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# Lower-Dose, Intravenous Chlorothiazide Is an Effective Adjunct Diuretic to Furosemide Following Pediatric Cardiac Surgery

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**OBJECTIVES** Postoperative fluid overload is ubiquitous in neonates and infants following operative intervention for congenital heart defects; ineffective diuresis is associated with poor outcomes. Diuresis with furosemide is widely used, yet there is often resistance at higher doses. In theory, furosemide resistance may be overcome with chlorothiazide; however, its efficacy is unclear, especially in lower doses and in this population. We hypothesized the addition of lower-dose, intravenous chlorothiazide following surgery in patients on high-dose furosemide would induce meaningful diuresis with minimal side effects.

**METHODS** This was a retrospective, cohort study. Postoperative infants younger than 6 months, receiving high-dose furosemide, and given lower-dose chlorothiazide (1–2 mg/kg every 6–12 hours) were identified. Diuretic doses, urine output, fluid balance, vasoactive-inotropic scores, total fluid intake, and electrolyte levels were recorded.

**RESULTS** There were 73 patients included. The addition of lower-dose chlorothiazide was associated with a significant increase in urine output (3.8 ± 0.18 vs 5.6 ± 0.27 mL/kg/hr, $p < 0.001$), more negative fluid balance (16.1 ± 4.2 vs −25.0 ± 6.3 mL/kg/day, $p < 0.001$), and marginal changes in electrolytes. Multivariate analysis was performed, demonstrating that increased urine output and more negative fluid balance were independently associated with addition of chlorothiazide. Subgroup analysis of 21 patients without a change in furosemide dose demonstrated the addition of chlorothiazide significantly increased urine output ($p = 0.03$) and reduced fluid balance ($p < 0.01$), further validating the adjunct effects of chlorothiazide.

**CONCLUSION** Lower-dose, intravenous chlorothiazide is an effective adjunct treatment in postoperative neonates and infants younger than 6 months following cardiothoracic surgery.

**ABBREVIATIONS** AKI, acute kidney injury; CHD, congenital heart defect; CHLA, Children's Hospital Los Angeles; CTICU, cardiothoracic intensive care unit; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1

**KEYWORDS** chlorothiazide; critical care; diuresis; pediatrics; water-electrolyte balance

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## Introduction

The repair or palliation of congenital heart defects (CHDs) involves significant challenges. Although mortality has improved, barriers remain in mitigating complications and improving outcomes.[1,2] Fluid overload, defined as excess body water and tissue edema, is a ubiquitous postoperative problem following surgical repair of CHD with potentially important sequela.[3–5]

Postoperative fluid overload has been associated with increased mortality.[4,6] Lex et al[4] demonstrated that of 1520 neonates, infants, and children who underwent CHD surgery, early fluid overload was independently associated with in-hospital mortality (OR, 1.14; CI, 1.008–1.303; $p = 0.04$). Further, excess body water has been associated with postoperative morbidity, including prolonged time on vasoactive medications and inotropes, prolonged time to chest closure, increased risk of nosocomial infection, increased hospital cost, and prolonged hospitalization.[7–11]

The cause of fluid overload is multifactorial. Prior to surgery, many neonates and infants are overcirculated because of their CHD.[3] During cardiopulmonary bypass, patients are exposed to significant amounts of exogenous fluids. Relative to older children and adults, infants and neonates require increased amounts of fluid to safely undergo cardiopulmonary bypass, thus making them more likely to develop fluid overload.[12] Because of the neurohormonal and inflammatory response to cardiopulmonary bypass, patients develop capillary leak syndrome mediated by antidiuretic hormone, adenosine, and the angiotensin renin pathway.[7,13,14]

Following surgery, secondary to cardioplegia and reperfusion injury, many patients experience low cardiac output syndrome, which necessitates additional fluid resuscitation.[15] Finally, after CHD repair or palliation, acute kidney injury (AKI) has been described as occurring in 52% to 64% of patients, further compounding a patient's risk for fluid overload.[16,17]

Inotropic support and diuretic therapy are the mainstay of postoperative care in these patients. In particular, intravenous furosemide is known to enhance diuresis and is widely used.[18,19] Furosemide is well tolerated in critically ill infants following CHD surgery in continuous and bolus form.[14,20] However, the development of furosemide resistance has been described in adults and children, making adequate diuresis more difficult. The mechanism of this resistance is potentially due to various counterregulatory responses during both acute and chronic use of loop diuretics, such as the "braking phenomenon," postdiuretic effect, rebound sodium retention, and renal adaptation.[21,22] Resistance to furosemide administration can be noted within as few as 3 doses. A study by Segar et al[23] showed significant urinary response attenuation between a first and a third dose of furosemide in infants with bronchopulmonary dysplasia when given 1 mg/kg intravenously every 24 hours.

Furosemide resistance can theoretically be overcome by sequential nephron blockade with the addition of a thiazide diuretic that works downstream from the loop of Henle at the distal convoluted tubules. Unfortunately, adjunctive thiazide diuretics use is not well studied in pediatric populations, particularly in infants and neonates after CHD surgery.[20,24,25] Adult studies in patients after cardiothoracic surgery with inadequate diuresis to furosemide have demonstrated benefit from adjunct thiazide administration, as well as those with acute exacerbations of congestive heart failure.[26,27] In pediatrics, one study of children, mostly with nephrotic syndrome, and another study of children with bronchopulmonary dysplasia resistant to furosemide demonstrated robust urine output with the addition of metolazone.[23,28] In the literature there are 2 studies by the same institution looking at postoperative infants and neonates following CHD surgery; they demonstrated certain patients appeared to be responders to the addition of metolazone, but they concluded that there is no consistent response to chlorothiazide.[29,30] As such, the benefit of thiazides, most specifically chlorothiazide, as an adjunct to furosemide in patients with CHD remains unclear.

Given that standard doses of thiazides have demonstrated side effects, including hypokalemia, azotemia, and hyponatremia, we aimed to discover whether using lower doses of chlorothiazide could be an effective adjunct diuretic regimen with minimal electrolyte abnormalities.[31,32] Previous studies have demonstrated clinically significant shifts in electrolytes, at times requiring discontinuation, with adjunct use of standard doses of thiazide diuretics in patients receiving furosemide.[28,33] Current dosing recommendations for intravenous chlorothiazide are 10 to 20 mg/kg/day divided into 1 to 2 doses per day.[30,34] We aimed to study whether lower-dose, intravenous chlorothiazide (1–2 mg/kg per dose every 6–12 hours) in children undergoing an operation for CHD could serve as an effective adjunct to high-dose furosemide. We hypothesized that the addition of lower-dose, intravenous chlorothiazide to high-dose, intravenous furosemide following CHD surgery would induce clinically meaningful diuresis with minimal side effects.

## Materials and Methods

This was a single-center, retrospective, cohort study in a 24-bed cardiothoracic intensive care unit (CTICU) at a large, stand-alone children's hospital. The study was approved by the Internal Review Board at The University of Southern California and Children's Hospital Los Angeles (CHLA) for waiver of consent (CHLA-18-00169, April 19, 2018). All procedures contributing to this work complied with the ethical standards of the relevant national guidelines on human experimentation (United States of America) and with the Helsinki Declaration of 1975, as revised in 2008. The CHLA Department of Pharmacy database was used to identify all patients in the CTICU who received chlorothiazide in addition to high-dose furosemide between March 2009 and February 2011.

**Definition.** For the purposes of this study, we defined high-dose furosemide as 4 mg/kg/day or more of intravenous furosemide either as a continuous infusion of 0.2 to 0.4 mg/kg/hr or intermittent dosing of 1 mg/kg every 6 hours. When the medical team clinically determined the patient was inadequately responding to high-dose furosemide, the CTICU standard was to add approximately 1 to 2 mg/kg intravenous chlorothiazide every 6 to 12 hours. All doses of chlorothiazide are given 30 minutes prior to concomitant doses of loop diuretics when possible at our institution. Repletion of electrolytes occurred by standard practice of the unit, which includes intravenous fluids, as well as parenteral and enteral nutrition, and in the form of repletion boluses as deemed necessary by the care team.

**Inclusion and Exclusion Criteria.** Inclusion criteria for this study were patients who had undergone an operation for CHD, who had a chronological age of less than or equal to 6 months on the day of surgery, who had undergone treatment with high-dose furosemide for at least 24 hours prior to the addition of chlorothiazide, and who had started chlorothiazide within 14 days of cardiac surgery. Patients were excluded if they required any type of dialysis or extracorporeal membrane oxygenation during their hospitalization, had a serum creatinine >1.5 mg/dL during the 48-hour study period, were given a diuretic other than furosemide and

chlorothiazide during the study period, had received chlorothiazide previous to the study period during the hospitalization, or had incomplete data.

**Data Collection.** Patient demographics, including age on day of surgery, weight, sex, gestational age at birth, and Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) classification, were recorded for each patient. Diuretic doses and frequency, urine output, fluid balance, vasoactive and inotrope doses, and total fluid intake were recorded for the 48-hour study period around the addition of chlorothiazide. Serum blood urea nitrogen, serum creatinine, sodium (Na), potassium (K), chloride (Cl), and bicarbonate values ($HCO_3$) were recorded for the 24-hour period preceding and the 24-hour period following the addition of chlorothiazide. Given the complexity of electrolyte repletion methods, including fluids, nutrition, and repletion boluses, it was decided that attempts to measure repletion would be challenging and likely inaccurate.

**Calculations.** Vasoactive-inotropic scores were used to compare vasoactive and inotrope doses. Vasoactive-inotropic scores were calculated as follows: vasoactive-inotropic score = dopamine + dobutamine + [100 × (epinephrine + norepinephrine)] + [10 × milrinone] + [10,000 × vasopressin].[35] All doses of vasoactive-inotropes were expressed in mcg/kg/min except vasopressin, which was expressed in U/kg/min.

**Outcomes.** The primary outcome measure was the difference in urine output and fluid balance during the 24 hours preceding the addition of chlorothiazide with the 24 hours immediately following. Secondary outcomes included changes in vasoactive-inotropic score, blood urea nitrogen, creatinine, and measured electrolytes.

**Statistical Analysis.** Statistical analyses were performed with the use of Stata 11.0 (Stata Corp, College Station, TX). Univariate analysis was performed via a paired *t*-test for normally distributed variables and a paired Wilcoxon rank-sum test for non-parametric data. Multivariate analysis with linear regression was used to determine the independence of any effect of chlorothiazide on outcomes. Subgroup analysis was undertaken for patients who had no change in their furosemide dosing during the 48 hours around the addition of chlorothiazide. Normally distributed results were reported as mean ± SD of the mean, and non-parametric results were reported as median plus interquartile range. Statistical significance was accepted with a p value <0.05.

## Results

A total of 246 patients who received chlorothiazide and high-dose furosemide postoperatively in the Children's Hospital Los Angeles CTICU were identified by the pharmacy database. Of those 246 patients, 100 did not meet inclusion criteria and 73 met exclusion criteria (Table 1). A total of 73 patients were included. On the day of surgery, included patients had a median age of 91 days, average weight was 4.5 kg, 59% were male, 16 were born less than 37 weeks' gestational age, and median RACHS-1 classification was 3 (Table 2).

**Table 1.** Patient Inclusion and Exclusion Criteria

| No. | Parameter |
|---|---|
| 246 | Total patients identified |
| 100 | Did not meet inclusion criteria:<br>3 were older than 6 mo<br>91 started chlorothiazide prior to 24 hr of high-dose furosemide therapy<br>6 chlorothiazide added more than 14 days after surgery |
| 73 | Met exclusion criteria<br>5 required peritoneal dialysis<br>7 required extracorporeal membrane oxygenation<br>25 additional diuretic used during the study period (nesiritide, acetazolamide)<br>32 repeat trial of chlorothiazide<br>1 data were incomplete |
| 73 | Patients included |

During the study period, 21 patients were on a continuous infusion of furosemide, 28 were on intermittent dosing, 7 were initially on an infusion but were converted to intermittent dosing, and 17 were initially on intermittent dosing but were converted to a continuous infusion. Daily furosemide exposure was 5.28 ± 1.68 mg/kg/day during the study. Chlorothiazide was added a median of 3 days after surgery (range, 1–14 days), with an average dose of 3.8 ± 1.93 mg/kg/day.

Analysis of the 73 included patients demonstrated a urine output of 3.8 ± 0.18 mL/kg/hr during the 24-hour period preceding the addition of chlorothiazide and 5.6 ± 0.27 mL/kg/hr during the 24-hour period immediately following the addition of chlorothiazide ($p < 0.001$; Figure 1). Fluid balance during the first 24-hour study period was 16.1 ± 4.2 mL/kg/day, compared with −25.0 ± 6.3 mL/kg/day in the 24-hour period after the addition of chlorothiazide ($p < 0.001$; Figure 2). Univariate analysis of secondary outcomes of the 73 patients revealed no significant change in total fluid intake, blood urea nitrogen, and creatinine. Marginal decreases in sodium (−1.1 mEq/L), potassium (−0.12 mEq/L), and chloride (−4.9 mEq/L) levels, and an increase in bicarbonate levels (2.9 mEq/L), were noted in the 24 hours after the addition of chlorothiazide (Table 3).

There was a significant decrease in vasoactive-inotropic scores from before to after the addition of chlorothiazide (8.3 ± 5.9 versus 4.3 ± 5.8, $p < 0.001$), and furosemide dose after the addition of chlorothiazide was slightly higher (0.20 ± 0.01 vs 0.24 ± 0.01 mg/kg/hr, $p < 0.001$). However, in a linear regression analysis adjusting for change in furosemide dose, vasoactive-inotropic score, fluid intake, blood urea nitrogen, and creatinine, an increase in urine output and a more

**Table 2.** Patient Demographics and Exposure of Included Patients (n = 73)

| Characteristics | Result |
|---|---|
| Age upon admission to the hospital, days, median (IQR) | 61 (3–150) |
| Age at day of surgery, days, median (IQR) | 91 (9–162) |
| Weight, kg, mean ± SD | 4.5 ± 1.6 |
| Sex, male, n (%) | 43 (59) |
| Prematurity, gestational age <37 wk at birth, n (%) | 16 (22) |
| RACHS-1 classification, median (IQR) | 3 (2–3) |
| Postoperative day at addition of chlorothiazide, median (IQR) | 3 (2–5) |
| Chlorothiazide dose exposure, mg/kg/day, mean ± SD | 3.83 ± 1.93 |
| Furosemide dose exposure, mg/kg/day, mean ± SD | 5.28 ± 1.68 |

*RACHS-1, Risk Adjustment for Congenital Heart Surgery-1*

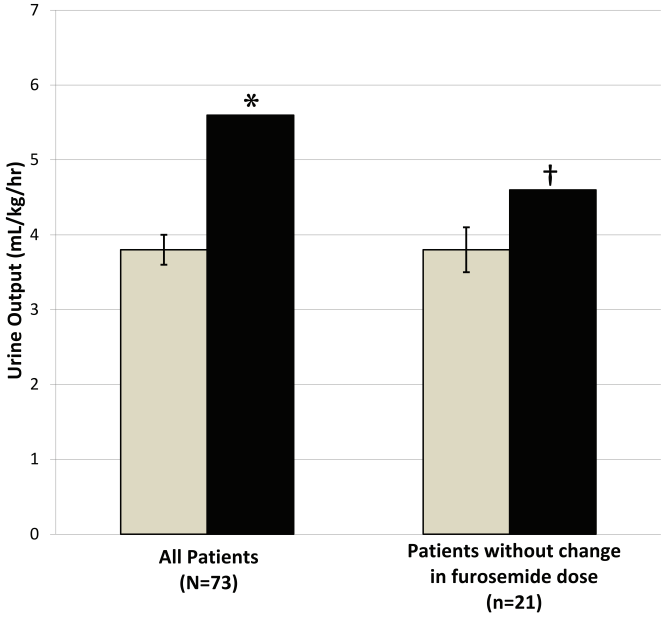
negative fluid balance were independently associated with the addition of chlorothiazide ($p < 0.01$; Table 4).

We further analyzed only patients who had no change in their furosemide dose during the 48-hour study period (n = 21). In these patients there was a significant increase in urine output during the 24-hour period after the addition of chlorothiazide compared with the 24-hour period immediately prior (3.8 ± 0.30 vs 4.6 ± 0.33 mL/kg/hr, $p = 0.03$; Figure 1). Fluid balance was found to be less positive (25.1 ± 6.8 vs 0.35 ± 4.6 mL/kg/day, $p < 0.01$; Figure 2). There was no significant change noted in total fluid intake, vasoactive-inotropic scores, serum creatinine levels, blood urea nitrogen, bicarbonate, or potassium levels. There was a decrease in sodium levels (−1.8 mEq/L) and chloride levels (−4.3 mEq/L) after the addition of chlorothiazide in these 21 patients (Table 3).

## Discussion

Our results demonstrate the addition of chlorothiazide led to a significant increase in urine output and reduction in fluid balance. This was true when furosemide dosing and vasoactive-inotropic scores were controlled

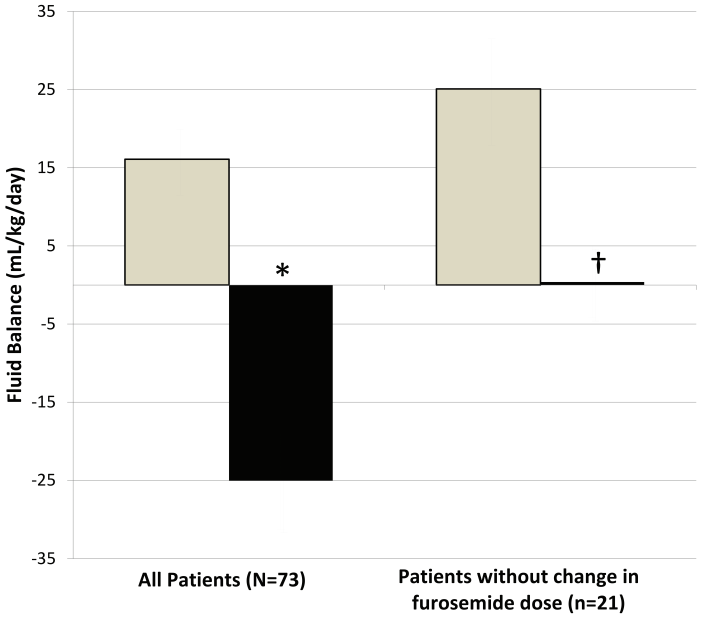
**Figure 1.** Urine output in response to chlorothiazide.




Urine output significantly increased following the addition of chlorothiazide in the 73 study patients (*$p < 0.001$). This remained the case in the 21 patients who had no change in furosemide dosing during the study period (†$p = 0.03$). Values are expressed as mean ± SEM.

□ Before chlorothiazide; ■ After chlorothiazide

**Figure 2.** Fluid balance in response to chlorothiazide.




Fluid balance was significantly more negative following the addition of chlorothiazide in the 73 study patients (*$p < 0.001$). Fluid balance remained significantly more negative in the 21 patients who had no change in furosemide dosing (†$p < 0.01$). Values are expressed as mean ± SEM.

□ Before chlorothiazide; ■ After chlorothiazide

by way of multivariate analysis, as well as in patients who had no change in their furosemide dosing during the 48-hour period of the study. The improved urine output and more negative, daily fluid balance were in the setting of lower-dose chlorothiazide (1–2 mg/kg per dose every 6 to 12 hours). The addition of lower-dose chlorothiazide marginally decreased chloride levels, and to a lesser degree sodium levels, when controlling for changes in furosemide dosing.

This association supports the employment of chlorothiazide as an adjunct to furosemide in postoperative neonates and infants undergoing CHD surgery. Presumably, with sequential nephron blockade chlorothiazide can increase urine output and lead to a more negative fluid balance, in spite of high doses of furosemide. Reports that at high doses of furosemide patients acquire relative resistance to furosemide as a diuretic supports the possibility that chlorothiazide may help overcome such resistance.[24,25]

Notably, only lower-dose chlorothiazide was needed to accomplish this synergy, with clinically marginal effects on sodium and chloride levels, when controlling for furosemide dosing changes. Even when not controlled for furosemide dosing changes, the clinical effect of adding chlorothiazide on most electrolytes was minimal. For example, there was a decrease in sodium of only 1.1 mEq/L and potassium of only 0.12 mEq/L. The greatest electrolyte effect of lower-dose, intravenous chlorothiazide was on chloride, decreasing by approximately 5 mEq/L in the 24 hours after the addition of chlorothiazide. The change in chloride persisted even after controlling for furosemide dosing, whereas the effects on potassium and bicarbonate levels no longer remained.

Similar to the work of Moffett et al,[30] our study focused on the impact of intravenous chlorothiazide on diuresis in critically ill neonates and infants in a CTICU already on furosemide. However, our studies differ in conclusion and key methodologic ways. Their work suggests intravenous chlorothiazide does not induce meaningful diuresis. To reach this conclusion the authors arbitrarily divided patients into responders if urine output increased by greater than 0.5 mg/kg/hr following the addition of chlorothiazide, and non-responders if it did not. Responders made up 43% of their patients. From this they concluded adjunct chlorothiazide is not associated with meaningful diuresis. They did not compare *change* in fluid balance or weight across chlorothiazide introduction, to determine the individual patient's clinically meaningful response to the addition of chlorothiazide. Further, their study did not exclude those on other diuretics, it did not exclusively examine *postoperative* patients, where the gains are likely most meaningful, and it did not standardize or adjust for the dose of furosemide given.[30] Other studies that have demonstrated the benefit of adjunct diuretics

**Table 3.** Secondary Outcomes Before and After the Addition of Chlorothiazide in All Patients and in Those Without a Change in Furosemide Dosing

| | All Patients, Mean ± SD (n = 73) | | | Patients Without Change in Furosemide Dose, Mean ± SD (n = 21) | | |
|---|---|---|---|---|---|---|
| | 24 hr Before Chlorothiazide | 24 hrs After Chlorothiazide | p value* | 24 hr Before Chlorothiazide | 24 hr After Chlorothiazide | p value |
| Total fluid intake, mL/kg/day | 114 ± 27 | 115 ± 29 | 0.8 | 121 | 114 | 0.16 |
| Vasoactive-inotropic score | 8.3 ± 5.9 | 4.3 ± 5.8 | **0.001** | 2.5 | 2.4 | 0.84 |
| Blood urea nitrogen, mg/dL | 13 ± 74 | 13 ± 8 | 0.09 | 13 | 15 | 0.17 |
| Serum creatinine, mg/dL | 0.38 ± 0.13 | 0.40 ± 0.14 | 0.4 | 0.37 | 0.42 | 0.11 |
| Serum sodium, mEq/L | 136.6 ± 3.6 | 135.5 ± 3.2 | **<0.01** | 136.9 ± 3.5 | 135.1 ± 3.0 | **0.04** |
| Serum potassium, mEq/L | 3.36 ± 0.36 | 3.24 ± 0.40 | **0.02** | 3.46 ± 0.40 | 3.40 ± 0.41 | 0.68 |
| Serum chloride, mEq/L | 101.0 ± 5.2 | 96.1 ± 4.5 | **<0.001** | 99.3 ± 5.5 | 95.0 ± 4.3 | **<0.001** |
| Serum bicarbonate, mEq/L | 29.1 ± 3.5 | 32.0 ± 4.1 | **<0.001** | 30.9 ± 3.8 | 32.0 ± 3.7 | 0.17 |

* Bold values indicate statistical significance.

to furosemide used change in urine output, fluid balance, or weight before and after in the same patient as a standard means to determine response, not an arbitrary urine output cutoff.[23,26–28,33] As such, we used similar methodology to determine an individual patient's response to adjunct chlorothiazide.

From a pharmacologic standpoint, our study sought to isolate the effect of chlorothiazide. It is for this reason that we used paired analyses (where patients act as their own controls), multivariate analysis, and a subgroup analysis of patients without any change in their furosemide dosing. Our study is also the only study in pediatrics that excluded important confounding variables, such as the use of other diuretics (e.g., nesiritide, spironolactone), dialysis, significant renal failure, extracorporeal membrane oxygenation, and others. The benefit of lower-dose chlorothiazide in increasing urine output and leading to a more negative fluid balance persisted when stringent methods were used to prevent confounding variables. Shy of a prospective randomized controlled trial, such methods improve the validity of such a retrospective study.

There are several limitations to the study. The data collection and analysis of this study were retrospective, which precludes comprehensively controlling for potential confounding variables. The statistical methods described above, including use of a paired analysis, attempt to minimize differences around the addition of chlorothiazide. However, a paired analysis cannot fully control for improvements in a patient's clinical status and renal function as the possible basis for improved urine output and fluid balance after addition of chlorothiazide. In the 21 patients whose furosemide dosage did not change during the study period we demonstrated no change in blood urea nitrogen, creatinine, and vasoactive-inotropic scores as an attempt to demonstrate the patients' clinical status had no significant improvement, and thus the significant improvement in urine output and fluid balance is attributed to the addition of low-dose chlorothiazide. Secondly, the data set was collected between March 2009 and February 2011. We feel the older nature of this data is unlikely to have any impact on outcomes because the treatment of furosemide resistance and fluid overload, as well as the use of IV chlorothiazide, have not changed significantly in the interim. Finally, this is a single-center study, with a number of inclusion and exclusion criteria, which may preclude the generaliz-

**Table 4.** Multivariate Analysis of Outcomes*

| Variable | Chlorothiazide Coefficient | p value |
|---|---|---|
| Intake (mL/kg/day) | 0.022 | 0.979 |
| Urine output (mL/kg/hr) | 0.242 | **0.000** |
| Fluid balance (mL/kg/day) | −5.700 | **0.001** |
| Vasoactive-inotropic score | −0.216 | **0.041** |
| Serum blood urea nitrogen (mg/dL) | 0.185 | 0.440 |
| Serum creatinine (mg/dL) | 0.004 | 0.294 |

* Multivariable analysis of outcomes, as a product of furosemide and chlorothiazide dosing (n = 73). The p values represent the effect of chlorothiazide when controlled for furosemide dosing and the other variables. The variables were added in a stepwise fashion to determine independence of effect.

ability of the findings to patients outside those criteria and in other institutions. We elected to exclude patients who underwent dialysis to minimize confounding the assessment of chlorothiazide's effect on fluid balance by dialysis and severe AKI factors. This may limit the generalizability to those centers that more readily use dialysis in postoperative management, as opposed to those using dialysis in advanced AKI, as in our center.

A prospective trial in which patients resistant to high-dose furosemide are randomized into varying treatment arms would be an important next step in determining the utility of thiazides in patients with CHD. Although we have demonstrated that lower-dose, intravenous chlorothiazide can be impactful as an adjunct, it is unclear whether higher doses or different times of dosing chlorothiazide relative to intermittent furosemide would have additional benefits and/or different side effect profiles (e.g., electrolyte effects).

## Conclusions

Lower-dose, intravenous chlorothiazide is an effective adjunct in postoperative neonates and infants following CHD surgery who may be resistant to high-dose furosemide. The effect on electrolytes included lower chloride levels and a lesser decrease in sodium levels, both of marginal clinical significance.

## ARTICLE INFORMATION

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