Cardiology in the Young (2017), **27**, 1104–1109
doi:10.1017/S1047951116002122

Original Article

Efficacy of sequential nephron blockade with intravenous chlorothiazide to promote diuresis in cardiac intensive care infants

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Abstract *Background:* Sequential nephron blockade using intravenous chlorothiazide is often used to enhance urine output in patients with inadequate response to loop diuretics. A few data exist to support this practice in critically ill infants. *Methods:* We included 100 consecutive patients <1 year of age who were administered intravenous chlorothiazide while receiving furosemide therapy in the cardiac ICU in our study. The primary end point was change in urine output 24 hours after chlorothiazide administration, and patients were considered to be responders if an increase in urine output of 0.5 ml/kg/hour was documented. Data on demographic, clinical, fluid intake/output, and furosemide and chlorothiazide dosing were collected. Multivariable regression analyses were performed to determine variables significant for increase in urine output after chlorothiazide administration. *Results:* The study population was 48% male, with a mean weight of 4.9 ± 1.8 kg, and 69% had undergone previous cardiovascular surgery. Intravenous chlorothiazide was initiated at 89 days (interquartile range 20–127 days) of life at a dose of 4.6 ± 2.7 mg/kg/day (maximum 12 mg/kg/day). Baseline estimated creatinine clearance was 83 ± 42 ml/minute/1.73 m^2. Furosemide dose before chlorothiazide administration was 2.8 ± 1.4 mg/kg/day and 3.3 ± 1.5 mg/kg/day after administration. A total of 43% of patients were categorised as responders, and increase in furosemide dose was the only variable significant for increase in urine output on multivariable analysis ($p < 0.05$). No graphical trends were noted for change in urine output and dose of chlorothiazide. *Conclusions:* Sequential nephron blockade with intravenous chlorothiazide was not consistently associated with improved urine output in critically ill infants.

Keywords: Diuretic resistance; chlorothiazide; loop diuretics; furosemide; paediatrics; intensive care

Received: 4 May 2016; Accepted: 8 October 2016; First published online: 11 November 2016

Background

The use of thiazide diuretics in conjunction with loop diuretics has long been a strategy to augment urine output in adult patients with heart failure.[1,2] The impetus for this therapy relates to the site of action of each diuretic in the tubule. Loop diuretics such as furosemide act on the ascending loop of Henle to prevent resorption of sodium, potassium, and chloride and increase osmotic pull of water into the tubule.[3] Thiazide diuretics act on the distal convoluted tubule of the nephron, downstream from the loop diuretic site of action. Theoretically, the addition of thiazide diuretics to a loop diuretic regimen can increase urine output by further decreasing electrolyte resorption, particularly when loop diuretics become less effective[4]; however, data for this practice in the paediatric population are sparse.

Intravenous chlorothiazide, a thiazide diuretic, has been used as a strategy to augment urine output in patients with inadequate response to loop diuretics in the critically ill paediatric population at our institution. Anecdotally, this is a practice that occurs at many institutions; yet, there are currently no data describing the efficacy of this practice in this population. Characterisation of this practice and assessment of

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efficacy are necessary to improve patient outcomes. Our hypothesis is that the addition of intravenous chlorothiazide to concomitant furosemide therapy improves urine output in paediatric cardiac intensive care patients.

Methods

Institutional review board approval from Baylor College of Medicine was obtained, and a pilot retrospective cohort study was designed. Data were queried from the hospital electronic medical record from 31 December, 2014 until 100 sequential patients who met study criteria were retrospectively identified. Patients were included if they were <1 year of age, admitted to the cardiac ICU at our institution, were receiving furosemide, and had intravenous chlorothiazide administered concomitantly with furosemide. Patients were excluded if fluid intake or output data were missing or if patients were undergoing mechanical circulatory support or renal replacement therapy during the 24 hours before or after chlorothiazide administration.

Patient demographic variables were collected. The following variables were collected at the time of intravenous chlorothiazide initiation: serum potassium, serum sodium, serum chloride, serum creatinine, vasopressor or inotrope use, and use of other diuretics. Estimated creatinine clearance was calculated according the Modified Schwartz equation.[5] Furosemide dose was collected for 24 hours before and after chlorothiazide initiation. Fluid intake and output data and urine output were collected for 24 hours before and after chlorothiazide initiation.

Overall change in urine output in millilitre per kilogram per hour (ml/kg/hour) for the study population at 24 hours after chlorothiazide initiation was calculated. An increase in urine output by 0.5 ml/kg/hour from before chlorothiazide initiation was deemed clinically relevant by the authors as a significant change in urine output, and patients were categorised as responders if they met this criterion or else as non-responders (<0.5 ml/kg/hour response). This is also a breakpoint noted in the pRIFLE criteria for a change in acute kidney injury staging.[6] The percentage of patients responding was calculated. Patient demographic, laboratory, and medication variables were compared between patient responders and non-responders.

Descriptive statistical methods – means, standard deviations, medians, and interquartile ranges – were used to characterise the study population. Student's t-test, Wilcoxon's Rank-Sum test, and Fisher's exact test were used as univariable methods to determine differences in responders and non-responders. Multivariable linear regression analysis was used to determine variables significant for a urine output response to intravenous chlorothiazide. All the analyses were performed using Stata IC v.12 (StataCorp, College Station, Texas, United States of America), and a p-value of <0.05 was selected as significant a priori.

Results

A total of 100 infants <1 year of age were identified (48% male), and 28% were ⩽30 days of age. The mean weight was 4.9 ± 1.8 kg. Among all, 69% of patients were admitted to the cardiac ICU after cardiovascular surgery, and 89% of those patients underwent cardiopulmonary bypass. Urine output was captured by the Foley catheter in 67% of patients. Baseline estimated creatinine clearance at chlorothiazide initiation was 83 ± 42 ml/minute/1.73 m^2. Baseline laboratory values were as follows: potassium = 3.7 ± 0.6 mmol/L, sodium = 139 ± 3 mmol/L, chloride = 102 ± 5 mmol/L, albumin = 3.1 ± 0.7 g/dl, and lactate = 1.0 ± 0.4 mmol/L.

Patients received the following continuous infusion vasoactive agents during chlorothiazide administration: milrinone (39%), epinephrine (4%), and vasopressin (1%). Other diuretics received during chlorothiazide initiation included spironolactone (6%) and acetazolamide (3%).

Patients were 89 days (interquartile range 20–127 days) of age at initiation of intravenous chlorothiazide. Chlorothiazide was initiated at a dose of 4.6 ± 2.7 mg/kg/day (maximum 12 mg/kg/day), and in patients who had a cardiovascular surgical procedure chlorothiazide was initiated on postoperative day 3 (interquartile range 2–5).

Furosemide dose before chlorothiazide initiation was 2.8 ± 1.4 and 3.3 ± 1.5 mg/kg/day after administration. Among all, 9% of patients received furosemide as a continuous infusion before chlorothiazide initiation and 14% received after chlorothiazide administration.

A total of 43% of patients were categorised as responders (Table 1). Variables significant on univariable analysis for response to intravenous chlorothiazide were baseline estimated creatinine clearance, postoperative day of chlorothiazide initiation, and furosemide dose before chlorothiazide initiation (Table 1). No difference was noted in the change in urine output by the method of urine capture (Table 2). Graphically, no trends were noticed in the change in urine output on the basis of the dose of intravenous chlorothiazide (Fig 1).

A multivariable linear regression analysis based on change in urine output (ml/kg/hour) from before to after chlorothiazide administration demonstrated that increased fluid intake before intravenous chlorothiazide ($\beta = -0.014$, $p = 0.017$) and an increased baseline estimated creatinine clearance ($\beta = -0.01$,

https://doi.org/10.1017/S1047951116002122 Published online by Cambridge University Press

Table 1. Comparison of responders and non-responders with chlorothiazide administration.

Category (n = 100)	Non-responder (<0.5 ml/kg/hour) (n = 57)	Responder (≥0.5 ml/kg/hour) (n = 43)	p value
Age (days) (median, IQR)	103 (17–197)	76 (21–157)	0.32
Cardiovascular surgery (%)	65.1	71.9	0.52
Cardiopulmonary bypass (%)	92.9	87.8	0.69
Baseline electrolytes			
Sodium (mEq/L)	139 ± 3	139 ± 3	0.93
Potassium (mEq/L)	3.8 ± 0.6	3.8 ± 0.6	0.67
Chloride (mEq/L)	101 ± 4	103 ± 5	0.26
Lactate (mmol/L)	0.9 ± 0.3	1.0 ± 0.5	0.29
Albumin (g/dl)	2.9 ± 0.8	3.2 ± 0.7	0.37
Estimated creatinine clearance (ml/minute/1.73 m^2)	95 ± 43	74 ± 39	0.02
Peritoneal dialysis (%)	4.7	14.0	0.18
Chlorothiazide postoperative day start (median, IQR)	4 (3–5)	2 (2–4)	0.01
Input before (ml/kg/day)	110 ± 38	99 ± 29	0.10
Input after (ml/kg/day)	112 ± 34	107 ± 30	0.49
Furosemide before (mg/kg/day)	3.3 ± 1.2	2.5 ± 1.4	0.004
Continuous infusion (%)	4.7	12.3	0.29
Furosemide after (mg/kg/day)	3.1 ± 1.4	3.5 ± 1.6	0.23
Continuous infusion (%)	11.6	15.8	0.77
Milrinone (%)	37.2	40.4	0.84
Epinephrine (%)	6.9	1.8	0.31
Vasopressin (%)	2.3	0	0.43
Spironolactone (%)	6.9	5.3	1.0
Acetazolamide (%)	4.7	1.8	0.58
Output capture			0.34
Catheter (n = 25) (%)	25.6	38.6	
Diaper (n = 33) (%)	30.2	21.1	
Diaper/catheter (n = 42) (%)	44.2	40.4	

IQR = interquartile range

Table 2. Comparison of urine output collection methods.

Category (n = 100)	Pre-chlorothiazide	Post-chlorothiazide
Input (ml/kg/day)	104 ± 34	109 ± 32
Urine output (ml/kg/hour)	3.2 ± 1.8	4.3 ± 1.7
Catheter (n = 25)	3.1 ± 1.8	4.2 ± 1.9
Diaper (n = 33)	3.5 ± 1.9	4.2 ± 1.7
Diaper/catheter (n = 42)	3.2 ± 1.7	4.4 ± 1.6

p = 0.036) resulted in decreased urine output and that increased per cent change in furosemide dose (β = 0.006, p = 0.003) was significant for increased urine output after chlorothiazide administration.

Discussion

This is the first evaluation of the effect of intravenous chlorothiazide on urine output in the paediatric intensive care population. There is relevance to this publication, and there remains a need for effective pharmacological methods of fluid mobilisation in this patient population. Fluid overload in critically ill children has been associated with increased morbidity and mortality.[7–9] The use of metolazone, an oral thiazide-type diuretic, has been used to improve urine output in infants with bronchopulmonary dysplasia, suggesting that addition of a thiazide diuretic to a loop diuretic is an effective strategy for fluid mobilisation.[10] Although the information presented is new, the basis for the benefit of intravenous chlorothiazide in sequential nephron blockade in the first place is surprisingly sparse.

A few publications have used intravenous chlorothiazide in addition to furosemide for sequential nephron blockade. Data for the use of chlorothiazide in the treatment of diuretic resistance have been primarily reported in adult patients with acute decompensated heart failure.[2,4,11] Overall, diuretic resistance is a poorly defined term, with the inability to decrease extracellular fluid or increase urine output after administration of intravenous loop diuretics as the most commonly used definition. Publications that demonstrate a benefit to the sequential nephron blockade approach to diuretic resistance often

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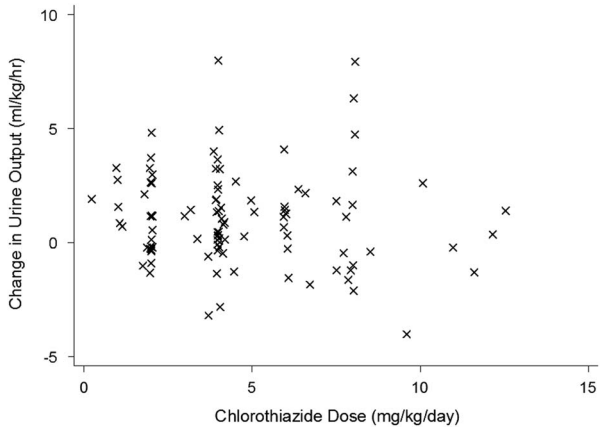

Figure 1.
Change in urine output as compared with intravenous chlorothiazide dose.

measure their outcomes in reduction in patient weight, which are not end points commonly used in paediatric cardiac intensive care patients. A recent review of combination diuretic use in adult patients with acute decompensated heart failure has noted that fewer than 500 patients have been described over a 40-year time period.[4] Publications that demonstrate a benefit to the sequential nephron blockade approach to diuretic resistance often measure their outcomes in reduction in patient weight, which are not end points commonly used in paediatric cardiac intensive care patients. Diuretics that have shown a benefit in adult patients with inadequate responses to loop diuretics and oedematous states include acetazolamide or metolazone but not intravenous chlorothiazide.[12]

It is apparent from this investigation that intravenous chlorothiazide did not consistently increase urine output in the presence of loop diuretics. The limited effect of intravenous chlorothiazide in this patient population is likely multifactorial. The maximum dose of chlorothiazide in our population was 12 mg/kg/day, which is below reported maximum doses of 20 mg/kg/day. Although we did not observe a trend in increasing doses and increased urine output, the use of higher doses of chlorothiazide could potentially be a limiting factor in the limited urine output response seen in the study population. The critically ill paediatric population can have many factors that may change the effectiveness of adding a thiazide diuretic to a loop diuretic regimen, including acute or chronic kidney injury, concomitant use of vasopressors or inotropes, or alterations in serum electrolyte concentrations. Patients with an increased response tended to have decreased fluid intake and were earlier in the postoperative period, as fluid restriction is a strategy at our institution in the first 72 hours after surgery. Aetiologies for decreased loop diuretic efficacy in adults, such as the "diuretic braking" phenomenon, which describes an acute decrease in the efficacy of loop diuretics, or post-diuretic sodium retention, have never been described in the paediatric population and is likely not an aetiology for variability in response. Interestingly, the timing of chlorothiazide administration in relation to furosemide administration has never been shown to alter the effectiveness of chlorothiazide.[4,13]

In addition, perfusion of the kidneys likely plays a significant role in diuretic efficacy in the paediatric cardiac intensive care population. In adult patients with acute decompensated heart failure, low systolic blood pressure, in addition to renal impairment, was associated with reduced loop diuretic efficacy.[14] The patient population with an improvement in urine output after chlorothiazide use were those with a lower estimated creatinine clearance and increased fluid administration before chlorothiazide, which both could potentially indicate haemodynamic instability. Serum creatinine has also been shown to be an inaccurate marker for kidney function in this patient population.[15] Chlorothiazide is actively secreted at the proximal convoluted tubule into the Loop of Henle and travels to its site of action in the distal proximal tubule, and furosemide has a similar mechanism by which it is actively secreted into the Loop of Henle.[1,12] Patients with decreased kidney blood flow should theoretically have decreased active secretion of drug into the lumen; however, serum lactate, a marker of perfusion, was similar in both responders and non-responders in our data. We theorise that the use of multiple sites of action in patients with decreased kidney function may overcome the limitations in active secretion associated with reduced kidney function. This requires further investigation, as acute kidney injury in the paediatric cardiac ICU occurs frequently.[16]

In the patient population we have described, patients with an increase in urine output also had an increase in their dose of furosemide. As the pharmacokinetics of furosemide have not been described in detail in paediatric cardiac intensive care patients, dosing strategies such as use of continuous infusion furosemide may need to be aggressively implemented in order to maximise fluid mobilisation.[3] As mentioned previously, the increased use of diuretics, whether multiple or single classes, appears to be necessary to improve urine output in the setting of reduced kidney blood flow and/or function. Previous reports have demonstrated the effectiveness of continuous infusion of furosemide as compared with bolus dosing.[17] It is currently unknown whether the use chlorothiazide in this setting would be beneficial as the effect of furosemide would be theoretically maximised.

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The consequences of using intravenous chlorothiazide in the paediatric cardiac intensive care population are not trivial. Adverse events such as hyponatremia have been reported to occur relatively frequently.[3,4] The lack of effect reported in our data set and the effect of fluid overload in this patient population highlight the need for aggressive fluid mobilisation to prevent significant morbidity and mortality and the use of agents that will achieve a fluid balance end point in a timely manner.[7,9] The cost of intravenous chlorothiazide is significant, and reduction in use can lead to significant savings.[18] A recent publication by Thomas et al demonstrated the cost savings associated with a "diuretic stewardship" programme in a paediatric cardiac ICU. Intravenous ethacrynic acid was restricted to patients with sulphonamide allergies, and intravenous chlorothiazide was restricted to patients who were on maximal doses of loop diuretics. The programme had a reduction in costs of ~$182,000 in 1 year without any noticeable changes in clinical end points or outcomes.[13] These data, along with our findings, should encourage clinicians and administrators to evaluate drug cost reduction methods appropriate for their patient population.

The limitations associated with this report are those inherent to retrospective evaluations. The assessment of kidney function was estimated creatinine clearance, and did not include an assessment of acute kidney injury. As we have mentioned previously, the impact of kidney function appears to have significant affects on the efficacy of diuretic therapy, and studying the use of diuretic therapy in this setting should be a future goal. As we only reviewed the use of intravenous chlorothiazide, we cannot comment on the efficacy of other diuretic regimens or fluid management practices that are commonly used for paediatric cardiac intensive care patients. Future directions should include the evaluation of metolazone, acetazolamide, and other diuretics to identify optimal regimens from a clinical efficacy and pharmacoeconomic perspective.

Conclusion

Addition of intravenous chlorothiazide to furosemide therapy in paediatric cardiac intensive care patients did not consistently result in increased urine output. Appropriate patient selection for maximal results of sequential nephron blockade is necessary.

Acknowledgements

None.

Financial Support

This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Baylor College of Medicine and Affiliated Institutions Institutional Review Board.

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