University of Cincinnati

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I, David M Kwiatkowski, hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

It is entitled:
Improved Outcomes with Peritoneal Dialysis vs. Furosemide for Oliguria after Cardiopulmonary Bypass in Infants

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Improved Outcomes with Peritoneal Dialysis vs. Furosemide for Oliguria after Cardiopulmonary Bypass in Infants

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of the College of Medicine

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by

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Abstract

**Background:** Acute kidney injury (AKI) is a common complication in infants after heart surgery with cardiopulmonary bypass. Studies demonstrate that patients with AKI have worse clinical outcomes, including prolonged ventilation times and length of stay, likely secondary to fluid overload from oliguria. Studies suggest that early peritoneal dialysis (PD) may be superior management to diuretic medications (furosemide) for oliguria; however, this has not been proven. We aim to determine if early PD improves clinical outcomes compared to furosemide in infants with oliguria after cardiac surgery. We hypothesize that early initiation of PD will improve outcomes.

**Methods:** This was the pilot study for a fully powered single-center randomized clinical trial. Infants with PD catheters placed during bypass were included. If infants demonstrated oliguria within the first postoperative day, they were randomized to early PD use or furosemide. Clinical and laboratory data were collected and compared between groups. Power calculations were performed using the primary outcome of fluid balance.

**Results:** Data were collected on the first 20 patients who met criteria for randomization; 10 to each arm. Patients in the PD arm had higher likelihood of a negative fluid balance on postoperative day 1 (60 vs 90%), demonstrated negative fluid balance 8 hours earlier (16 vs. 24 hours), were extubated 3 days earlier (3 vs. 6 days), and were transferred from the intensive care unit and hospital 6 days earlier (7 vs. 13 days; 10 vs. 16.5 days) than patients treated with furosemide. No significant adverse outcomes were reported. Using the primary outcome of negative fluid balance on postoperative day 1, a sample size of 32 participants per group was calculated for study completion.

**Conclusions:** The use of peritoneal dialysis for patients with oliguria after heart surgery shows trends towards earlier negative fluid balance, and shorter duration of ventilation and CICU stays. Adverse outcomes were not significant in this limited review. Completion of the fully powered study is necessary to demonstrate causation of outcomes with the use of PD.
Acknowledgments

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Introduction

Acute kidney injury (AKI) is a common postoperative complication after heart surgery with cardiopulmonary bypass, occurring in 30-50% of adult and pediatric patients.\textsuperscript{1-4} Multiple studies have demonstrated that patients with AKI and fluid overload have higher mortality and morbidity including prolonged need for mechanical ventilation and longer intensive care unit and hospital stay.\textsuperscript{1,5-8} Neonates with congenital heart disease are particularly vulnerable to AKI, likely due to a combination of immaturity of the nephron system and higher complexity of surgical repair which requires prolonged bypass times, an independent predictor of AKI.\textsuperscript{1,2} Studies done at this and other institutions confirm that younger age is a strong risk factor for development of post-bypass AKI.\textsuperscript{2,9,10}

Although a rise in serum creatinine is currently used to define kidney injury, this is commonly preceded by low urine output, or oliguria\textsuperscript{2,3} and therefore recent consensus definitions of AKI include urine output criteria. Furosemide, a diuretic medication, is used as first-line therapy for oliguria in many cardiac intensive care unit (CICU) settings despite multiple studies questioning this practice in patients with AKI.\textsuperscript{11-13} Several studies have suggested that the use of peritoneal dialysis (PD), prior to a rise in serum creatinine, may be associated with improved outcomes in critically ill patients with AKI.\textsuperscript{14-17} It has become a common practice at Cincinnati Children’s Hospital Medical Center (CCHMC) and other institutions to electively insert PD catheters in high risk infants at the time of cardiac surgery. Furthermore, it has become routine at our hospital to begin the use of PD at time of oliguria. Recently published retrospective studies by our group and others have demonstrated improved mortality and other outcomes with use of PD;\textsuperscript{18,19} however these reviews are subject to biases inherent in retrospective design. At present time, there is a critical gap in knowledge as to whether PD or standard
Diuretic therapy is superior in preventing fluid overload, and the associated adverse outcomes, in infants with post-bypass AKI.

We proposed a randomized clinical trial to compare the use of PD and furosemide in infants with oliguria after surgery with cardiopulmonary bypass for congenital heart disease. This is a pilot study to prove concept for the fully powered study with similar aims and hypotheses. Our central hypothesis is that early initiation of PD instead of furosemide will result in improved clinical outcomes in infants with oliguria after bypass. Our primary hypothesis is that infants with oliguria will be more likely to have a negative fluid balance on the first postoperative day when early PD is utilized rather than standard diuresis. Our secondary hypothesis is that infants started on early PD will have multiple improved clinical outcomes, including decreased time to negative fluid balance, decreased duration of mechanical ventilation, shorter CICU and hospital stays and lower mortality.

Methods

Study Design and Participants

This study is a single-center randomized controlled trial comparing infants with oliguria who undergo peritoneal dialysis to those receiving furosemide after heart surgery. Only patients less than 6 months of age undergoing cardiac surgery at CCHMC with cardiopulmonary bypass and the pre-operative plan for placement of a PD catheter as part of routine practice (Table 1) were approached for study inclusion. Surgical placement of the PD catheter was not dependent on study enrollment. Patients with pre-existing kidney disease (estimated GFR<60ml/min/m2) or known allergy to furosemide were excluded. If a patient had an unplanned placement of a PD catheter, they were not included. Patients were removed from study if they did not undergo bypass or if the PD catheter was not placed as planned. They were
also removed if the patient died, or if they required reoperation or the use of extracorporeal membrane oxygenation (ECMO) within the first 24 postoperative hours. Patient screening was performed by daily review of the CICU census, surgical planning meetings and operating room schedule. The first 20 patients randomized were included in this pilot study. When a potential patient was identified and deemed eligible, legal guardians were approached for informed consent prior to surgery and study protocol, and the risks and benefits were reviewed. This study is blinded only to the statistician. All aspects of the study were conducted under approval of the CCHMC Institutional Review Board.

**Peritoneal Dialysis Catheter Placement**

Table 1 depicts the criteria for intraoperative PD catheter placement at the time of bypass. Per institutional protocol, a PDC was planned to be placed at the completion of bypass in patients deemed at high-risk for AKI, including all infants younger than 3 months undergoing any bypass procedure, infants younger than 6 months undergoing heart transplant, and those younger than 4 months undergoing Tetralogy of Fallot or double outlet right ventricle repair. Patients had a preoperative consultation by the Nephrology service when possible.

The pediatric Tenckhoff peritoneal dialysis catheter (Pediatric Tenckhoff, 37 cm, Quinton Instrument Company, Bothell, Wash.) was inserted via direct trans-diaphragmatic access through a purse-string suture in the diaphragm at the inferior aspect of the sternotomy incision and brought out of the abdominal wall through a stab incision in the left or right upper quadrant. In efforts to minimize infection, the PD system is a closed circuit which is replaced every 72 hours, and has minimal handling of the circuit by trained dialysis nurses.
Study Procedures

Baseline laboratory samples were collected prior to the initiation of bypass. Routine use of bypass was initiated with use of modified ultrafiltration as surgically indicated. PD catheter was placed as clinically indicated, regardless of study enrollment. Data collected within the OR included surgeon, bypass time, cross-clamp time, use of regional cerebral perfusion or deep hypothermic circulatory arrest, volume of intravenous fluid administered, and urine output. Patients received standard postoperative care, with inotrope use directed by the attending intensive care physician. By protocol, patients received intravenous fluids at 2/3 maintenance on postoperative day 1 (POD 1) and 100% maintenance thereafter.

Postoperative oliguria was defined as 4 total hours of urine output less than 1 ml/kg/hr within the first 24 postoperative hours. Patients who did not develop oliguria within the first 24 hours received standard care without further study intervention. Infants who developed oliguria were randomized to receive either PD or furosemide. Randomization was stratified by RACHS-1 (Risk Adjustment for Congenital Heart Surgery) severity score to ensure similar patient distribution and limit confounders. Due to the higher risk of AKI in more complex surgeries, patients were randomized using two strata: those with RACHS-1 score of 6 and those with scores <6.

Patients randomized to PD received an initial PD prescription of 10 ml/kg 1.5% Dianeal™ (Baxter Healthcare, McGaw Park, IL, USA) with potassium chloride 2-3 mEq/L and unfractionated heparin 200 units/L using a 5 minute fill, 45 minute dwell, and 10 minute drain, via Gesco™ setup (Utah Medical Products, Inc., Midvale, UT, USA). Dialysis was continued as clinically necessary to maintain fluid balance.
Patients randomized to furosemide were given 1 mg/kg intravenously every 6 hours for 2 doses and then adjusted as needed to augment urine output. Patients within this arm who had urine output <1 ml/kg/hr over 16 hours after the first dose of furosemide were be considered poor responders and were started on PD if clinically indicated. Those who showed good response (urine output > 1 ml/kg/hr over subsequent 16 hours) continued furosemide as needed. If they subsequently developed oliguria or fluid overload unresponsive to diuretic therapy, these patients were started on PD at discretion of the CICU attending. Clinical outcomes were collected. All patients received standard maintenance IV fluid during the first 48 hours with additional electrolyte supplementation and fluid boluses as needed. Ventilatory weaning and extubation, transfer from the CICU and discharge from hospital was directed by the attending physician.

Randomization envelopes were confidentially prepared by the statistician with a log of outcomes. The bedside nurse manually recorded hourly urine output, and with a designation for any hour with < 1 ml/kg/hr of urine. When 4 hours of oliguria occurred, the nurse notified the research team for treatment assignment.

**Study Variables**

Baseline data included: demographic information, primary cardiac diagnosis, age, surgical weight and length, and preoperative blood urea nitrogen (BUN) and creatinine. Intraoperative variables included: surgical procedure performed and associated RACHS-1 score, bypass and aortic cross clamp time; and use of deep hypothermic circulatory arrest, regional cerebral perfusion, or modified ultrafiltration.

Our primary outcome was fluid balance for the first full postoperative day, which was calculated as the difference between all fluid inputs and outputs as obtained from nursing documentation in 8-hour
intervals. Secondary outcome data included: number of 8 hour shifts until a negative fluid balance occurred, number of days to extubation, CICU and hospital length of stay, and in-hospital mortality.

**Data collection and management**

Medical records were manually interrogated with assistance by data managers from the CCHMC Heart Institute Research Core. Outcomes were transferred to a REDCap™ database using double data entry by separate research faculty with appropriate data cleaning methods prior to analysis.

**Significant Clinical Outcomes:**

The primary outcome was percentage of patients with a negative fluid balance on POD 1. A difference of 30% was considered clinically significant. Secondary outcomes were considered clinically significant different if patients had a negative fluid balance 2 8-hour shifts earlier, if patients were transferred out of the CICU one day sooner or discharged from the hospital one day sooner. Mechanical ventilation time was considered clinically significantly different if patients were extubated one day earlier. Any change in mortality was considered significant.

**Statistical Methods**

Median (25th, 75th percentile) is reported for continuous variables and frequency (percentage) is reported for categorical variables. A chi-square test was used to test if there is any association of the occurrence of negative fluid balance with treatment plan. Odds ratio of negative fluid balance was calculated with 95% confidence interval.

The final study will include full data analysis on all secondary outcomes as described below. For this pilot study only descriptions of the outcomes are included to maintain study ethical standards. Full data prepared by the team statistician were reviewed by the study’s independent data safety management board.
At completion of the full study, full analysis of secondary outcomes will be performed. Time to negative fluid balance is a discrete numeric integer value and will be compared using non-parametric Wilcoxon rank sum test. The normality of CICU stay, hospital stay and duration of mechanical ventilation will be compared with two-sample t-test if the normality holds; otherwise, Wilcoxon rank sum test will be used. In-hospital mortality rate will be compared using the probability difference and relative risk together with respective 95% confidence intervals. All tests are two-sided and a p-value of <0.05 will be considered significant. All data will be analyzed using SAS 9.3 (SAS Institute, Cary, NC).

The primary outcome of percentage fluid positive on postoperative day 1 was used to perform power calculations for full study enrollment goals.

**Results**

Study enrollment began in November 2011 and continues at present. Of the first 30 infants enrolled in the study, 8 were withdrawn per study guidelines for reasons discussed below, 20 met criteria for randomization and an additional 2 completed the study without oliguria. Of those randomized: 10 were randomized to PD, and 10 were randomized to furosemide.

**Baseline Data**

Patients randomized to PD and furosemide did not differ in baseline data (Table 2). The groups had similar mean weight and age at time of surgery, as well as similar baseline serum creatinine and BUN. The groups also had similar cross clamp and bypass times. There were 3 patients with the highest surgical severity score in the PD group and 4 in the furosemide group.
Fluid Balance

Infants who were randomized to the PD arm had a negative fluid balance on POD 1 in 90% of patients compared to 60% in the furosemide group (Table 3). The difference between the percentages is 30% (95% CI = -6% – 66%; p = 0.30). The odds ratio of 6.00 (95% CI = 0.53 – 67.65) was clinically, but not statistically significant. Patients who were randomized to peritoneal dialysis had a time to negative fluid balance one shift earlier.

Secondary Outcomes

Patients who were randomized to PD utilized mechanical ventilation for a median of 3 fewer days (Table 3). Time to discharge from the CICU was 6 fewer days in patients randomized to PD. Time to discharge from the hospital was 6.5 fewer days in the patients randomized to PD. Further analysis of these data were not completed for the pilot study, although will be assessed with completion of the full study.

Adverse Outcomes and Deaths

There were two potential adverse outcome reported, both occurring in patients without early oliguria and who were therefore not randomized, but later had use of their PD catheter per clinical decision. One patient had bleeding from a peritoneal dialysis catheter which spontaneously resolved allowing the catheter to be later used for dialysis without any problems. A second patient had the development of a hydrocele due to a patent processus vaginalis which allowed communication of dialysate fluids into the scrotum. PD was terminated and swelling resolved with no further intervention necessary.

There were two deaths among randomized patients, both within the furosemide group. An independent Data Safety Management Board agreed that these deaths were not related to fluid overload or any treatment involved within this study. There were three deaths among withdrawn patients, which were also felt to be unrelated to fluid overload or any study treatment.
Study withdrawals

Of the initial 30 patients consented, 8 were withdrawn. All withdrawals were per study protocol including surgeries that were modified to not utilize cardiopulmonary bypass (2), surgical decision to not place a PD catheter (3), and need for postoperative ECMO (1). One patient died before going to the operating room. One patient had postoperative surgical bleeding requiring reoperation, which was indication for withdrawal. No patients were withdrawn for provider preference or adverse outcome and no patients were withdrawn after randomization.

Power calculations

Based on the results from 20 randomized patients (10 in each group), 90% patients in PD group and 60% patients in furosemide group had negative fluid balance during the 24 hours from 6am on POD 1 to 6am on POD 2. Using the above numbers, at alpha = 0.05 level, a two-sided chi-square test required enrollment of 32 patients in each group to have 80% power to detect the difference (90% vs 60%, odds ratio=6) between the two groups.

Discussion

Fluid overload is a frequent complication after cardiopulmonary bypass in infants due to acute kidney injury, capillary leak, fluid resuscitation, and low cardiac output syndrome decreasing renal perfusion. In our critically ill cohort, balancing fluid restriction and aggressive diuresis with provision of adequate volume to maintain preload and prevent electrolytes imbalances often proves challenging. A persistent positive fluid balance after achieving hemodynamic stability may be harmful in the recovery phase and may negatively affect organ function. Recent studies have shown a relationship between positive fluid balance and cardio-respiratory complications, including impaired pulmonary gas exchange and reduced lung compliance. Increasing degrees of fluid overload may result in fewer ventilator free days along
with longer CICU and hospital length of stays.\textsuperscript{16,20} While removal or prevention of excess fluid accumulation is universally accepted as a post-operative goal, the most effective means of elimination remains debatable. Practitioners often rely upon loop diuretics such as furosemide, which are not uniformly effective, and potentially detrimental, in patients with AKI.\textsuperscript{11,12} An adult randomized trial showed that furosemide use post-bypass was associated with two-times the postoperative creatinine increase, and a significantly higher rate of AKI.\textsuperscript{21}

In this study of infants undergoing cardiopulmonary bypass, the use of peritoneal dialysis at the time of oliguria showed trends towards improved clinical outcomes. These infants were more likely to have a negative fluid balance in the critical first postoperative day and a shorter time to a negative fluid balance. Fluid balance is of utmost importance in critically ill infants and has been demonstrated to be an independent risk factor for death.\textsuperscript{16}

In this small sample, patients randomized to peritoneal dialysis had 3 fewer days of ventilator dependence, an important marker of critical care de-intensification. Early extubation is desirable for several reasons, including: decreased rates of ventilator-associated pneumonia, less need for sedative and paralytic agents, less CICU time, decreased costs and lower resource utilization.\textsuperscript{22,23} Furthermore, infants with congenital heart disease often have more favorable hemodynamics with spontaneous ventilation, underscoring the value of this outcome within this population. This limited pilot study is not powered to prove this outcome, but previous studies have shown this association.\textsuperscript{19}

Traditionally, PD has been reserved for patients who have developed AKI and fluid overload and have not responded to fluid restriction and diuretics.\textsuperscript{24-26} Recently, early initiation of PD, particularly in infants
at high-risk of developing AKI after bypass, is increasingly used to prevent fluid overload.\textsuperscript{14,18,19,27} However, a randomized trial comparing early PD to diuretic use has not previously been performed. Completion of this study is necessary to prove benefits of the use of PD.

Although it may be hypothesized that the presence of an indwelling catheter and need for removal may delay transfer out of the CICU, this has not proven true thus far. Patients randomized to PD were in the CICU for a median of 6 fewer days after their procedure. This can be explained by less fluid overload and de-intesification as previously mentioned. A previous report by our group describes that PD catheters are removed at a median of 5 (3, 7) days.\textsuperscript{19} The entire postoperative hospital stay was a median of 6.5 days fewer in the group randomized to PD. This is similar to the difference in CICU stays, suggesting that there is little effect on duration of hospital stay outside of the CICU.

The two adverse outcomes seen within this study were minor and none had an effect on patient outcome or resulted in intervention. Importantly, no patient had peritonitis or bowel injury. Although this study is not designed to prove safety, it does corroborate other studies which report very low complication rates associated with PD, which is largely attributed to intraoperative placement of the catheter under direct visualization with sterile fields.\textsuperscript{14,19,28} The most common complications noted in previous studies have been positive peritoneal culture, bowel injury and hemodynamic instability with drainage.\textsuperscript{14,29} Multiple techniques of catheter placement have been described including indirect or direct trans-peritoneal and trans-diaphragmatic approaches, with varying rates of complications.\textsuperscript{30} Our institution uses un-cuffed catheters placed by direct trans-diaphragmatic method. Intra-operative catheter placement under direct visualization decreases the likelihood of infectious and mechanical complications which were described in early use of PD. Our low complication rate can also be attributed
to the use of a closed circuit which is replaced every 72 hours, low dwell volumes (10 mL/kg), and minimal handling of the circuit by trained dialysis nurses.$^{31}$

**Limitations**

While this is the only existing randomized clinical trial designed to assess the benefits of peritoneal dialysis, it is not powered to provide answers to the central question, but merely provide the basis for full study completion. Results from this study are not adequate to answer questions of optimal management or safety, especially given the population heterogeneity. However, trends seen among limited participants can be used to guide further investigations. The freedom from significant adverse outcomes can be used to augment existing literature regarding safety within this population.

**Conclusions**

The use of peritoneal dialysis for patients with oliguria after heart surgery shows trends towards earlier negative fluid balance, and shorter duration of ventilation and CICU stays. Adverse outcomes were rare in this limited review. Completion of the fully powered study is necessary to demonstrate causation of outcomes associated with the use of PD.
Bibliography:


Tables

Table 1: Cincinnati Children's Hospital Medical Center protocol for peritoneal dialysis catheter placement with cardiac surgery

<table>
<thead>
<tr>
<th>1) High-Risk Patients: PDC placement planned pre-operatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age &lt; 3 months undergoing cardiopulmonary bypass</td>
</tr>
<tr>
<td>• Heart transplant ≤ 6 months of age</td>
</tr>
<tr>
<td>• Patients undergoing TOF/DORV repair, age ≤ 4 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2) Moderate-Risk Patients: PDC placement considered based on clinical condition in the operating room</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients undergoing cardiac transplant, age &gt; 6 months</td>
</tr>
<tr>
<td>• Patients undergoing TOF/DORV repair, age &gt; 4 months</td>
</tr>
<tr>
<td>• Cardiopulmonary bypass time &gt; 120 minutes</td>
</tr>
</tbody>
</table>

PDC – Peritoneal Dialysis Catheter, TOF – Tetralogy of Fallot, DORV – Double Outlet Right Ventricle,
Table 2: Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PD (N=10)</th>
<th>Furosemide (N=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>7 (70)</td>
<td>4 (40)</td>
<td>0.37</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>10 (100)</td>
<td>9 (90)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age at surgery, day</td>
<td>6.5 (4, 25)</td>
<td>7 (4, 13)</td>
<td>0.85</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>3.25 (3.11, 3.67)</td>
<td>3.26 (3.00, 3.69)</td>
<td>1.00</td>
</tr>
<tr>
<td>Height, cm</td>
<td>50.0 (48.0, 51.0)</td>
<td>48.0 (45.5, 52.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>Baseline Creatinine, mg/dl</td>
<td>0.40 (0.33, 0.52)</td>
<td>0.45 (0.40, 0.55)</td>
<td>0.44</td>
</tr>
<tr>
<td>Baseline BUN, mg/dl</td>
<td>14 (12, 20)</td>
<td>13 (8, 21)</td>
<td>0.97</td>
</tr>
<tr>
<td>RACHS-1 score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>7 (70)</td>
<td>6 (60)</td>
<td>1.00</td>
</tr>
<tr>
<td>6</td>
<td>3 (30)</td>
<td>4 (40)</td>
<td></td>
</tr>
<tr>
<td>Bypass time, min</td>
<td>188 (157, 225)</td>
<td>195 (141, 203)</td>
<td>0.66</td>
</tr>
<tr>
<td>Cross clamp time, min</td>
<td>65 (40, 145)</td>
<td>48 (31, 102)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Median (25th, 75th percentile) is reported for continuous variables with P-value from Wilcoxon rank sum test. Frequency (percentage) is reported for categorical variables with P-value from Fisher’s exact test. BUN – blood urea nitrogen, RACHS-1 – Risk Adjustment for Congenital Heart Surgery.
Table 3: Comparison of clinical outcomes between PD vs. furosemide patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PD (N=10)</th>
<th>Furosemide (N=10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative fluid balance on POD 1, n (%)</td>
<td>9 (90)</td>
<td>6 (60)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Secondary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to negative fluid balance, hr</td>
<td>16 (8, 16)</td>
<td>24 (24, 32)</td>
<td>-</td>
</tr>
<tr>
<td>CICU stay, day+</td>
<td>7 (6,11.5)</td>
<td>13 (5, 29)</td>
<td>-</td>
</tr>
<tr>
<td>Hospital stay, day+</td>
<td>10 (8, 22)</td>
<td>16.5(12, 27.5)</td>
<td>-</td>
</tr>
<tr>
<td>Ventilator, day</td>
<td>3 (3, 5)</td>
<td>6 (5, 7)</td>
<td>-</td>
</tr>
<tr>
<td>Death, n (%)*</td>
<td>0 (of 9)</td>
<td>2 (of 9)</td>
<td>-</td>
</tr>
</tbody>
</table>

Median (25th, 75th percentile) is reported for continuous variables. Frequency (percentage) is reported for categorical variables with P-value from Fisher’s exact test. POD – postoperative day, CICU – cardiac intensive care unit.