Published in final edited form as:

Pediatr Crit Care Med. 2016 August ; 17(8): 753–763. doi:10.1097/PCC.0000000000000834.

Comparison of Intraoperative Aminophylline Versus Furosemide in Treatment of Oliguria During Pediatric Cardiac Surgery*

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Abstract

Objectives—To determine if intraoperative aminophylline was superior to furosemide to prevent or attenuate postoperative cardiac surgery-associated acute kidney injury.

Design—Single-center, historical control, retrospective cohort study.

Setting—PICU, university-affiliated children's hospital.

Patients—Children with congenital heart disease in PICU who received furosemide or aminophylline to treat intraoperative oliguria.

Interventions—Intraoperative oliguria was treated either with furosemide (September 2007 to February 2012) or with aminophylline (February 2012 to June 2013). The postoperative 48 hours renal outcomes of the aminophylline group were compared with the furosemide group. The primary outcomes were acute kidney injury and renal replacement therapy use at 48 hours postoperatively. Surgical complexity was accounted for by the use of Risk Adjustment for Congenital Heart Surgery-1 score.

*See also p. 798.

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The remaining authors have disclosed that they do not have any potential conflicts of interest.

Measurements and Main Results—The study involves 69 months of observation. There were 200 cases younger than 21 years old reviewed for this study. Eighty-five cases (42.5%) developed acute kidney injury. The aminophylline group patients produced significantly more urine (mL/kg/hr) during the first 8 hours postoperatively than furosemide patients (5.1 vs 3.4 mL/kg/hr; $p = 0.01$). The urine output at 48 hours postoperatively was similar between the two groups. There was no difference in acute kidney injury incidence at 48 hours between the aminophylline and furosemide groups (38% vs 47%, respectively; $p = 0.29$). Fewer aminophylline group subjects required renal replacement therapy compared to the furosemide group subjects ($n = 1$ vs 7, respectively; $p = 0.03$). In the multi-variant predictive model, intraoperative aminophylline infusion was noted as a negative predictive factor for renal replacement therapy, but not for cardiac surgery-associated acute kidney injury.

Conclusion—The intraoperative use of aminophylline was more effective than furosemide in reversal of oliguria in the early postoperative period. There were less renal replacement therapy-requiring acute kidney injury in children in the aminophylline group. Future prospective studies of intraoperative aminophylline to prevent cardiac surgery-associated acute kidney injury may be warranted. (*Pediatr Crit Care Med* 2016; 17:753–763)

Keywords

acute kidney injury; adenosine; aminophylline; cardiopulmonary bypass; congenital heart surgery

Acute kidney injury (AKI) following surgery for congenital heart disease in infants and children is a well-defined and frequent complication (1, 2). AKI, which typically presents with decreased urine output, fluid overload and increase in serum creatinine, may be present alone or as part of multiple organ failure syndrome. Depending on the definition, AKI prevalence following cardiac surgery is reported to be 3–60% (1–4). Over the last few decades, the definition of AKI has been modified from requiring dialysis to a scale of increasing serum creatinine and decreasing urine output findings, as outlined in the pediatric Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (pRIFLE) and AKI network (AKIN) criteria (5–7). Previously reported risk factors for cardiac surgery-associated AKI (CSA-AKI) are as follows: young age, the complexity of the underlying heart defect and therefore the surgery (as described by Risk Adjustment for Congenital Heart Surgery [RACHS]-1 score), cardiac arrest, duration of cardiopulmonary bypass, and low cardiac output syndrome (LCOS) (1, 2). Despite the advances in surgical techniques and PICU medicine, management of CSA-AKI continues to be a challenge and CSA-AKI increases the morbidity and mortality for these children (8–10).

Prevention strategies for CSA-AKI are limited. Preventing AKI prior to surgery, avoiding intravascular depletion and nephrotoxic drugs, providing adequate ventilation and oxygenation, and adequate treatment of perioperative LCOS with milrinone are some of the well-described methods (11, 12). The loop diuretics are commonly used in poor urine output states. Dopamine, fenoldopam (selective dopamine-1 receptor agonist), milrinone, atrial natriuretic peptide, and N-acetylcysteine have been used with some success (13–16). Furthermore, some recent studies demonstrated that early start of dialysis may improve outcome in these patients, suggesting that CSA-AKI may be an independent factor for

morbidity and mortality (8, 17, 18). These data indirectly suggest that early intervention at the time of kidney injury to prevent CSA-AKI may improve the outcomes in these children.

Tubuloglomerular feedback (TGF) is an important intrinsic mechanism that adjusts the renal vasculature tone and therefore the glomerular filtration rate (GFR) according to tubular solute load and perfusion pressure (19, 20). During cardiac surgery, cardiopulmonary bypass stimulates a systemic inflammatory response, which likely further contributes to CSA-AKI (21). Hypoxic-ischemic injury to the kidney has been demonstrated to increase the adenosine concentration in the kidney interstitial space (22). Adenosine is the main messenger molecule for TGF and contrary to its effects in all other vascular beds, adenosine, in the presence of angiotensin II, causes vasoconstriction at the renal arterioles (23, 24). This vasomotor response may be the first event in the long process of CSA-AKI, and animal experiments demonstrated good renal outcomes when adenosine action was blocked by theophylline (nonspecific adenosine antagonist) in models of ischemic AKI (25). There are also reports of better renal outcomes in critically ill children and newborns with AKI when treated with theophylline (26–28). Therefore, even though cardiopulmonary bypass (CPB)-triggered inflammation is an important mechanism of kidney injury, adenosine blockade might still be good candidate for prevention of CSA-AKI since the injury time is known and at least part of the initial insult is renal ischemia, generating vasomotor response at the renal vasculature (22, 29, 30).

The perioperative approach to oligo-anuria during cardiac surgery in our institution was transitioned from furosemide to aminophylline in February 2011 due to our anecdotal positive experience with aminophylline in the postoperative period, concurrent publications for the use of aminophylline in pediatric AKI, and data from animal models of ischemic AKI treated with adenosine blockade (31–34). In order to evaluate the effectiveness of this change, we initiated this retrospective chart review due to observed decrease in the incidence of renal replacement therapy (RRT) on our postoperative cardiac patients after 18 months of follow-up on the aminophylline protocol.

The aim of this analysis is to determine if intraoperative adenosine blockade (with aminophylline) was superior to furosemide for either prevention or attenuation of postoperative CSA-AKI. The tested research hypothesis is that aminophylline, by blocking the intrarenal adenosine, will improve urine output and postoperative kidney outcomes (34, 35). Furosemide, on the other hand, acts on the sodium-potassium-chloride (Na-K-Cl₂) cotransporter at the intraluminal side of the ascending limb of the loop of Henle, is a potent diuretic and commonly used to promote urine output in cardiac surgeries (36). To our knowledge, this is the first article that compares aminophylline versus furosemide in pediatric cardiac patients for postoperative renal outcome variables.

Materials and Methods

Sample Review

The Institutional Review Board of West Virginia University approved the study protocol. Retrospective chart review was performed using the data from the files of all children less than 21 years old who underwent cardiac palliation surgery for congenital heart defects at

West Virginia University Children's Hospital between September 1, 2007, and June 31, 2013. We conducted a historical control retrospective cohort study that used a historical closed cohort for the furosemide group and a postintervention closed cohort for the aminophylline group (37). All data were collected retrospectively. The protocol change for intraoperative management of oliguria was implemented on February 24, 2011. A total of 200 charts were reviewed. All consecutive patients fulfilling the enrollment criteria were included in the study. Children who had cardiac surgery for patent ductus arteriosus (PDA) or noncardiac thoracic surgery were not included in the review procedures (60 PDA corrections during the study period). Surgical complexity was accounted for by the use of RACHS-1 score (38). Peritoneal dialysis (PD) was the initial RRT method throughout the study.

Definitions

Intraoperative oliguria—Urine output less than 0.5 mL/kg/hr for 60 minutes prior to CPB during surgery and/or anuria for 20 minutes during CPB.

Urine output—All urine output results are reported as mL/kg/hr.

Postoperative 8 hours—Eight-hour period starting at the time of patient arriving to PICU after completion of the cardiac surgery.

RACHS-1 score grouping—Cardiac defects are further grouped as mild (RACHS-1 score, 1), moderate (RACHS-1 score, 2–3), and severe (RACHS-1 score, 4–6) to increase the statistical power to analyze the data.

Surgery

Surgical care of these patients were delivered by the same pediatric cardiothoracic surgeon (R.G.), the same certified clinical perfusionist (K.G.), and the same pediatric cardiothoracic anesthesiologist (D.R.) during the entire study period. The anesthetic maintenance technique was a balanced anesthetic with epidural narcotics, propofol, an opioid (remifentanyl or fentanyl), and dexmedetomidine. Desflurane was administered through the oxygenator during the cardiopulmonary bypass period. All children in the study underwent surgical treatment of their lesions utilizing CPB or with clamping of the aorta as with coarctation of aorta. Hypothermia was used where needed and hypothermic-circulatory arrest was used in children with single ventricle diagnosis undergoing first- and second-stage repairs. The bypass circuit was primed with Plasma-Lyte (Baxter Healthcare, Deerfield, IL), albumin 25%, mannitol 0.5 g/kg, calcium chloride 20 mg/kg, heparin 1,000 units, sodium bicarbonate 2 mEq/kg plus another 10 mEq/unit of washed RBCs. The target was to obtain a hematocrit of at least 30% during CPB. Pulsatile perfusion was used during aortic cross clamp in children less than 25 kg. Furosemide 1 mg/kg/dose or aminophylline 5 mg/kg/dose was administered when the child developed intraoperative oliguria.

When needed, a Dacron single-cuffed straight silicone rubber acute PD catheter (Tenckhoff catheter; Cook Medical, Bloomington, IN) was inserted under general anesthesia below the umbilicus during the index surgery or postoperatively. The catheter exit site was sealed with

Dermabond (Ethicon, Somerville, NJ). The main indications to place the PD catheter were ascites formation, long duration of CPB (> 90 min), deep hypothermic circulatory arrest, and LCOS at the time of disconnecting for the CPB.

Postoperative Period

Patients are followed for urine output, arterial blood gases, central venous pressure (CVP), and systemic arterial pressure, and the data were recorded hourly as the unit protocol. A urinary catheter was inserted into the bladder in the operating room and remained during the 48 hours postoperative period for all patients. Systemic arterial pressures were continuously measured in the radial or femoral artery, and CVPs were measured using a central venous catheter. IV fluids were used to maintain CVP and rescue arterial hypotension episodes. Plasma-Lyte (Baxter Healthcare, Deerfield, IL), 0.9% normal saline, and albumin 5% were the main solutions used. Dopamine, dobutamine, epinephrine, and vasopressin were all used as needed, and the doses were recorded hourly. All patients with LCOS received milrinone. Furosemide, chlorothiazide, aminophylline, and mannitol-bumetanide solutions were used to support urine output. The most frequently used antibiotics were cefotaxime, cefazolin, vancomycin, and piperacillin-tazobactam.

AKI Stage

Postoperative AKI stage was assessed using the AKIN criteria (Table 1) using both serum creatinine and urine output criteria (5). Baseline serum creatinine was the most recent serum creatinine within 24–48 hours prior to surgery. Serum creatinine was measured in the immediate postoperative period and then at least every 24 hours for the first 48 hours postoperatively. Urine output was recorded hourly. Subjects who have never increased their serum creatinine greater than 50% from baseline (or 0.3 mg/dL absolute increase) and whose urine output was greater than 0.5 mL/kg/hr for all 8-hour periods during the first 48 hours postoperative was evaluated as “AKI stage 0 (no AKI).” Each subject's AKI stage was evaluated using both criteria. The final AKI stage was determined by the maximum level achieved by either criteria. Poor response to intervention (for both furosemide and aminophylline) is defined as inability to achieve or maintain 1 mL/kg/hr urine output during CPB.

Furosemide Group

This era was from September 1, 2007, to February 23, 2011. During this era, when a patient developed oligo-anuria during the surgery time, he or she received furosemide 1 mg/kg/dose for rescue. Poor response to furosemide or recurrence of oligo-anuria was then intervened with a second dose of furosemide or ethacrynic acid (1 mg/kg/dose). None of these patients received aminophylline during the surgery.

Aminophylline Group

This era was from February 24, 2011, to June 31, 2013. During this era, when a patient developed oligo-anuria during the surgery time, he or she received aminophylline 5 mg/kg/dose for rescue. Poor response to aminophylline or recurrence of oligo-anuria was then intervened with a second dose of aminophylline after at least 6 hours (two patients).

RRT/PD

Indications to start PD were as follows: worsening generalized edema with positive fluid balance, oligo-anuria (< 1 mL/kg/hr) for more than 24 hours that was unresponsive to fluid administration and diuretics, electrolyte and acid-base disorders not responding to medical treatment, need to restrict nutrition intake due to edema, increasing serum creatinine levels, and persistent LCOS. The ultimate decision to start PD was made by the attending physician. There were five pediatric intensivists and one pediatric nephrologist deciding on the initiation of RRT during the study period.

Manual continuous cyclic PD were performed by the bedside nurses. Commercially available dialysate bags (lactate as buffer, 1.5%, 2.5%, and 4.25% dextrose concentration) were typically used and were switched if necessary to custom-made bicarbonate solutions for treatment of resistant metabolic acidosis. The typical exchange volumes were 10–20 mL/kg/cycle and the dextrose concentration was decided by the attending physician.

Outcome variables and Study Design

Our primary outcomes were AKI and RRT requirement at 48 hours postoperatively. Our secondary outcomes were urine output (mL/kg/hr) at 8 hours and 48 hours postoperatively, percent change in serum creatinine at 48 hours and at discharge from PICU and death. A predictive model was subsequently developed for the clinical outcomes of AKI, RRT, and death.

Subjects' gender, gestational age at birth (classified as term or preterm babies), age (mo), and weight (kg) at time of surgery were recorded. Surgical data were obtained on type of congenital heart defect, type of cardiac surgery, RACHS-1 score, duration of cardiac surgery (< 180 min, > 180 min), CPB (< 60 min, > 60 min), and aorta cross-clamp times (< 60 min, > 60 min) and whether or not pulsatile perfusion was used on CPB. Data were obtained as whether or not the patients received aminophylline postoperatively, and serum creatinine at admission to PICU, and at 24 and 48 hours postoperatively were recorded. Clinical data were collected for the early postoperative PICU admission time, at 24 and 48 hours postoperatively. Variables collected were urine output, hematocrit, serum albumin, arterial pH, serum lactate, serum anion gap, CVP, inotropic score, and whether or not epinephrine was being used. Inotropic scores were calculated using Vasoactive Inotropic Score and Wernovsky Inotropic Score formulas, as indicated (39, 40). The score was calculated using the doses at 6 am for the calendar day or within 60 minutes of PICU arrival. The serum creatinine at the time of PICU discharge or the most recent value prior to discharge was also obtained.

Data Analyses

All study variables were examined for normality. Descriptive statistics were conducted to calculate the means, sds, and ranges for all study variables of a continuous nature. The number of participations from each study group (aminophylline and furosemide) were examined based on the distribution of patients across three RACHS-1 score categories (RACHS 1, RACHS 2–3, and RACHS 4–6). To examine potential differences in treatment outcomes based on group assignment, we conducted a multivariate analysis of variance with

group assignment (two groups) and RACHS-1 score (three levels) serving as the fixed factors and the following outcome variables: urine output at 8 and 48 hours postoperatively, δ (%) serum creatinine at 48 hours and at discharge from PICU. Main and interaction effects of the fixed variables were examined. Bonferroni post hoc analyses were used to examine particular differences between the groups. To examine potential predictors of AKI, RRT, and death, we first identified associated variables using a bivariate correlation. Variables significantly associated with AKI, RRT, and death were then entered into separate nominal regression models predicting these clinical outcomes. A significance level of p value less than 0.05 was used to assess statistical significance. SPSS version 20.0 (IBM Corporation, Armonk, NY) was used to complete all statistical analyses.

A retrospective power calculations using G*Power software (Heinrich-Heine University of Dusseldorf, Dusseldorf, Germany) was completed. Under assumptions of a medium effect size, α at 0.05, and power at 0.80, we confirmed the collected sample was adequate for detecting potential differences between groups for AKI outcomes. This study, however, was not appropriately powered to detect potential differences in RRT and death outcomes. For death and RRT outcomes, under assumptions of small effect size at 0.02, α at 0.05 and power at 0.80, we needed a sample size of 395 subjects in total (198 in each group). When we modified the power to 0.60, we would need a total sample size of 247 (124 each group). Therefore, these outcomes (RRT and death) would need to be restudied in more detail with appropriate samples to properly determine statistical differences.

Results

Sample Characteristics

Two hundred medical charts were reviewed for this study. The sample included 100 children in aminophylline group and 100 children in furosemide group. One hundred twenty-one children (60.2% of total sample) were males; 64.7% ($n = 130$) were term births. Sixty-four (31.8%) of children were less than 1 month old, 10 (5.0%) were between 1 and 2 months old. Half of the participants (100; 50%) were between 2 and 24 months old and remaining 26 participants (13.0%) were greater than 25 months old. The different types of surgeries and their incidences for the two treatment groups are presented in Table 2. Children in the two groups are further classified according to their RACHS-1 scores to compare the surgical complexities between the treatment groups (Table 3). The two intervention groups were compared for their demographics, types of congenital heart disease, surgery-related duration, postoperative care and for the various diuretics used postoperatively (Table 4)

AKI

There were 113 children (56.5%) who did not fulfill the criteria for AKI during the study period; 85 children (42.5% of final sample) were diagnosed with AKI. For two children in the furosemide group, the urine output and the serum creatinine at 48 hours postoperatively were not available to decide on the AKI status. At 48 hours postoperatively, 38 children (19%) were diagnosed as stage I AKI, 30 children (15%) as stage II AKI, and 17 children (8.5%) as stage III AKI. There was no difference in AKI incidence at 48 hours between the aminophylline and furosemide groups (38% vs 47%, respectively, $p = 0.29$). Among all the

children, 92 (46%) of them were assigned to their maximum AKI stage using serum creatinine value, 51 of them (25.5%) were assigned using their urine output criteria, and finally 55 children (38.4%) were assigned to their maximum AKI stage using both the serum creatinine and the urine output criteria during the 48-hour follow-up of this study (Table 5).

Group assignment independently affected mean patient urine output during 8 hours postoperatively ($F = 3.778$; $df = 3$; $p = 0.011$; partial $\eta = 0.029$). No main effect for RACHS-1 score or interaction effect was found. Patients receiving aminophylline produced significantly more urine at this time point than those who received furosemide (5.1 vs 3.4 mL/kg/hr; $p = 0.015$) (Fig. 1). However, based on group assignment, there was no statistically significant difference in the mean urine output at 48 hours between the aminophylline and the furosemide groups (Fig. 2).

Requirement for RRT

Eight children required RRT during the study period (2.2%). Aminophylline group had significantly less number of RRT requiring subjects compared to furosemide group (1 vs 7; $p < 0.05$) (Table 5). All the children requiring RRT were started with PD using manual treatment. Four of them were later switched to continuous renal replacement treatment (CRRT) due to poor results in PD. All four PD-failure cases were furosemide group subjects. Three of them died during the CRRT treatment course or within 24 hours of discontinuing CRRT.

δ Serum Creatinine at 48 Hours Postoperatively and at Discharge From PICU

No main or interaction effects were found in this study explaining mean δ serum creatinine at 48 hours. However, a main effect was found for RACHS-1 score on patient δ serum creatinine at discharge ($F = 4.93$; $df = 3$; $p = 0.04$; partial $\eta = 0.017$). Aminophylline group mean δ serum creatinine at discharge was significantly lower than furosemide group subjects with RACHS-1 score 1 (61.3% vs 105.4%; $p = 0.01$). No other significant differences were noted across groups (Fig. 3).

Predictors of Developing AKI, Requiring RRT, and Death

We examined the potential associations across a series of surgical and PICU-related factors and AKI, RRT requirement, or death. Significant factors positively associated with AKI, RRT, or death among the study groups included: male gender ($p = 0.03$), RACHS-1 score ($p = 0.01$), epinephrine use at baseline, day 1 and day 2 (0.01, 0.04, 0.05, respectively), serum albumin ($p = 0.03$), CVP ($p = 0.04$) and inotropic score at baseline, day 1 and day 2 (0.03, 0.03, 0.04, respectively). Factors negatively associated with AKI, RRT, or death included: patient age ($p = 0.03$), weight ($p = 0.01$), intraoperative use of aminophylline ($p = 0.03$), and aminophylline use at 24 and 48 hours ($p = 0.02$ and 0.03, respectively). Interestingly, neither serum lactate nor hematocrit values at baseline postoperatively and at 24 and 48 hours postoperatively were associated with AKI, RRT, or death in these subjects.

A series of nominal regression models revealed no significant predictors for any AKI stages from this list that were statistically significant. Several factors were significant in the patients' RRT requirement model including group assignment (furosemide group; Wald =

279.99; $df = 1$; $p = 0.01$). Use of aminophylline at the intraoperative phase (Wald = 149.85; $df = 1$; $p = 0.01$) was a strong preventive factor in this model. A final nominal regression model was conducted to explain death outcomes. This model also identified the intraoperative use of aminophylline as a preventive factor against death (Wald = 550.64; $df = 1$; $p = 0.01$). Similar to the remaining models, group assignment (furosemide group; Wald = 613.98; $df = 1$; $p = 0.01$) was a significant predictor of death in this model.

Complications

None of the patients required/received IV adenosine treatment for any tachyarrhythmia during the study period. The serum theophylline levels were not checked during the study. This was because of the findings in previous studies that revealed nontoxic levels at 5 mg/kg/dose of theophylline dosing (25, 27). There were no clinically significant side effects of aminophylline in any of the patients. Specifically, there were no clinical seizures documented during the study period for either intervention groups.

Discussion

This is the first article that compares intraoperative aminophylline versus furosemide in pediatric cardiac patients for postoperative renal outcome variables. This study demonstrates that intraoperative use of IV aminophylline at detection of oliguria during pediatric cardiac surgery may decrease the need for postoperative RRT when compared with furosemide. There was clearly no inferiority of aminophylline for renal outcomes at postoperative 48 hours when compared with furosemide. Patients receiving aminophylline had more urine output during the first 8 hours postoperatively. At 48 hours, the incidence of AKI at different stages were similar between the two groups. The urine output advantage of aminophylline was not maintained at 48 hours. In the regression models, intraoperative aminophylline use was a strong protective factor for RRT and death models.

In this study, AKIN criteria were chosen over pRIFLE because of the following: 1) Instead of GFR changes, it uses changes in absolute serum creatinine values, which we thought were more reproducible compared to estimated GFR values with our datasets; 2) The postoperative percent changes in absolute serum creatinine allowed us to compare our full cohort; and 3) Urine output criteria in AKIN is more sensitive in detecting stage I and stage II AKI.

Preserving kidney function and maintaining steady urine output are important factors in the outcomes of these cardiac patients. Despite the fact that it is a less potent diuretic compared to furosemide, aminophylline provided significantly more urine output in the first 8 hours postoperatively. This may be due to improved GFR by attenuated afferent arteriole vasoconstriction. This positive impact on urine output was not maintained at 48 hours because aminophylline peaks serum levels at 30 minutes after IV administration, and its half-life is 3–30 hours depending on the age and prematurity of the subject, heart function, and liver function. Therefore, the serum levels were probably too low to maintain the positive impact at 48 hours. This can be overcome by routinely using aminophylline during the postoperative period to maintain adequate serum levels. CVP was positively associated

with AKI, RRT, or death in this study, further promoting the importance of fluid balance by maintaining urine output.

There was no difference between the intervention groups when compared at 48 hours for incidence of AKI stages, δ serum creatinine, or urine output. This may be due the dose or the administration of aminophylline. The 5 mg/kg dose may not be sufficient enough to block the released adenosine and/ or repeat dosing may be needed. Patients may need continuous infusions and higher cumulative doses to counteract the adenosine actions. The high-dose bolus administration of aminophylline may be critical at the time of documented insult (new onset oliguria) to minimize the initial adenosine-mediated vasoconstriction. However, despite getting off the CPB, the stimulus for renal vasoconstriction may continue postoperatively in patients with LCOS, requiring large inotropic support. As this is a more continuous insult, it is yet not clear whether a continuous infusion or intermittent bolus doses of aminophylline will be more efficacious in reversing renal vasoconstriction, and improving urine output in these cases. More importantly, since the TGF starts with the furosemide-sensitive cotransporter (Na/K/2Cl transporter), aminophylline may be combined with furosemide to block TGF at two different spots, causing synergistic effect (16). These possibilities need to be investigated in well-designed studies to define the optimum dose, combination and the method of administration.

Despite the lack of difference of AKI incidence for all three stages, aminophylline was able to decrease the RRT-requiring AKI incidence. This is theoretically expected because by blocking vasoconstriction of the renal vasculature, aminophylline not only is expected to improve the GFR but also provide better flow at vasa recta and therefore prevent ischemic injury to the tubules. This may prevent acute tubular necrosis, tubular sloughing, and later blocking of the renal tubules, which could lead to protracted renal failure requiring RRT. It is well demonstrated that RRT requirement is a major morbidity and mortality factor, prolonging duration of hospital stay (1, 8, 41).

Our findings demonstrated that patients with RACHS-1 score 1 actually improved their discharge serum creatinine compared to baseline preoperative serum creatinine if they received intraoperative aminophylline. This further suggests that the milder renal insults (either due to simpler cardiac defects or better tolerated surgeries) may be mainly due to renal vasoconstriction, rather than acute tubular injury (42, 43).

There were several interesting and unexpected findings when predictors of poor outcomes were investigated by regression models. It was expected that RACHS-1 score, inotropic score, and epinephrine use to be positively associated with AKI, RRT, and death (36). Elevated CVP contributed to poor outcomes possibly due to of increased venous pressures (systemic venous hypertension). The surgical, CPB, or aorta cross clamp times were not predictors of poor outcomes. This may be due to selection bias. We only included subjects that developed intraoperative oliguria, making them high risk for poor outcomes. The majority of the patients being on the higher end of the RACHS-1 score scale supports that. Therefore, this finding should not be extrapolated to all children undergoing cardiac surgery. All three of these factors promote renal ischemia, which is the main pathogenesis of CSA-AKI.

Aminophylline and theophylline have abundant systemic effects, and it can be argued that the observed beneficial effects may be irrelevant to renal adenosine blockade. Several animal studies have demonstrated that IV aminophylline actually lowers the systemic blood pressure with no change in cardiac output while improving the GFR (44, 45). Our patients were all well-ventilated patients, and the small dose of aminophylline is unlikely to make a difference in ventilation (31, 32). Several studies have demonstrated that the serum concentration needed to block the phosphodiesterase enzyme to cause diuresis is significantly higher than the serum concentration that can be achieved with the doses used in this study (31). Therefore, even though we do not have the theophylline serum levels, or cardiac output calculations for our subjects during the study period, it is reasonable to believe that the positive effects were mainly due to aminophylline's adenosine blockade at the renal vasculature.

Major placebo-controlled randomized clinical trials investigating the effects of specific A1R antagonists on renal function in patients with decompensated acute heart failure have been recently reported (46–48). Rolofylline (selective A1R antagonist) was the investigated agent in these trials. These trials failed to demonstrate a positive effect in renal outcomes. There are several possible explanations for this failure. First of all, adult patients have many comorbid conditions, such as atherosclerotic peripheral vessel disease, on-going hypertension, and underlying chronic kidney disease, that may make the kidney more vulnerable to injury, with many different mechanisms and less likely to recover. Secondly, the mechanism of pediatric CSA-AKI is more likely to be CPB-induced inflammation, and hypoxic-ischemic injury, later followed by reperfusion, but the mechanism of worsening renal function in adult decompensated heart failure is probably as much venous congestion and systemic venous hypertension as it is pump failure and poor renal perfusion. Renal vasoconstriction may not play as important of a role in the adult, making adenosine-mediated effects less significant in the pathophysiologic pathways. Therefore, the specific A1R antagonist study should be repeated in the pediatric population (42, 43, 49).

In a recently reported, double-blinded, randomized, placebo-controlled clinical trial, Axelrod et al (50) compared aminophylline to placebo to prevent CSA-AKI in children following congenital heart surgery with CPB. In this well designed and adequately powered study, the authors failed to demonstrate any positive effect of aminophylline to prevent CSA-AKI. Even though the domains of our study and Axelrod et al (50) study are very similar, there is yet one very important difference in the intervention. Axelrod et al (50) administered aminophylline postoperatively to all the randomized intervention group subjects regardless of their intraoperative or early postoperative urine outputs. Therefore, their intervention may be considered late relative to the time of renal insult (CPB), causing the treatment to be less effective. The two strengths of our clinical protocol were administering aminophylline at the time of early documented insult (oligo-anuria on CPB) and selecting subjects that were negatively affected. So better timing and treatment of clinically affected patients may have positively impacted our results. With that, despite the negative outcomes of Axelrod et al (50) study, we still need prospective randomized clinical trials investigating the impact of aminophylline on CSA-AKI when administered at the time of documented injury (decreased urine output on CPB).

The retrospective cohort study design is our major limitation. The different treatment modalities (aminophylline vs furosemide) were historically compared rather than the preferred prospective randomized controlled manner. The measurement of variables at 8 hours after PICU admission reflects significant variability in the duration of time after CPB was initiated, depending on the type of surgery. Most importantly, the main outcome of the study, RRT start, is not based on objective, reproducible indication criteria but rather was attending physician's decision, mainly triggered by significant fluid overload that is resistant to medical therapy. Considering the long study period, the effect of practice change cannot be completely ruled out for the decrease in RRT outcome. Finally, it is well known that serum creatinine is subject to muscle mass, and fluid overload, and only rises after significant renal injury is already ongoing, making it possible that we may have missed some of the AKI events. We could have provided more insight to the process if we further had data on intake/output results with documentation of the degree of fluid overload state, theophylline drug levels and documentation of other renal insults, such as nephrotoxic medications, during pre and early postoperative period. However, at the same time, there are several very unique aspects of this study. All of the children were operated by the same CT surgery team during the study period, being the same CT surgeon, same CT anesthesiologist and the same CPB perfusionist. There were five pediatric intensivists and one pediatric nephrologist deciding on the initiation of RRT during the study period. Both intervention groups had similar subject distribution for demographics, surgery durations, postoperative inotropic scores, cardiac disease severity (RACHS-1 score), and surgery type (Tables 3 and 4). Having said that, we realize that this RACHS-1 score grouping is not a previously validated method and may group patients into categories that do not actually represent accurate complexity-matched groups. It is very difficult to dissect the effect of having more cyanotic congenital heart disease patients in the aminophylline group and how it effects our primary end-points. Well-designed animal experiments are needed to be able to detect the effect of ongoing cyanosis for the vulnerability of the kidney when challenged with further insult. There were minimal exclusion criteria (PDA patients and noncardiac thoracic surgery) and all consecutive children were included and analyzed in the study. The decision to treat each patient was a clinical decision, rather than study protocol and therefore our results may be relevant for the current clinical practice.

Conclusions

Our study demonstrated a decrease in the need for postoperative RRT in the second intervention era, and this might have been associated with intraoperative aminophylline use. When compared with furosemide, aminophylline did not show inferiority in any of the primary or secondary renal outcome markers. Intraoperative aminophylline at the described dose was safe, without any documented adverse events. The finding that children with milder cardiac defects may be associated with the best potential benefit from aminophylline may justify its use regardless of risk stratification. The previously failed clinical trials with A1R antagonists in adults with decompensated heart failure should not prohibit prospective randomized clinical trials in pediatric CSA-AKI. The promise and association for positive impact on postoperative GFR and urine output may predict better in-hospital and overall outcomes (9, 10, 45, 51). Adenosine blockade (selective or nonselective) currently stands as

the only mechanism-driven targeted therapy in attenuation of AKI secondary vasoconstriction induced hypoxic-ischemic injury (29, 34, 42, 49).

Acknowledgments

Dr. Rosen disclosed a relationship with the Editorial board of pediatrics (at annual meeting they provide hotel room and food) and disclosed off-label product use (The literature has a number of papers where aminophylline has been used for renal rescue. There is one other paper that used it in the pediatric cardiac setting). His institution received funding from Nichd, Medicines Corporation, and Maquet. Dr. Mullett disclosed off-label product use (the use of aminophylline for renal Dr. Rosen disclosed a relationship with the Editorial board of pediatrics (at annual meeting they provide hotel room and food) and disclosed off-label product use (The literature has a number of papers where aminophylline has been used for renal rescue. There is one other paper that used it in the pediatric cardiac setting). His institution received funding from Nichd, Medicines Corporation, and Maquet. Dr. Mullett disclosed off-label product use (the use of aminophylline for renal protection and diuresis in pediatric congenital cardiac surgery patients). Dr. Kanosky disclosed off-label product use (This use of aminophylline is not part of the package insert but there are a number of papers in the literature describing its effect on adenosine blockade.). Dr. Seachrist disclosed off-label product use (use of aminophylline for renal protection during cardiac surgery in pediatric population).

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Figure 1. Comparative urine outputs (mL/kg/hr) of the intervention groups for the first postoperative 8 hours.

Figure 2.
Mean urine outputs (mL/kg/hr) at postoperative 48 hr based on group assignment and Risk Adjustment for Congenital Heart Surgery (RACHS)-1 score.

Figure 3.

Comparison of mean δ serum creatinine values (percent change of creatinine compared to preoperative baseline serum creatinine) at discharge from PICU for the two intervention groups, according to their Risk Adjustment for Congenital Heart Surgery (RACHS)-1 score classifications.

Table 1
Pediatric Modified Acute Kidney Injury Network Criteria (5, 7)

Acute Kidney Injury Stage	Urine Output Criteria	Serum Creatinine Criteria (in 48 Hr)
I	< 0.5 mL/kg/hr for 8 hr	Increase in serum creatinine level by 0.3 mg/dL or increase to 150–200% of reference value in 48 hr
II	< 0.5 mL/kg/hr for 16 hr	Increase of serum creatinine level to 200–300% of reference value in 48 hr
III	< 0.3 mL/kg/hr for 24 hr or anuria for 16 hr	Increase of serum creatinine level to > 300% of reference value or serum creatinine level of 4.0 mg/dL with an acute rise of 0.5 mg/dL in 48 hr

Table 2
**Cumulative Cardiothoracic Surgery Demographics in the Two Treatment Eras and Their
 Respective Distribution According to the Surgery Type in both Eras**

Type of Surgery	Aminophylline Era, <i>n</i> (%)	Furosemide Era, <i>n</i> (%)
Atrial septal defect	5 (5.0)	4 (4.0)
Ventricular septal defect	15 (15.0)	13 (13.0)
Repair atrioventricular canal	9 (9.0)	7 (7.0)
Norwood/Glenn shunt	11 (11.0)	16 (16.0)
Blalock-Taussig shunt	0 (0.0)	1 (1.0)
Arterial switch	4 (4.0)	8 (8.0)
Pulmonary valvotomy/valvulotomy	11 (11.0)	10 (10.0)
Aortic valvotomy/valvulotomy	5 (5.0)	5 (5.0)
Repair coarctation of aorta	9 (9.0)	5 (5.0)
Mitral valvotomy/valvulotomy	6 (6.0)	1 (1.0)
Repair total anomalous pulmonary veins	4 (4.0)	1 (1.0)
Repair tetralogy of Fallot	9 (9.0)	16 (16.0)
Fontan procedure	2 (2.0)	4 (4.0)
Tricuspid valvotomy/valvulotomy	0 (0.0)	3 (3.0)
Repair truncus arteriosus	4 (4.0)	0 (0.0)
Other surgeries	6 (6.0)	6 (6.0)
Total Number	100	100

Noncardiac thoracic surgeries are not included.

Table 3
Comparative Distribution of the Children in Different Treatment Groups According to the Risk Adjustment for Congenital Heart Surgery-1 Score Classification

Group/Severity	RACHS-1 Score 1/Mild	RACHS-1, Score 2–3/Moderate		RACHS-1, Score 4–6/Severe	Total
Aminophylline group	3	73	24		100
Furosemide group	3	75	22		100
Total	6	148	46		200
<i>p</i>	NS	NS	NS		Not applicable

NS = not significant, RACHS = Risk Adjustment for Congenital Heart Surgery.

Both intervention groups have comparable number of subjects in each severity category (p = not significant [NS]). The mean Risk Adjustment for Congenital Heart Surgery-1 score for the aminophylline group is 2.93 ± 1.3 and for the furosemide group is 2.98 ± 1.3 (p = NS).

Table 4
Study Subject Comparison: Demographic Characteristics, Surgical Durations, and Treatment Modalities of the Aminophylline Group and Furosemide Group

Variable	Aminophylline Group, <i>n</i> = 100	Furosemide Group, <i>n</i> = 100	<i>p</i>
Newborn (< 1 mo) (%)	35 (35)	26 (26)	NS
Young infant (1–3 mo) (%)	14 (14)	10 (10)	NS
Term baby (%)	70 (70)	57 (57)	NS
Risk Adjustment for Congenital Heart Surgery-1 score (mean ± SD)	2.97 ± 1.3	2.94 ± 1.3	NS
Cyanotic heart disease (% of the group)	72 (72)	37 (37)	0.001
Duration of surgery (minutes ± SD)	272.26 ± 110.4	296.96 ± 135.6	NS
Duration of cardiopulmonary bypass (minutes ± SD)	112.66 ± 56.5	105.88 ± 67.7	NS
Duration of aorta cross-clamp time (minutes ± SD)	56.21 ± 33.0	58.88 ± 39.0	NS
Inotropic score at postoperative 8 hr	26.70 ± 69.7	15.20 ± 11.4	NS
Peritoneal dialysis catheter placed in the operating room/first 24 hr postoperative, <i>n</i> (%)	9 (9)	14 (14)	NS
Diuretics at postoperative 48 hr, <i>n</i> (%)			
Bumetanide-mannitol continuous drip ^a	7 (7)	13 (13)	0.05
Furosemide continuous drip ^a	30 (30)	38 (38)	NS
Chlorothiazide intermittent	28 (28)	24 (24)	NS
Furosemide/bumetanide intermittent	63 (63)	49 (49)	0.03
Aminophylline intermittent	21 (21)	31 (31)	0.03

NS = not significant.

^a If the subject received > 24 hr of continuous diuretic regimen, the subject is evaluated in that group. If the subject only received intermittent diuretics, the subject is considered in the intermittent group. Chlorothiazide is an addendum to different loop diuretic treatment regimens.

The demographics, Risk Adjustment for Congenital Heart Surgery-1 score, type of congenital heart disease, surgical and cardiopulmonary bypass durations as well as postoperative care findings are compared between the two intervention groups.

Table 5
Cumulative Distribution of Children for Their Acute Kidney Injury Stage at 48 Hours Postoperative, Renal Replacement Therapy Requirement, and Death in PICU According to Their Intervention Group

Outcomes	Aminophylline Group, <i>n</i> = 100 (%)	Furosemide Group, <i>n</i> = 100 (%)	<i>p</i>
AKI stage 0 at 48 hr	62 (62)	51 (51)	NS
AKI stage I at 48 hr	18 (18)	20 (20)	NS
AKI stage II at 48 hr	12 (12)	18 (18)	NS
AKI stage III at 48 hr	8 (8)	9 (9)	NS
Renal Replacement Therapy	1 (1)	7 (7)	0.03
Death	12 (12)	17 (17)	NS

AKI = acute kidney injury, NS = not significant.

For two children in the furosemide group, the urine output and the serum creatinine at 48 hr postoperative information were not available to decide on the acute kidney injury status.