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Peritoneal dialysis does not adversely affect kidney function recovery after congenital heart surgery

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Abstract

Purpose—Acute kidney injury (AKI) after cardiopulmonary bypass surgery to correct congenital heart disease is common. We prevent fluid overload and further cardiac compromise in oliguric infants with continuous peritoneal dialysis (CPD). The effect of CPD on kidney recovery is unknown, thus indications to discontinue CPD are unclear. We aimed to determine if CPD affects kidney recovery, measured by urine output and novel urinary AKI biomarker concentrations.

Methods—Twenty infants <90 days old with congenital heart disease who underwent bypass surgery and were post-operatively treated with CPD were randomized at the time of clinical readiness for CPD discontinuation to 1) discontinue CPD (control) or 2) continue 24 h more CPD (experimental). Urine output (ml/kg per h), total output (ml/kg per h) and urinary neutrophil gelatinase-associated lipocalin, interleukin-18, liver-type fatty acid binding protein, and kidney injury molecule-1 were assessed post-surgery until CPD catheter removal.

Results—24 hours preceding randomization, there were no differences in mean urine output or total output; 24 hours post-randomization, the control group had higher mean urine output (4.2 ± 2.6 ml/kg per h vs. 2.8 ± 2.0 ml/kg per h, $p = 0.02$) but lower total output (6.3 ± 2.1 ml/kg per h vs. 4.7 ± 2.7 ml/kg per h, $p = 0.01$). Median biomarker concentrations did not differ significantly between groups at any time point.

Conclusions—Our results suggest renal replacement therapy does not change the time course of kidney function recovery.

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Conflict of Interest: PD has submitted patent applications regarding the use of NGAL as a biomarker of kidney injury. The other authors have no conflicts of interests or financial disclosures to make pertaining to the contents of the manuscript.

Meeting Presentations: Data from this study have been presented in poster presentations at the 2010 International Conference on Continuous Renal Replacement Therapies, San Diego, CA, USA (Feb 24–27, 2010); at the 2010 ASN Annual Meeting and Scientific Exposition, Denver, CO, USA (Nov 16–21, 2010); and at the 2011 World Congress of Nephrology Annual Meeting, Vancouver, BC, Canada (April 8–12, 2011).

Keywords

Acute kidney injury; Cardiopulmonary bypass; Congenital heart defect; Peritoneal dialysis; Recovery of function; Urinary biomarker

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication following surgery for congenital heart disease associated with cardiopulmonary bypass (CPB) procedures and has been associated with poor clinical outcomes (1–5). In addition, cardiac disease is a common primary underlying systemic disease in patients with AKI, with the most common cause of AKI being ischemic injury (6). The development of AKI may result in fluid overload and AKI, further comprising the clinical course, which increases a patient's mortality risk (4, 7). Continuous peritoneal dialysis (PD) can be used to prevent excess fluid accumulation and/or remove excess fluid during the period of AKI until there is adequate kidney function recovery. As an acute form of renal replacement therapy, indications for initiation of PD are not standardized in the literature; indications of routine clinical practice in our institution include oliguria, electrolyte imbalance, and prevention of fluid overload (8). PD has few complications and has been shown in multiple studies to be a safe method to provide electrolyte and fluid homeostasis in the acute setting, and may reduce systemic levels of interleukin (IL) inflammatory markers IL-6 and IL-8 (9–15).

Indications for PD discontinuation are also not standardized in the literature (8, 16, 17). It has been hypothesized that any form of dialysis may reduce renal blood flow, potentially prolonging kidney recovery in critically ill patients. On the other hand, the potential benefits of PD may include increased clearance of cytokines and inflammatory mediators, rapid removal of excess fluid in hemodynamically unstable patients, and/or increased mesenteric blood flow following congenital heart surgery, which could hasten kidney recovery following CPB (15, 18). There are currently no published data to provide an evidence-based algorithm to discontinue dialysis therapy.

Novel urinary biomarkers, such as interleukin-18 (IL-18), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM)-1, and liver-type fatty acid binding protein (L-FABP), have been shown to predict AKI earlier and precede the rise in serum creatinine (SCr) in patients following CPB surgery (1, 2, 19–21). Furthermore, these biomarkers may predict AKI severity (5, 22, 23). While work continues to detect AKI earlier, few data exist with respect to the timing of recovery of kidney function. Reduced SCr and increased urinary output are clinical signs of improving kidney function; however, in the setting of dialysis, they lose clinical utility. Urinary biomarkers have not yet been studied as an indicator of acute kidney function in the setting of dialysis and only one published study assesses NGAL as a predictor of acute kidney function recovery (24). The aims of this study were to determine if 1) PD affects kidney function recovery as demonstrated by change in urinary output while on PD, and if 2) PD leads to prolonged kidney injury as assessed by changes in novel urinary injury biomarker concentrations.

MATERIALS AND METHODS

We conducted a prospective randomized controlled study approved by the Baylor College of Medicine Internal Review Board for Human Subject Research. All infants less than 90 days of age undergoing CPB surgery for correction of congenital heart disease in whom PD catheter placement at the time of CPB was planned as part of our standard of care were considered for the study. Patient caregivers provided written informed consent for the study prior to enrollment.

Patients were excluded from the study for: 1) a preexisting clinically significant genitourinary abnormality identified by renal ultrasound; 2) a pre-operative SCr >1 mg/dl; 3) an active urinary tract infection at the time of surgery; 4) requiring more than 72 h continuous use of nephrotoxic medications, including aminoglycosides, vancomycin, and non-steroidal anti-inflammatories, so as to prevent confounding by the potential for subclinical kidney injury, 5) prior extracorporeal membrane oxygenation (ECMO), prior surgery requiring CPB, prior renal replacement therapy, all of which may have introduced prior episodes of acute kidney injury, 6) or enrollment in another study deemed to be of conflicting interest. Patients were eligible for enrollment until five hours following admission to the CVICU after surgical correction of congenital heart disease.

Study design

Demographics and data for this study were collected as standard clinical practice in our hospital for all patients who undergo surgical correction of congenital heart disease. Surgical complexity was categorized using the Risk Assessment Score for Congenital Heart Surgery 1 (RACHS-1) scoring system (25). All patients included in the study were treated as per Texas Children's Hospital Cardiovascular Intensive Care Unit (TCH CVICU) standard of care with regards to post-operative management and the clinical need to initiate PD. Since 1996, PD initiation has been standard of care in the TCH CVICU for management of patients at high risk for AKI or early oliguria (<1 ml/kg per h of urine output for 4 h) following surgical correction of complex congenital heart disease in patients during the first 90 days of life.

Enrolled subjects were categorized into two initial study groups: 1) PD patients who were treated with PD as part of standard treatment where clinically indicated; and 2) non-treated patients in whom a PD catheter was placed as a part of standard clinical care, but never used to provide PD (although these may have been left open to passive drainage). Patients in the PD group were treated with a standard dialysis prescription of 10 ml/kg exchange volume per cycle with continuous cycles of 5 min fill, 45 min dwell, and 10 min empty. The initial dialysis fluid used was 1.5% Dianeal™ (Baxter, McGaw Park, IL, USA) with 200 units/l heparin sodium. All PD was performed via manual exchanges. The need for continuation of heparin sodium in the dialysis fluid, addition of potassium to the dialysis fluid, and/or increased Dianeal™ dextrose concentration were determined clinically. Data collection pertinent to PD included: 1) post-operative hour of PD initiation; 2) dialysis prescription changes; 3) hours of PD duration; and 4) PD catheter complications including malfunction, leak, or infection.

The primary endpoint of the study was to assess differences in urine output between patients randomized to stop PD or continue PD for an additional 24 h.

Randomization for effect of PD on kidney function recovery

At the point of clinical readiness to discontinue PD (defined below), patients were randomized to one of two groups, matched for ventricular physiology: *control* - discontinuation of PD and 24 h observation; or *experimental* - 24 additional hours of PD. Standard criteria for discontinuation of PD included demonstration of at least 1–2 ml/kg per h urine output for six hours, urine output sufficient to maintain euvolemic fluid balance, hemodynamic stability, and euvolemic appearance on physical examination. When patients were observed to have increasing urine output and thus anticipated to discontinue PD in the subsequent 12 to 24 h, a 1 mg/kg trial dose of intravenous furosemide was administered and patients were assessed for additional increased urine output of at least 1 ml/kg per h for four hours. Additional furosemide doses were withheld until 8 to 12 h after randomization, so as to maintain a period of equipoise for comparison of urine output between the two groups. Data were collected until the PD catheter was removed. Since it is our standard practice to leave PD catheters in place at least 24 h after patients reach criteria for PD discontinuation, participation in the trial did not prolong the length of time the PD catheter was in place, or the ICU length of stay.

Urinary AKI biomarker assessment

Urine samples were collected for AKI biomarker measurements at 6 h post-operatively and then twice daily at 12-h intervals. Urine bags were emptied two hours prior to collection time points to obtain fresh specimens. If insufficient urine was available for adequate collection, notation was made and collection resumed at the next sample time point. Urine samples were collected until 24 h after randomization, or until removal of PD catheter in patients who were not randomized. Upon collection, urine samples were immediately placed on ice. Samples were centrifuged at 3000 rpm for 5 min and frozen in 1 mL aliquots at –80°C until processed for urine biomarker assays, which were performed in the Devarajan laboratory at Cincinnati Children's Hospital Medical. Laboratory personnel were blinded to the patient randomization. NGAL was assayed using a human-specific commercially available ELISA (AntibodyShop, Grusbakken, Denmark) (23). IL-18 and L-FABP were measured using commercially available ELISA kits (Medical & Biological Laboratories, Nagoya, Japan; and CMIC, Tokyo, Japan, respectively) per manufacturers' instructions. The KIM-1 ELISA was constructed using commercially available reagents (R & D Systems, Minneapolis, MN, USA) as described previously (26). Urine creatinine was measured by colorimetric enzyme assay using a Siemens Dimension Xpand plus HM clinical analyzer (Siemens, Munich, Germany).

The period of study was concluded 24 h after the point of randomization for all patients treated with PD. Once clinically indicated, PD catheters were removed in both groups approximately 24 h following randomization. If an enrolled patient was not treated with PD, then the study period ceased once the PD catheter was removed.

Statistical methods

A pre-study power analysis was performed to calculate sample size using urine output data from 37 neonates treated previously with PD after correction of congenital heart disease. For each subsequent post-operative day the patients were treated with PD, average urine output increased by 25% to 30%. Eight hours after discontinuation of PD, patients had average urine output 4.2 ± 1.8 ml/kg per h. Using $\alpha = 0.05$ and power = 0.8, our analysis indicated 20 patients would be needed for each arm of randomization to show a 30% difference in urine output between the experimental and control groups. Additional calculations showed a sample size of 16 total patients (eight per randomized group) would detect a difference of 50%, and a difference of 20% would require 80 total patients (40 per randomized group). An adaptive study design was planned *a priori* once preliminary data from the initial ten randomized patients demonstrated >50% difference in urine output, revealing adequate power would be achieved with only 20 randomized patients (10 per randomized group) (27, 28). Statistical analysis of data was performed with STATISTICA™ software version 9 (StatSoft, Tulsa, OK, USA). Descriptive analysis, including birth weight (kg), current weight (kg), gestational age (weeks), pre-operative SCr and BUN, RACHS-1 score, cardiopulmonary bypass time (min), aortic cross-clamp time (min), urine output (ml/kg per h) eight hours before and after surgery, inotrope scores, time to initiation of and time on PD (h), fluid intake (mL) before discontinuation of PD, is reported with mean and standard deviation for each variable. The Student's *t*-test and Mann-Whitney *U* test were used to calculate differences between continuous data, and the χ^2 or Fisher's exact test were used for categorical variable.

As our standard unit practice is to record urinary output in eight-hour increments, mean urine output (ml/kg per h) in eight-hour intervals was calculated for 24 h before and after randomization, along with standard deviation. Student's *t*-test was used to assess the difference in change in urine output between the randomized groups. Median urinary biomarker concentrations (normalized for urine creatinine) were aggregated in 12-h intervals, interquartile ranges were calculated, and data was compared over 24 h before and after randomization using the Mann-Whitney *U*-test, since the Shapiro-Wilkes test was used to determine that urinary biomarker data were not normally distributed. Urinary biomarker concentrations were also compared between single and biventricular cardiac physiologies. A *p*-value <0.05 was considered significant for all statistical analyses.

RESULTS

Study population

We assessed 106 consecutive patients with congenital heart disease for eligibility; 41 were enrolled. Twenty-one of the enrolled patients were excluded from randomization post-operatively, leaving 20 patients who were randomized to either stop PD or continue PD for an additional 24 h (Fig. 1). All patients received their randomization assignment at the clinically determined time to discontinue PD. Ten patients were assigned each group, matched for cardiac physiology. Each group had five patients with single ventricle and five patients with bi-ventricular physiology. None of the randomized patients experienced complications due to presence of a PD catheter, nor did any of the randomized patients

require re-initiation of peritoneal dialysis. The additional baseline characteristics of each group were similar (Tab. I).

Primary outcome

The primary outcome of the study was to assess the change in urine output for 24 h following randomization to either stop (control) or continue PD (experimental). For 24 h *prior to* randomization, urine output did not differ between the control and experimental groups (3.4 ± 2.0 vs. 2.7 ± 1.9 ml/kg per h, $p = 0.17$). For 24 h *after* randomization, the control group had higher mean urine output (4.2 ± 2.6 ml/kg per h vs. 2.8 ± 2.0 ml/kg per h, $p = 0.02$) (Fig. 2).

Secondary outcomes

Total output—Total output, the combined urine output, peritoneal effluent, and chest tube output, was compared for the 24-h periods before and after randomization. There was no difference in total output between the control and experimental groups 24 hours *prior to* randomization (6.6 ± 2.6 ml/kg per h vs. 6.4 ± 2.4 ml/kg per h, $p = 0.72$). However, in the 24 hours *after* randomization, patients in the experimental group had higher total output (6.3 ± 2.1 ml/kg per h vs. 4.7 ± 2.7 ml/kg per h, $p = 0.01$) (Fig. 3).

Urinary biomarkers—Median urinary NGAL, IL-18, L-FABP, and KIM-1 concentrations did not differ between groups when aggregated for comparison at 12-h time intervals for 24 h before and after randomization (Fig. 4); urinary biomarker concentrations continued to decrease after randomization in both groups. There was no statistically significant difference between the two groups when comparing biomarker concentrations between single and bi-ventricular cardiac physiology. Correlation analyses showed no significant relationship between six-hour post-operative urinary biomarker concentrations and eight-hour post-operative urine output, CPB time, aortic cross-clamp time, or time on PD and between peak urinary biomarker concentrations and CPB time, aortic cross-clamp time, time on PD, administration of additional nephrotoxic medications (gentamicin, vancomycin), or time of chest closure.

DISCUSSION

In this prospective, randomized, controlled trial, we have shown that continuation of PD was associated with lower urine output compared to PD discontinuation, suggesting the potential for delayed kidney function recovery based solely on urinary output; however continuation of PD was associated with increased total fluid output during the additional 24 h of dialysis. Additionally, continuation of an additional 24 h of PD did not show a difference in measured urinary biomarkers NGAL, IL-18, KIM-1, and L-FABP, suggesting no difference in exacerbation or improvement of structural kidney injury. Children undergoing CPB are at high risk for developing AKI; AKI rates of 40% to 50% have been observed in well-designed prospective studies (1, 4). This population provides an informative cohort for diagnostic and therapeutic study. First, the timing of bypass induced renal ischemia leading to AKI is known, so patients can be followed closely for signs of AKI and randomized in therapeutic trials. Secondly, children do not possess many of the co-morbidities seen in

adults, which confound diagnostic and therapeutic study. All of the patients in our current study received PD as part of our standard clinical protocol to manage fluid balance, with a goal towards preventing fluid overload and providing a negative fluid balance. We contend our study design provided an ideal clinical model to assess the effect of continued dialysis in children who were deemed to have recovered baseline kidney function to determine if dialysis would delay recovery from and/or exacerbate kidney injury. Once initiated on renal replacement therapy (RRT), data from the BEST Kidney (Beginning and Ending Supportive Therapy for Kidney) study showed that increased urine output may successfully predict ability to discontinue RRT for patients; however the predictive ability of urine output was negatively affected by diuretic use (29). While we showed urine output was lower in patients who continued PD, we standardized intravenous diuretic use in an attempt to assess readiness for discontinuation systematically. All the patients in our study successfully discontinued dialysis without need for re-initiation after demonstrating increased urine output of at least 1 ml/kg per h over at least four hours. We suggest urinary response to diuretic administration may be a useful marker for assessing recovery of kidney function and timing for discontinuation of RRT.

In a recent review of timing and stopping RRT in critically ill adults, Cruz et al suggest that stopping RRT should be at a point when patients can maintain both adequate urine output without use of diuretics and optimized SCr values (30). Our data showing increased total output on continued PD supports the potential for augmented fluid removal, which, as demonstrated by Blackwood et al, may be beneficial to the patient while awaiting clinical determination of these parameters, which are somewhat qualitative (31). Maintenance of urine output is subjective not only to functional kidney status, but also to total volume status and cardiac output. SCr reflects a delayed functional measure and is cleared by dialysis, thus less useful in assessing day to day recovery. A quantitative measure of kidney function has not been established, with or without provision of RRT. It is notable that in a small study by de Geus et al, plasma NGAL was not significantly cleared during continuous RRT (32). In our study, after PD was stopped there was no appreciable change between measured urinary biomarkers for the control group when compared to the experimental group. Further research is needed to determine how PD affects urinary biomarker levels, as they may prove to be a powerful tool for assessing recovery from kidney injury (24).

Our study has several strengths. It is a prospective, randomized, controlled trial that was adequately powered to achieve significant results regarding change in urine output on and off PD after randomization. By studying neonates and infants, we utilized a population of patients who sustain a well-defined kidney injury during CPB surgery and have few confounding co morbidities. While SCr was less useful since patients were on CPD, the elevated post-operative biomarkers concentrations observed in both groups were similar to those in previous studies, and thus consistent with structural AKI. The cardiac physiology (single- or bi-ventricle) of each patient was matched between the two study groups in case this had an effect on kidney function measureable by urinary biomarker concentrations. Despite the specific population of our sample, studying this group with a definite source for AKI and no measurable differences between the groups based on cardiac physiology contributes towards better understanding of kidney function recovery and may be applied to other categories of patients with AKI.

Limitations of the study include a small number of patients despite adequate sample size achieved based upon a pre-study and planned interim adaptive power analysis. The renal physiology of infants is not as well understood as in other age groups, and due to changing function, AKI in this population is difficult to define. Additionally, plasma and urinary biomarker concentrations in neonates have not been broadly investigated (33). Due to patients frequently being enrolled during the intra-operative period, we were unable to obtain adequate numbers of pre-operative urine samples to assess urinary biomarkers before CPB surgery. This would have been useful for further assessing the change in urinary biomarkers following surgery. The addition of plasma biomarkers may have also provided more information, particularly in instances where patients were oligoanuric and a urine sample could not be obtained. Finally, since it is our practice to begin PD for oliguria observed shortly after surgery (mean time to start PD 9.5 ± 6.6 h for all patients); it is unlikely that every patient for whom PD was initiated would necessarily be considered a RRT candidate in other ICU settings.

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Fig. 1.
Screening and randomization of patients for study enrollment.

Fig. 2. Mean urine output (ml/kg/hr) at 8 hour intervals before and after randomization to stop (control) or continue (experimental) peritoneal dialysis. The whiskers at each point represent one standard deviation from the mean. There is a significant difference in urine output 9–16 hours after randomization (* $p < 0.05$).

Fig. 3. Mean total output (ml/kg/hr) at 8 hour intervals before and after randomization to stop (control) or continue (experimental) peritoneal dialysis. The whiskers at each point represent one standard deviation from the mean. There is a significant difference in urine output at 1–8 hours after randomization (* $p < 0.05$).

Fig. 4.

Urinary biomarker concentrations for 24 hours before and after randomization to stop (control) or continue (experimental) peritoneal dialysis. Median and interquartile ranges are presented. Statistical analysis showed no significant difference between experimental and control groups using $p < 0.05$. An extreme outliers has been truncated where indicated by *with values shown to better highlight range of median biomarker concentrations. (A) urine neutrophil gelatinase-associated lipocalin (NGAL); (B) urine interleukin-18 (IL-18); (C) urine liver-type fatty acid binding protein (L-FABP); (D) urine kidney injury molecule (KIM)-1.

TABLE I

BASELINE CHARACTERISTICS OF THE STUDY PATIENTS^a

Characteristics	Experimental (N = 10)	Control (N = 10)	p-value
Male sex - no. (%)	5 (50)	4 (40)	0.65
Birth Weight (kg)	3.1 ± 0.4	3.0 ± 0.9	0.58
Current Weight (kg)	3.1 ± 0.4	3.1 ± 0.9	0.85
Gestational Age (wks)	38.7 ± 1.4	37.7 ± 2.3	0.26
Physiology - no. (%)			
Single Ventricle (N)	5 (50)	5 (50)	
Bi-ventricular (N)	5 (50)	5 (50)	
Serum creatinine (mg/dL)			
Pre-operative	0.6 ± 0.1	0.5 ± 0.1	0.05
24 hours post-operative	0.7 ± 0.2	0.6 ± 0.1	0.11
48 hours post-operative	0.7 ± 0.4	0.7 ± 0.2	0.76
Aortic cross-clamp time (min)	100 ± 35	110 ± 66	0.61
Median RACHS-1 score (25%, 75%)	5 (4, 6)	4 (4, 5.5)	0.08
12 hour post-operative inotrope score	13.4 ± 6.3	13.2 ± 4.8	0.94
Time before initiating peritoneal dialysis (hr)	10.1 ± 8.6	8.8 ± 4.3	0.53
Total hours on peritoneal dialysis (hr) ^c	54 ± 2	62 ± 24	0.46
Total fluid intake 24 hours before stopping peritoneal dialysis (ml/kg/day)	90 ± 18	85 ± 23	0.59
Mortality within 30 days of surgery (N)	1	0	

^aPlus-minus values are means ± SD, except where indicated as median. There were no significant between-group differences at baseline values. P-values for mean data were calculated using Student's *t*-test. P-values for median data were calculated using Mann-Whitney *U* test.

^cThe point of stopping peritoneal dialysis is considered to be at the time of randomization, where total hours on peritoneal dialysis does not include 24 hours additional peritoneal dialysis after randomization.