with NGAL $<$ 50 ng/ml at 12 and 24 hours after the initiation of CPB, respectively.

5) Cardiac well-being: Brain natriuretic protein (BNP) will be used as a marker of cardiac well-being and will be checked at 24 and 48 hours after the initiation of CPB. Lower BNP represents better cardiac well-being.

We hypothesize that infants who are initiated on early PD will have lower BNP at 24 and 48 hours after the initiation of CPB than those trialed on furosemide.

Secondary Outcome 4 is to determine if patients started on PD will have lower levels of serum inflammatory markers and if drained PD effluent contains inflammatory markers. PD effluent will be collected at 6, 12, and 24 hours post bypass and analyzed for levels of inflammatory markers (IL-6,IL-10, TNF- α an IL-1 β) and NGAL. Serum will be tested for similar inflammatory markers at 6, 12, and 24 hours post bypass initiation.

We hypothesize that infants on PD will show decreased rise in inflammatory markers demonstrated through AUC calculations. We also hypothesize that the effluent collected will contain elevated presence of inflammatory markers in patients with AKI demonstrating clearance through PD.

3. BACKGROUND

Acute kidney injury (AKI) is a common postoperative complication after heart surgery with cardiopulmonary bypass (CPB), occurring in 30-40% of adults and children [1-3]. Multiple studies have demonstrated that patients with AKI have worse clinical outcomes, including prolonged need for mechanical ventilation, longer intensive care unit (ICU) and hospital stays and higher mortality [4-6]. Neonates with congenital heart disease are particularly vulnerable to AKI, likely due to a combination of immaturity of the kidney and higher complexity of surgical repair [3, 7]. Studies done at this institution confirm that younger age is a consistent risk factor for development of post-CPB AKI [3, 8, 9].

Although a rise in serum creatinine has been used to define kidney injury, this is commonly preceded by oliguria [3, 10]. In many ICU settings, furosemide is used as first-line therapy for oliguria, despite multiple studies questioning this practice in the setting of AKI. Several studies have suggested that early use of renal replacement therapy (RRT) prior to a rise in serum creatinine, may be beneficial supportive therapy in the AKI setting among critically ill patients and associated with improved clinical outcomes [11-13]. However no universal guidelines exist suggesting what clinical factors should be used to determine initiation of RRT, most commonly in the form of peritoneal dialysis (PD). Although serum creatinine is the most commonly used laboratory marker for AKI, it has significant delays in elevation, making it a poor tool for directing time-sensitive interventions. The recent discovery of novel biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) have proved effective in earlier detection of AKI [1, 7, 14-17], yet little investigation has been done to help guide therapeutic decisions based upon these data. Clinical studies have demonstrated an association of elevated urine and plasma NGAL concentrations (NGAL>150 ng/ml) at 2 hours post initiation of CPB with later increased creatinine and AKI [1].

As such, it has become a common practice at CCHMC to electively insert peritoneal dialysis catheters in high risk infants at the time of cardiac surgery. These infants have a preoperative consultation by the nephrology service and thus are enabled to have easy and rapid initiation of dialysis if necessary. There are active guidelines used to stratify the risk of developing AKI, and direct PD catheter placement accordingly. It has become standard of care, at this and other institutions, to begin the use of PD at time of oliguria, making it somewhat of a misnomer to use phrase “early PD.”

4. STUDY DESIGN

Study Design Overview: The study will be a single-center randomized clinical trial among neonates undergoing cardiac surgery with CPB and who have planned placement of a PD catheter due to high-risk of AKI. Postoperatively, if patients demonstrate oliguria within the first postoperative day, they will be randomized to early PD or trial of furosemide. Those randomized to furosemide who demonstrate poor response (lack of improvement in urine output) will be initiated on PD. Clinical and laboratory data and markers of AKI will be collected and compared. Full details of study are described below.

5. DURATION

The study is anticipated to take approximately 36 months to complete, including 18-24 months for patient recruitment and data collection and an additional 12 months for data QA/QC, final data cleansing, statistical analysis, and completing a manuscript.

6. SELECTION & RECRUITMENT OF PARTICIPANTS

- Inclusion Criteria.
 - Age less than 6 months of age;
 - Undergoing cardiothoracic surgery with CPB;
 - Planned placement of PD catheter per established standard of care criteria, (see attachment).
- Exclusion Criteria.
 - Have pre-existing chronic kidney disease stage 3 or above (correlating with estimated GFR<60 ml/min/m², which will be calculated using routine preoperative serum creatinine value using the modified Schwartz equation).
 - Known history of allergy to furosemide.

The study Principal Investigator (PI), PI designate, or research coordinator (Research Team) will have the responsibility for case finding and subject recruitment. Potential study participants will be identified by reviewing the surgical schedule and in-house patients daily and by attending Surgical Conference and Pediatric/Cardiac CICU rounds. The majority of patients will be neonates. Although this population is particularly vulnerable, involvement in this study is comparing two different standard practices. It will be made

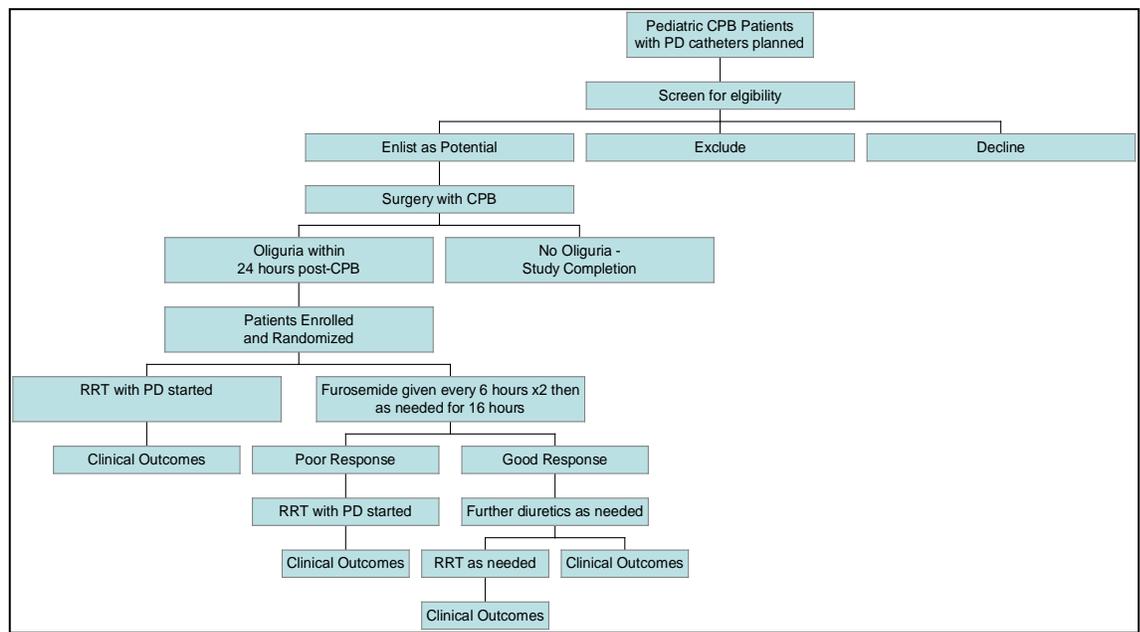
clear that neonates will not have any negative impacts on their care if they decide not to enroll. Data (demographic, eligibility criteria, and informed consent status) will be recorded on a screening form for all eligible patients, regardless of their inclusion in the study, for definition of the study population. The medical records of eligible patients who are not enrolled because of parent or physician preference will be reviewed for baseline demographic information only. Such information will be used to evaluate for possible recruiting bias.

7. PROCESS OF OBTAINING CONSENT

The Research Team will discuss appropriateness for study inclusion with the clinical team, and contact the family pre-operatively, either in the Cardiac CICU (if inpatient) or during the pre-admission visit (rarely, if outpatient.) Details of the study will be reviewed with one or both parents prior to obtaining consent. All patients will be under the age of 6 months and therefore only parental consent will be necessary. Through our AKI studies at CCHMC since 2003, in which we have successfully recruited over 900 subjects for the identification of biomarkers and follow-up of AKI, we have created and sustained a robust system for patient recruitment, specimen collection, and biomarker testing.

8. STUDY PROCEDURES

All patients below 6 months of age scheduled for cardiac surgery with CPB and planned placement of a PD catheter as part of our standard of care, will be screened. Legal guardians of the patient will be approached for informed consent prior to enrollment. Patients are typically inpatients



preoperatively. In most cases there is adequate time during preoperative planning to obtain consent. However, in the event that an emergent procedure was necessary, that patient may not be able to be included. Based on our past numbers, this is an exceedingly rare occurrence (<1% of cases). All patients will receive standard of care regardless of treatment assignment. As per routine, all patients will have a preoperative nephrology consult for determination and preparation of PD dialysate prior to surgery.

Intraoperative treatment

Following placement of routine indwelling venous or arterial line, patients will have plasma and urine samples collected for NGAL and BNP testing prior to the initiation of CPB (baseline). At 2 hours after onset of CPB plasma and urine will be collected for NGAL testing. Intravenous (IV) fluid management and use of inotropes will be at the discretion of surgeon and anesthesiologist assigned to the case but will follow standard protocol. These will be recorded for comparison purposes. Routine use of CPB will be initiated. PD catheter will be placed as clinically indicated, regardless of study enrollment. Data collected within the OR will include surgeon, bypass time, cross-clamp time, use of regional cerebral perfusion or deep hypothermic circulatory arrest, and intraoperative fluid administered and urine output. Time at initiation of CPB will be considered hour 0.

Postoperative management and treatment

Upon returning to the CICU, patients will receive routine postoperative care including IV fluids and inotropic medications. As part of our current clinical standard of care, infants who develop oliguria as evidenced by < 1 ml/kg/hr. during any cumulative 4 hour time period within the first 24 hours after initiation of CPB, will be

randomized to either the PD arm or the furosemide arm. Randomization will be stratified by RACHS-1 risk stratification score to ensure similar patient distribution. Two strata will be used: RACHS-1 score of 6 (i.e. patients undergoing Norwood procedures) and RACHS-1 score less than 6. This will ensure similar patient populations in each arm of the study. Patients who do not develop oliguria within the first 24 hours after surgery will receive standard care without further study intervention but will have data collected until hospital discharge. Patients within the PD arm will begin PD with a standardized dialysis plan of 10ml/kg of 1.5% Dianeal™ with 1 hours cycles (5 minute fill, 45 minute dwell and 10 minute drain). Further PD management will be directed by CICU attending and Nephrology service.

Patients randomized to the furosemide arm will be given 1 mg/kg intravenously every 6 hours for 2 doses and then as directed by CICU attending to augment urine output. Patients within this arm who have urine output <1 ml/kg/hr over 16 hours after the first dose of Lasix will be considered poor responders. These patients may be started on PD if clinically indicated. Those who show good response (urine output >1 ml/kg/hr over subsequent 16 hours) will continue furosemide as needed to augment urine output. If they subsequently develop oliguria or fluid overload unresponsive to diuretic therapy, these patients may later be started on PD at discretion of CICU attending with consultation of nephrology service. Clinical outcomes will be collected.

Administration of IV fluids, inotropic drugs, other diuretics and similar basic care will be unaffected in both arms. Patients will receive IV fluids 80% of maintenance during the first 24 hours, and 100% for the subsequent postoperative day. Management of PD will be directed by the nephrology service and standardized in the PD arm. Ventilatory weaning and extubation, transfer from the CICU and discharge from hospital will be directed by the attending physician.

To ascertain the rise and fall (and AUC) of urine and plasma NGAL, urine (0.2-5 ml) and blood (1.5 ml) will be collected from indwelling catheters preoperatively and at 2, 6, 12, 24 and 48 hours after CPB. NGAL concentrations will be collected from all potential participants throughout the first 24 hours, while determining if they will develop oliguria. Serum BNP (1ml) will be collected preoperatively and at 24 and 48 hours after initiation of CPB. Serum will be measured for cytokine concentration (no additional collection required) at 6, 12, and 24 hours post bypass. At these time points PD effluent will also be collected for measurement of cytokines and NGAL, for assessment of PD clearance. Representative cytokines will include IL-6, IL-10, IL-1β and TNF-α (or others as commercially available). In order to not influence fluid balance outcome, only 5ml will be collected. Collected effluent will be counted in fluid balance for primary outcome. Serum creatinine and BUN will be measured daily as part of routine postoperative care and values recorded. No venipuncture will be performed solely to obtain blood for study purposes. Total blood collected for the study is 11ml over 48 hours. Given an estimated patient weight of 3kg, the estimated blood loss is 4ml/kg, which is not expected to increase the need for blood transfusion or other complications.

| Randomization | PreOp / Pre CPB | | Post CPB | | | | | | | | | |
|--------------------------------|----------------------|---------|----------|----------|---------|----------|---------|----------|---------|---------|---------|--|
| | X (only if oliguric) | | | | | | | | | | | |
| Study Hour | | 2 hours | 6 hours | 12 hours | AM POD1 | 24 hours | AM POD2 | 48 hours | AM POD3 | AM POD4 | AM POD5 | |
| Urine NGAL # | 1 | 2 | 3 | 4 | | 5 | | 6 | | | | |
| Blood NGAL # | 1 | 2 | 3 | 4 | | 5 | | 6 | | | | |
| BUN/SCr | 1 | | | | 2 | | 3 | | 4 | 5 | 6 | |
| BNP | 1 | | | | | 2 | | 3 | | | | |
| Serum Cytokines | | | 1 | 2 | | 3 | | | | | | |
| PD effluent NGAL and cytokines | | | 1 | 2 | | 3 | | | | | | |
| Oxygenation Index | | | | | | 1 | | 2 | | | | |
| Clinical Information | x | x | x | x | x | x | x | x | x | x | x | |
| Adverse Event | x | x | x | x | x | x | x | x | x | x | x | |

Data Collection Points by time: BUN- Blood Urea Nitrogen, SCr – Serum Creatinine, BNP – Brain Naturetic Protein, POD –Postoperative Day, PD - peritoneal dialysis

BNP, electrolyte panels will be sent to hospital laboratory for analysis with standard identifying data. NGAL and cytokine samples will be labeled with a non-identifying, study-specific, subject code and sent to laboratory run by Prasad Devarajan in CCHMC hospital for analysis.

Modified oxygenation index will be calculated at 24 and 48 hours after the initiation of CPB using data obtained from ventilator settings and data. Modified oxygenation index will be calculated by the product of mean airway pressure (MAP) and FiO₂ as calculated by ventilator settings - (MAP x FiO₂). Lower oxygenation indices demonstrate less need for respiratory support and thus improved status. Ventilator settings will be dictated by CICU attending. MAP and FiO₂ data will be recorded by respiratory therapist managing patient.

Study Completion

In subjects who do not have oliguria during the first 24 hours, no additional study procedures will be performed, but outcome information will be collected until hospital discharge. If a patient does not have a PD catheter placed as part of the operative procedure, samples will be collected during the first 24 hours only as the patient is still considered at risk for AKI. If a patient does not undergo CPB, no further labs will be collected. Collected information will be all information in primary aim (hospital and ICU stay duration, duration of mechanical ventilation, fluid balances as above and mortality in hospital). Those randomized will be considered to have completed the study at the time of hospital discharge. If patients randomized to the PD arm have termination in the use of PD for any reason, they will be kept in that arm as intention to treat, regardless of future use of the PD catheter.

Indications for withdrawal from the study

Indications include: 1) Patient/Guardian desire to discontinue in the study or 2) Further participation in the study is felt to be contraindicated by the attending cardiologist or study investigator. 3) Any potential allergy or reaction to furosemide. The reason for withdrawal and the circumstances of withdrawal will be documented for all patients that withdraw

9. DATA ANALYSIS/METHODS

Sample size

The sample size estimate is based on the primary outcome and the primary hypothesis. An internal review of internal clinical experience showed that among the most recent 17 patients started on PD after CPB, seven (41%) patients had negative fluid balance on postoperative day 2. Using this data, we estimate 40% of the patients in the PD group will have negative fluid balances in the time of interest. We estimate that 10% or less of the patients in the furosemide group will have negative fluid balances during the time of interest, although at highest could expect 15% with negative outputs. With goals of minimum 80% power, we determined the number of subjects necessary in each group under different assumptions. Using our most conservative estimations, 49 subjects in each treatment group are needed to have 80% power to detect the difference between the two treatment groups (40% vs. 15%, odds ratio=3.778) using a two group chi-square test with 0.05 two-sided significance level. Fewer subjects are needed to have 80% power when the incidence rate in furosemide group decreases. Because we do not know the incidence of negative fluid balance in actual practice, after the first 20 patients enroll and complete study, we will complete an adaptive study design to define appropriate sample sizes given primary outcomes obtained thus far. nQuery Advisor 7.0 (Statistical Solutions, Cork, Ireland) is used for the sample size calculation. Study will be closed after 84 patients have fulfilled study completion.

| | | | |
|------------------------------------|----|-----|-----|
| Incidence rate in furosemide group | 5% | 10% | 15% |
| N per group for 80% power | 22 | 32 | 49 |

In general, there are 6-8 infants per month in CCHMC who would meet the inclusion/exclusion criteria for this study. Assuming a consent rate of 50%, enrollment of 3-4 patients per month is anticipated. We plan an 18 to 24-month enrollment period. To achieve the goal of at least 49 subjects in each treatment group, we will extend the enrollment period as necessary to make sure the study sample has enough power to address the research question.

Randomization

Before the cardiopulmonary bypass (CPB) surgery, a unique patient identifier will be assigned to each subject who meets the inclusion/exclusion criteria and consents to participate in this randomized study. However, only patients who develop oliguria after CPB will be randomly assigned to one of the two treatment arms (early PD or trial on furosemide) according to the randomization scheme.

Stratified block randomization will be utilized to assign subjects into two treatment arms. RACHS-1 score, a measure of the complexity of surgery, is used as the stratification factor with two levels (RACHS-1 =6 and RACHS-1 <6). Subjects will be randomized at a ratio of 1:1 (early PD : trial on furosemide) within each RACHS-1 stratum. Random block sizes of 2,4, and 6 will be used to ensure the balance of subjects in each treatment arm.

The randomization scheme will be created using the permuted blocks method with a computer random number generator at www.randomization.com (Gerard E. Dallal, Ph.D.). A log of subject number assignments will be maintained in order to avoid assignment errors such as duplicating or skipping numbers. The treatment group assignment will be placed in a sealed numbered envelope to main the concealing. A master sheet of the randomization list will be created by the project statistician. There is no blinding during the process of patient care, but the treatment group assignment will be blinded to lab technicians who perform the measurement of urine and plasma NGAL levels, BNP and electrolyte panels.

Statistical analysis

Study Population Characteristics

Demographic and clinical characteristics of the study sample, including age, weight, sex, RACHS-1 score, CPB time and preoperative serum creatinine, will be summarized using measures of central tendency, variability and frequency. Mean and standard deviation or median and interquartile range (IQR) will be reported for continuous variables. Frequency and proportion will be reported for categorical variables. Appropriate statistical tests will be applied to compare the characteristics between the two treatment groups.

Analysis for Primary Aim

The primary aim of this study is to determine if infants with oliguria after CPB will have better clinical outcomes when initiated on early PD rather than trialed on furosemide.

The primary analysis is to test the primary hypothesis for the primary outcome. A chi-square test will be used to test if there is any association of the occurrence of negative fluid balance with treatment plan. Odds ratio of negative fluid balance will be calculated with 95% confidence interval (CI).

The secondary analysis is to test the secondary hypotheses for the secondary outcomes.

Time to negative fluid balance is a discrete numeric integer value. Non –parametric Wilcoxon rank sum test will be used to compare the time to negative fluid balance.

The normality of ICU stay, hospital stay and duration of mechanical ventilation will be checked. Two-sample t-test will be used to compare those outcomes between the treatment groups if the normality holds; otherwise, Wilcoxon rank sum test will be used instead.

The in-hospital mortality rate will be calculated for each treatment group and compared between the groups using the probability difference and relative risk together with respective 95% CI.

Analysis for Secondary Aims

There are multiple secondary aims. For each aim, the analysis plan is specified as follows.

Secondary aim 1: Patients who are randomized to the furosemide treatment group will be included in the analysis. The disparity between the two groups of patients (good response to furosemide vs. poor response to

furosemide) will be summarized by the differences in the outcomes. For numerical outcomes, differences in means or medians with 95% CI will be reported; for incidence of negative fluid and in-hospital mortality, differences in the incidence rates with 95% CI will be reported.

Secondary aim 2: Patients who are randomized to furosemide treatment group will be included in the analysis for this aim. Patients will be classified as poor response to furosemide or good response to furosemide. Simple logistic regression analysis will be utilized to determine the predictability of poor response to furosemide using urine or plasma NGAL at 2hrs after the initiation of CPB, as well as if higher NGAL level predicts higher risk of poor response. If both urine and plasma NGAL are significant predictors of poor response to furosemide, a multiple logistic regression model will be developed to test the predictability of combined urine and plasma NGAL at 2 hrs after the initiation of CPB.

Secondary aim 3: All patients randomized to one of the two treatment groups will be included in the analysis. Two sample t-test or Wilcoxon rank sum test will be used to compare respiratory indices between two treatment groups at 24 hours and 48 hours after the initiation of CPB. The electrolyte derangement score at each of the four consecutive days will be compared between two treatment groups using Wilcoxon rank sum test. The doses of medication used for correcting electrolyte abnormalities will be compared between two treatment groups using two sample t-test or Wilcoxon rank sum test. AUCs of the 48-hour NGAL concentration curves will be calculated for urine NGAL and plasma NGAL, respectively, and compared between two treatment groups using two sample t-test. The proportion of patients with NGAL level < 50 ng/ml will be compared between groups. The difference of the proportions will be reported with 95% CI. Finally, BNP indices at 24 hours and 48 hours after the initiation of CPB will be compared between two treatment groups using two sample t-test or Wilcoxon rank sum test as appropriate.

SAS 9.2 (Cary, NC) will be used for the analysis. All tests will be two-sided and $\alpha=0.05$ will be used as the significance level. No multiplicity adjustment is applied and all reported p-values are unadjusted.

10. FACILITIES AND PERFORMANCE SITES

The research study will be performed at CCHMC. There will be no external performance sites. The administration of the study will be directed by the Principal Investigator (David Kwiatkowski) and coordinated through the Heart Institute Research Core staff at CCHMC. Strong mentorship and research guidance will be provided by Catherine Krawczeski MD and Stuart Goldstein MD to ensure successful completion of this proposal.

11. POTENTIAL BENEFITS

There is unknown direct medical benefit for patients. Both treatment arms are currently considered standard of care and there is no existing knowledge of treatment superiority. There is the benefit of increased postoperative monitoring. There is the indirect benefit of increasing knowledge regarding postoperative management of patients with AKI.

12. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS

Traditionally, the risk of maintaining a patient on long-term peritoneal dialysis is associated with a substantial risk of peritonitis, and catheter leak. However, this study is among a unique patient population, which uses dialysis for a significantly shorter period and has surgically placed PD catheters with relatively small dialysis volumes and a different risk profile.

The largest study of infants who used PD after intraoperative placement of PD catheters during cardiac surgery with CPB showed such practice does not carry significant risk. This study of 209 infants found complications in 4.8% of patients. Six patients had omental hernias upon catheter removal requiring brief operative reductions. Two patients had minor wound dehiscence at catheter insertion sites requiring local wound care. One had a small bowel obstruction requiring laparotomy and adhesion take-down, and one patient developed culture negative peritonitis treated with intraperitoneal antibiotics. Although theoretical, no patients had adverse outcomes related to hypotension, or documented peritonitis. It should be noted that nearly all adverse

outcomes in this study are related to PD placement and removal, not use of catheter, suggesting the increased risk in our study is minimal. In fact, the only additional complication noted related to use of catheters was slight leakage of dialysate fluid from the exit site. This study cites no catheters removed prematurely due to primary non-function or exit site infections. No patients died during dialysis or required discontinuation due to adverse cardiorespiratory effects.[11] A similar study of 87 patients showed peritonitis in 2 patients, both of which had fatal multi-organ failure and multisite sepsis sites, making it unknown what was the primary source of infection. No other patients in that review had other adverse outcomes. [18]

Therefore rare risks of PD include local wound infection or peritonitis, catheter leakage, omental hernia, and wound dehiscence.

All infants considered for inclusion already have plan for placement of PD catheter and no extra surgical interventions or risks are added for this study. No IVs or PD catheters will be placed for study purposes. All blood draws will take place from existing IV lines.

Risks of furosemide are low, particularly when used with close monitoring. Common side effects include mild hypovolemia, hypokalemia, hypophosphatemia, hypomagnesemia, and metabolic alkalosis. This is monitored closely with electrolyte panels and markers for dehydration. High doses of furosemide with impaired renal clearance can potentially cause ototoxicity,[19] however this is not a risk within this study, as patients are closely monitored and if they display worsening renal function, they will be switched to the PD group. Furosemide is a sulfonamide-based medication and can rarely cause allergic reaction, although this is easily treated medically and with discontinuation. Furosemide is used commonly (in virtually 100%) of postoperative cardiac patients. Although electrolyte derangements are common, allergy or serious side effects are rare. Dosing for this study is consistent with our usual standard postoperative dosing.

Both treatment arms are currently considered standard of care and at current there is no known risk of being randomized to one treatment arm as opposed to the other. Inclusion in treatment arm does not exclude option of the other treatment; patients with PD may receive furosemide as clinically indicated and patients trialed on furosemide are started on PD if they subsequently develop oliguria or fluid overload unresponsive to furosemide within 16 hours.

Blood is drawn for this study, causing rare risk of infection. Blood drawn specifically for this study totals 9ml over 48hrs (approximately 3ml/kg). It is unlikely that volume will contribute to the need for a blood transfusion or cause other adverse outcome.

There is the potential risk that confidentiality will be lost allowing diagnosis to be linked to patient's identification. Measures to prevent this risk are discussed below.

The length of hospital stay will not be affected by this study and there are no follow-up visits.

13. RISK/BENEFIT ANALYSIS

Individuals may benefit from increased monitoring, as patients can be switched to the other treatment group if necessary. Indirect benefit is present as information gathered may be used to guide the management of future patients. The risk of participation is greater than minimal and described above.

14. DATA SAFETY & MONITORING

Both treatment arms are currently used as part of standard postoperative management and no additional safety monitoring systems need to be created. Standard postoperative and dialysis monitoring, testing, treatments and medications are appropriate for all participants.

To monitor for adverse outcomes, a Drug and Safety Monitoring Board (DSMB) will be assembled consisting of a cardiologist, a nephrologist and a biostatistician (Dr. Russel Hirsch, Dr Mark Mistnefes, Jessica Woo). After

each 20 patients are enrolled for study participation, or every 3 months, the board will review enrollment, subject eligibility, and clinical safety data. After 50 subjects have completed the study, an interim analysis of safety and outcomes will be completed by the statistician and the DSMB will review the analysis.

Adverse events will be reported using a grading and attribution scale consistent with CCHMC IRB policy (Grading = Mild, Moderate, Severe; Attribution = Definite, Probable, Possible, Unlikely, Unrelated). The DSMB chair (or designee) will be asked to review reportable serious adverse events (SAEs) within 48 hours after initial receipt of the information by the investigator. Significant adverse events will be reported to the IRB on an individual basis per institutional policy. All serious or unanticipated significant adverse events will be reported in writing to the IRB per institutional policy. All adverse events will be reported to the IRB in summary form at the time of annual progress reports or at the close of the study, whichever occurs first.

15. PRIVACY AND CONFIDENTIALITY

Completed forms and other records will be kept in a secure location. Computerized data will be stored in a password protected network database maintained by CCHMC. Only the Principal Investigator and designees will have access to the database. This dataset will only be used for research purposes. Each subject will be assigned a study identification code so that the study information will be confidential. All specimens will be destroyed at the earliest opportunity as consistent with the conduct of the research, after all data on that patient has been collected.

Information from this research study may be published. However, participants will not be identified in any publication. All subject identifiers (e.g. medical record number, date of birth) as defined by HIPAA will be removed, so that identities are not traceable within or outside the study. The privacy and confidentiality of patient information will be maintained in accordance with HIPAA regulations.

16. COST OF PARTICIPATION

There is no cost to participate in this study.

17. PAYMENT FOR PARTICIPATION

There is no payment to patients for participation in this study.

18. FUTURE USE

All data collected will be stored in a data repository for future analysis regarding similar research interests. All future projects will undergo separate IRB approval. The repository will be stored on a password protected file. There will be no linking information to patient identifier numbers and it will not be used as a means for future recruitment. Blood and urine samples will be stored indefinitely in lab of Prasad Devarajan for potential future biomarker studies without further identification of patients unless parental decision to “opt-out” of storage.

19. REFERENCES

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