Original article

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The response of furosemide or chlorothiazide in critically ill pediatric patients

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Abstract

***Introduction/background*: Fluid overload is common in critically ill children and is associated with significant morbidity and mortality. Furosemide is the most widely used diuretic to manage excess fluid. In addition to loop diuretics, thiazide diuretics may be used to enhance urine output. Data and information regarding safe and effective dosing of furosemide and chlorothiazide in the critically ill pediatric population are lacking. The primary objective of this study was to compare urine output 24 hours after initiation of furosemide or chlorothiazide in critically ill children.**

***Methods*: This was a multi-center retrospective cohort study conducted at 3 academic medical centers. Children between the ages of 1 day and 17 years that received at least one dose of intravenous or oral diuretics from February 2013 to January 2017 were included. Patients with bronchopulmonary dysplasia or on home diuretics were excluded. Only the first dose of diuretic was included in the study. Patients were divided into two groups: furosemide versus chlorothiazide. Urine output 24 hours prior to the diuretic was compared to urine output 24 hours after initiation of the diuretic.**

***Results*: There were 133 patients identified who met the inclusion criteria for the study. There were 88 patients that received at least one dose of furosemide and 45 that received at least one dose of chlorothiazide. Most patients were male (49, 55.7%) with a median age of 2.3 years. The median dose for furosemide was 0.7 mg/kg and for chlorothiazide was 2.4 mg/kg. There were no statistically significant differences between baseline urine output for furosemide (2.9 ml/kg/hr) or chlorothiazide (2.8 ml/kg/hr), p=0.6. Although not statistically different, urine output 24 hours after the diuretic dose increased by 0.84 ml/kg/hr for furosemide and 0.73 ml/kg/hr for chlorothiazide, p=0.45.**

***Conclusion*: Furosemide and chlorothiazide resulted in similar urine output changes 24 hours after an intravenous dose.**

Key words: Pediatrics, critical care, diuretics, electrolytes, urine output.

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Introduction

Fluid overload is common in critically ill children and is associated with significant morbidity and mortality. (1) Loop diuretics are commonly used for diuresis in children due to their rapid onset of action and enhanced efficacy based on their mechanism of action. (2) Loop diuretics are potent diuretics that inhibit the reabsorption of Na^+ and Cl^- in the ascending loop of Henle. (3,4) In addition to loop diuretics, thiazide diuretics may be used to enhance urine output. Thiazide diuretics are less potent and inhibit Na^+ reabsorption in the early distal convoluted tubule. (4,5)

Significant literature exists documenting the combined use of furosemide and chlorothiazide to take advantage of the different mechanisms of action to enhance urine output. Also, the literature supports using furosemide as a continuous infusion. However, there is a scarcity of literature available on the pharmacokinetics, dosing, and adverse effects of the individual use of furosemide or chlorothiazide in critically ill pediatric patients. (6) This study was conducted to fill in the gaps in the literature for single-dose administration on clinical parameters. The primary objective of this study was to compare urine output 24 hours after initiation of furosemide or chlorothiazide in critically ill children. The secondary objectives were to compare the impact of furosemide or chlorothiazide on electrolytes, kidney function, and blood pressure.

Methods

This was a multi-center retrospective convenience sample study conducted at three academic medical centers. Children between the ages of 1 day and 17 years that received at least one dose of intravenous or oral furosemide or chlorothiazide in the Pediatric Intensive Care Unit (PICU) from February 2013 to January 2017 were included. All three PICUs offer similar services for children and are regional referral centers. Patients with bronchopulmonary dysplasia or on home diuretics were excluded. Urine output 24 hours prior to the diuretic was compared to urine output 24 hours after initiation of the diuretic. Additionally, baseline electrolyte values were also collected and compared to values 24 hours after diuretics. Blood pressure values prior to the diuretic dose were compared to values immediately following the initiation of diuretics to determine the incidence of hypotension. Hypotension was defined as a 20% decrease in blood pressure after the administration of the diuretic dose.

Patients were divided into 2 groups: furosemide versus chlorothiazide. Mann-Whitney U test was used for the primary endpoint to compare urine output and to compare blood urea nitrogen (BUN), serum creatinine, potassium, bicarbonate, and chloride levels. Demographic data such as age, weight, and diuretic dose were analyzed using Mann-Whitney U, and gender and diuretic route of administration were analyzed using chi-square. Also, adverse effects such as hypotension were compared using chi-square. This study was approved by the Institutional Review Boards at each academic center.

Results

There were 133 patients identified who met the inclusion criteria for the study. There were 88 patients that received at least one dose of furosemide and 45 that received at least one dose of chlorothiazide. Most patients were male (49, 55.7%) with a median age of 2.3 years. The groups were statistically different in weight with a median weight of 12.9 kg for furosemide and 5.1 kg for chlorothiazide, p=0.02. More than 90% of patients received the diuretic intravenously. The median dose for furosemide was 0.7 mg/kg and for chlorothiazide was 2.4 mg/kg. There were no statistical differences in demographics for age, gender, and diuretic route of administration between furosemide and chlorothiazide (**Table 1**).

There were no statistically significant differences between baseline urine output for furosemide (2.9 ml/kg/hr) or chlorothiazide (2.8 ml/kg/hr), p=0.6. Although not statistically different, urine output 24 hours after the diuretic dose increased by 0.84 ml/kg/hr for furosemide and 0.73 ml/kg/hr for chlorothiazide, p=0.45.

The secondary outcomes were to evaluate the impact of diuretics on electrolytes, renal function, and the incidence of hypotension. For effect on renal function, serum creatinine values were similar before and after the diuretic dose for both furosemide and chlorothiazide (**Figure 1**), however average BUN values significantly increased from 12 mg/dl to 16 mg/dl after the chlorothiazide dose ($p<0.0001$). BUN value changes for furosemide were not significantly different (**Figure 2**). Potassium levels decreased for both furosemide and chlorothiazide from baseline to 24 hours after the diuretic dose, however, the change of 0.2 mmol/l was not significantly different (**Figure 1**). The chloride and bicarbonate levels were different after the diuretic dose for both diuretics (**Figures 3-5**). The chloride levels decreased by 2 mmol/l for furosemide and 3 mmol/l for chlorothiazide. The bicarbonate levels increased by 3 mmol/l for both furosemide and chlorothiazide. Hypotension after the diuretic dose occurred in 9 patients (10%) in the furosemide group and 1 patient (2%) in the chlorothiazide group (p=0.09).

Discussion

This study evaluated urine output, electrolytes, kidney function, and blood pressure for critically ill pediatric patients in three centers using single-dose furosemide and chlorothiazide. We found overall furosemide and chlorothiazide resulted in similar changes in urine output 24 hours after a dose (0.84 and 0.73 ml/kg/hr, respectively). Limited data exist on the single-dose administration of diuretics, especially in critically ill pediatric patients. Only one other comparative study was found which included preterm infants and their response to bumetanide. (7) In this study, there was an increase in the urine output of 2.4 ml/kg/hr after non-responsiveness to furosemide. The baseline urine output in the premature infants was 0.6 ml/kg/hr which was much lower than our patients' baseline of 2.9 ml/kg/hr. This difference, in conjunction with neonatal kidney function vs older children, and their previous unresponsiveness to furosemide may account for the differences seen between the studies.

For the secondary objectives, adverse effects on electrolytes and renal function were overall similar between furosemide and chlorothiazide, however, chlorothiazide increased BUN and furosemide did not. The changes in chloride and bicarbonate while statistically significant were not clinically significant after the one diuretic dose. In the early diuretic literature, increases in BUN with chlorothiazide were reported as reversible in patients without renal disease. (8) A more recent, study by Laughon of diuretic exposure in premature infants also found a higher incidence of increase in BUN in patients on any diuretic (including chlorothiazide) compared to furosemide. (9) In a study by Hastings et al. of pediatric cardiac surgery patients, electrolyte abnormalities in patients on furosemide were uncommon and not different compared to those not on furosemide. (10) A study by Dartois et al. evaluated electrolyte abnormalities in Neonatal Intensive Care Unit (NICU) patients on diuretics. (11) The study found the most clinically significant alterations were with potassium and bicarbonate, and furosemide had the most profound changes on potassium as compared to other diuretics.

An additional adverse effect measured in our study was hypotension. Furosemide trended towards more episodes of hypotension in our study, which is a known side effect of loop diuretics. Administration of loop diuretics as a continuous infusion, instead of bolus administration may minimize the effects on hemodynamics in pediatric patients. (2)

There are some limitations in our study. First, it was retrospective in nature, so true causative relationships cannot be determined. Secondly, urine output was measured over 24 hours, which may be too long of a time frame since both diuretics when administered intravenously have a duration of about 2 hours. (12) Thirdly, this was single dose administration, therefore, further evaluation would be needed to see the effects of cumulative doses of these agents on electrolytes and other clinical parameters.

The strengths of this study included a diverse group of pediatric patients in terms of age, weight, length, and gender. Another strength of this study included the use of data from three centers, one on each coast of the United States.

Conclusion

Furosemide and chlorothiazide resulted in similar urine output changes 24 hours after an intravenous dose with clinically insignificant electrolyte changes in pediatric critically ill children.

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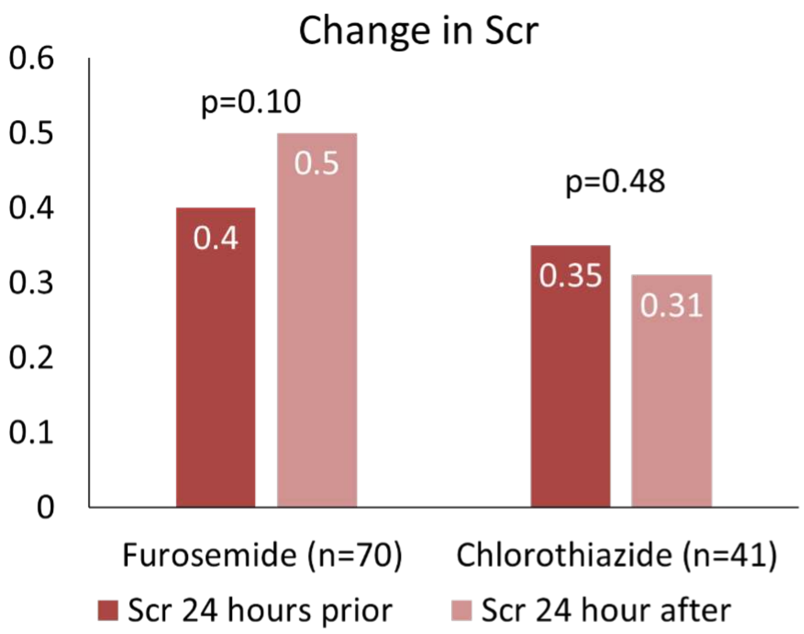
Table 1. Demographics

	Furosemide (n=88)	Chlorothiazide (n=45)	p-value
Age (years)	2.3 (0.12, 10)	0.42 (0.19, 5.5)	0.06
Gender (male), n (%)	49 (55.7)	20 (44.4)	0.14
Weight (kg)	12.9 (3.9, 37.8)	5.07 (3.2, 13.4)	0.02
Diuretic dose (mg/kg)	0.69 (0.5, 1)	2.4 (1.9, 4.3)	N/A
Diuretic route (IV), n (%)	81 (92)	41 (91)	0.55

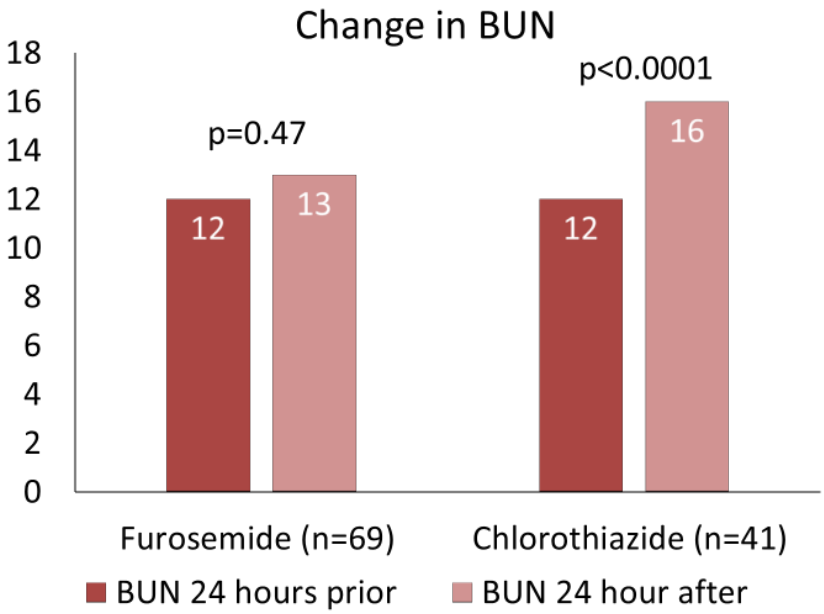
Legend: Values represent median (interquartile range) unless noted otherwise.
IV=intravenous; N/A=not available.

Figure 1. Change in scr in 24 hours



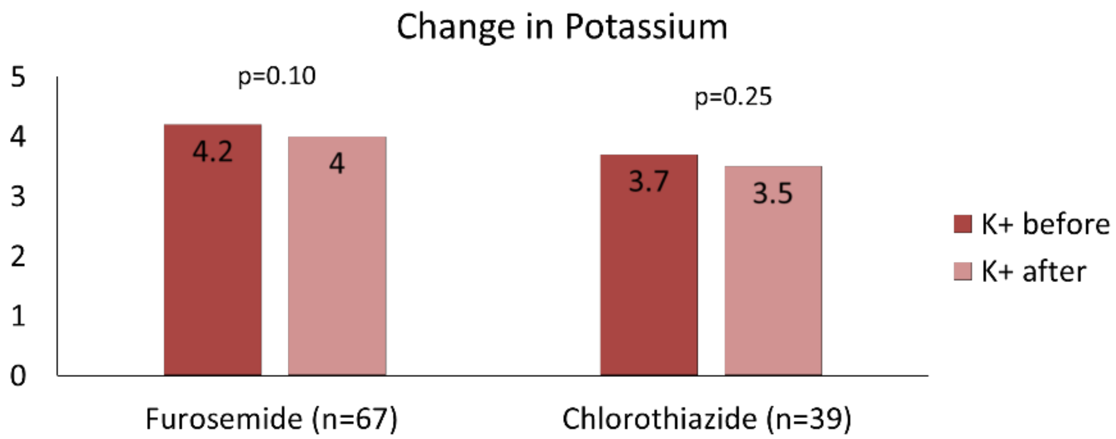
Legend: Scr=serum creatinine.

Figure 2. Change in BUN in 24 hours



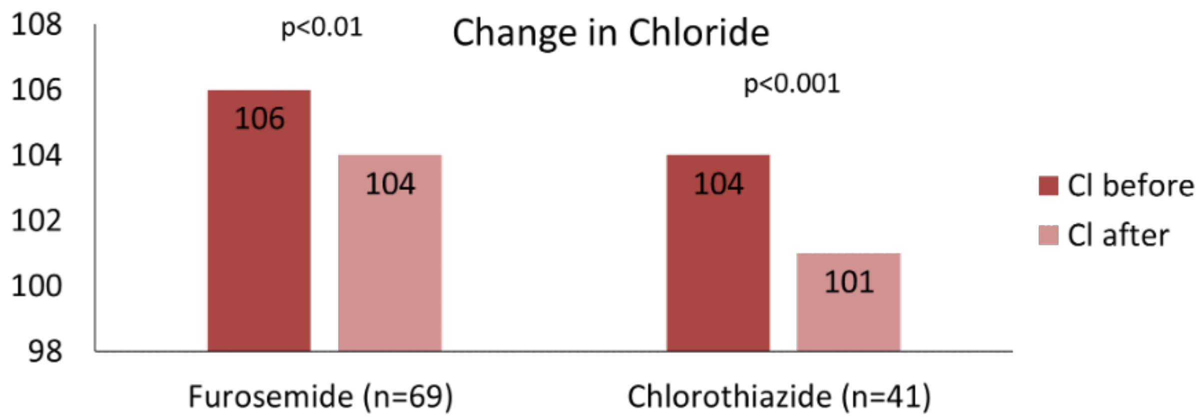
Legend: BUN=blood urea nitrogen.

Figure 3. Change in potassium levels



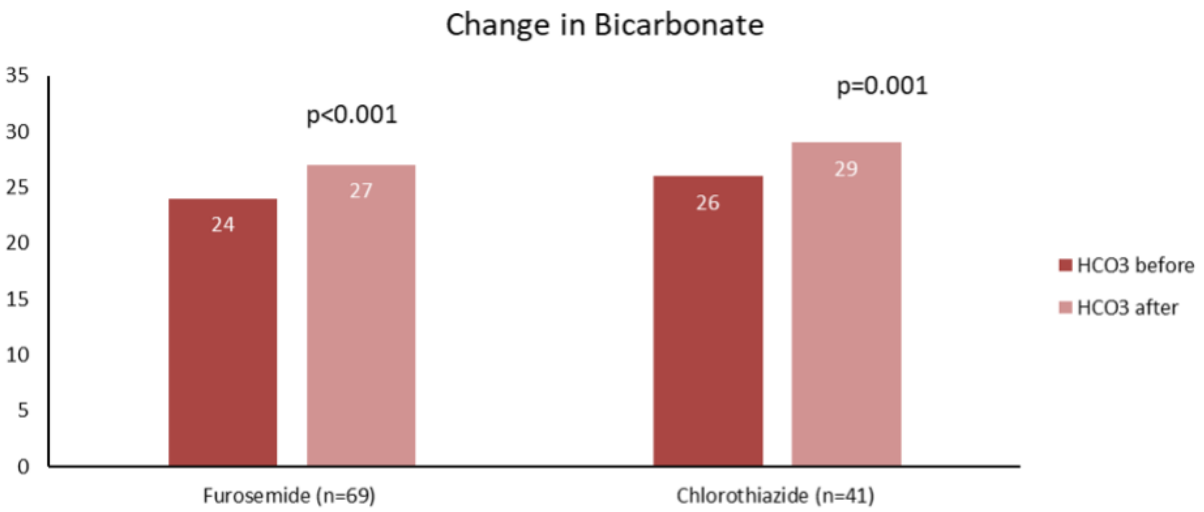
Legend: K^+=potassium.

Figure 4. Change in chloride levels



Legend: Cl=chloride.

Figure 5. Change in bicarbonate levels



Legend: HCO3=bicarbonat.

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