The Effects of Furosemide on Oxygenation in Mechanically Ventilated Children with Bronchiolitis

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Abstract

Fluid balance management, including diuretic administration, may influence outcomes among mechanically ventilated children. We retrospectively compared oxygenation saturation index (OSI) before and after the initial furosemide bolus among 65 mechanically ventilated children. Furosemide was not associated with a significant change in median OSI (6.25 [interquartile range: 5.01–7.92] vs. 6.06 [4.73–7.54], $p = 0.48$), but was associated with expected changes in fluid balance and urine output. Secondary analysis suggested more favorable effects of furosemide in children with worse baseline OSI. The reported common use of furosemide by pediatric intensivists obligates further study to better establish its efficacy, or lack thereof, in mechanically ventilated children.

Keywords
- bronchiolitis
- mechanical ventilation
- diuretics

Introduction

In adults with the acute respiratory distress syndrome (ARDS), a conservative fluid strategy is associated with improved oxygenation and more ventilator-free days.[1] Though similar data from interventional trials are lacking in children, fluid overload in pediatric intensive care unit (PICU) patients is associated with worsened oxygenation and unfavorable outcomes, including increased mortality and longer PICU length of stay.[2] The current Pediatric Acute Lung Injury Consensus Conference (PALICC) guidelines for pediatric ARDS (pARDS) recommend "goal-directed fluid therapy" that avoids a positive fluid balance.[3] Those guidelines also called for further research pertaining to fluid management strategies in pARDS.

Diuretics such as furosemide may be used as part of a conservative fluid management strategy and may directly improve oxygenation by reduction of pulmonary edema and by vasodilation of pulmonary capillaries to improve ventilation–perfusion matching.[1,4] In animal models of ARDS, these effects have been observed approximately 4 hours after intravenous administration of furosemide.[5,6] In hypoproteinemic adults with ARDS, furosemide administration in conjunction with albumin is associated with transient improvement in PaO_2/FiO_2.[7] However, the physiologic effects of furosemide on oxygenation in children receiving mechanical ventilation (MV) have not been thoroughly described.

Bronchiolitis, a lower respiratory tract infection often caused by respiratory syncytial virus (RSV), is a common indication for MV in children admitted to the pediatric intensive care unit.[8] Fluid overload has been associated with unfavorable outcomes among children with bronchiolitis on MV.[9] Furosemide has been proposed to have beneficial effects in children with bronchiolitis, and some clinicians

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prescribe it to children with bronchiolitis receiving MV.[10] The aim of this study is to provide insight into the effects of furosemide on lung function during MV in children with bronchiolitis. We hypothesized that oxygenation would improve in the 6 hours following a subject's first bolus of furosemide compared with the 6 hours preceding the bolus.

Methods

With IRB approval, we retrospectively collected data from the electronic medical record on children meeting the following inclusion criteria: (1) admission to our tertiary-level PICU between January 2012 and April 2016, (2) age less than 2 years, (3) primary diagnosis of bronchiolitis, and (4) receipt of at least one intravenous bolus dose of furosemide while receiving invasive MV. Children who received a continuous furosemide infusion as their initial diuretic were excluded. Children with a tracheostomy were also excluded, as were children who did not have sufficient data to calculate the measures of oxygenation. We extracted data on viral etiology, demographics, and pediatric index of mortality-2 (PIM-2) score on all patients. Comorbid conditions were also reported for all patients and included prior surgery or cardiac catheterization, gestational age <37 weeks, chromosomal abnormalities, developmental delay, cerebral palsy, or any disease requiring home medications other than vitamins or antibiotics. All of the children in our study received pressure-regulated volume control as their ventilation strategy, which is the standard of care at our institution.

Vital signs, oxygenation index (OI; calculated as mean airway pressure $\times$ FiO2/PaO_2), urine output, and fluid balance (calculated as [total fluid administered − total fluid output]/weight) were measured for the 6 hours before and the 6 hours after each patient's initial bolus of furosemide. Subsequent doses of furosemide were not evaluated. Patients were evaluated for acute kidney injury (AKI) during the 24 hours preceding the furosemide bolus using the previously described modified RIFLE criteria which uses the Schwartz equation for calculation of creatinine clearance.[11] For patients who did not have sufficient data to calculate OI (e.g., no arterial blood gas measurements), we calculated the oxygen saturation index (OSI; calculated as mean airway pressure $\times$ FiO2/SpO_2) if SpO2 was 81 to 97%.[12] The pARDS criteria outlined by the PALICC guidelines were employed to determine which patients met criteria for pARDS at the time of their furosemide bolus.[3] For variables that were measured (e.g., heart rate) or calculated (e.g., OSI) more than once during each 6-hour epoch, the mean values for the 6-hour period were used in the analysis.

Values from the 6 hours before the administration of furosemide were compared with the values from the 6 hours after administration using the Wilcoxon signed-rank test. Arterial blood gas measurement was uncommon, so OSI was used preferentially when both OI and OSI were available. If only OI was available, it was converted to OSI ($OSI = 2.76 + 0.547 \times OI$) as previously described.[13] Correlations between the change in OSI (calculated as OSI after furosemide − OSI before furosemide) and several other variables (the dose of furosemide, the duration of MV before the first bolus of furosemide, subject age, and the pre-furosemide OSI) were individually evaluated using Spearman's correlation (ρ). Wilcoxon rank sum and Kruskal–Wallis test by ranks were used to compare the change in OSI between groups of patients that were stratified by viral etiology, pARDS classification, furosemide dose, and pre-furosemide oxygenation status. The latter two variables were analyzed by comparing patients with values greater than the median and those with values less than the median. Data shown as median (interquartile range) or n (%), and $p < 0.05$ determined statistical significance. All data analysis was completed using SigmaPlot v12.5 (San Jose, California, United States).

Results

Our cohort consisted of 65 patients (►**Table 1**). The median age of the subjects was 2 (1–6) months and 70.8% had a positive RSV test. About half (50.8%) had no comorbid conditions, and the most common comorbidity was gestational age <37 weeks (32.3%). The vast majority of patients did not have an AKI (83.1%) and the majority of patients met criteria for pARDS at the time of furosemide administration (46.2% mild and 27.7% moderate/severe).

As shown in ►**Fig. 1**, there was no significant difference in OSI in the 6 hours before and the 6 hours after the administration of furosemide (6.25 [5.01–7.92] vs. 6.06 [4.73–7.54], $p = 0.48$). There were significant differences in fluid balance (19 [8.87–26.01] vs. −5.42 [−17.51 to 4.41] mL/kg, $p < 0.01$) and urine output (10.62 [4.29–16.13] vs. 31.26 [20.46–43.56] mL/kg, $p < 0.01$) between the two 6-hour periods. There were no significant changes between time periods in heart rate, systolic blood pressure, or diastolic blood pressure (►**Table 2**). Of the correlation analyses, only the pre-furosemide OSI (►**Table 3**) was found to correlate significantly with the change in OSI ($\rho = -0.29$, $p = 0.02$).

In our secondary analyses, children stratified by viral etiology (RSV positive vs. RSV negative), furosemide dose ($\leq$0.5 vs. $>$0.5 mg/kg), median pre-furosemide duration of MV, and median PIM-2 score had no differences in the change in OSI (►**Table 4**). When the cohort was stratified by the median pre-furosemide OSI ($\leq$6.25 vs. $>$6.25), children with a higher initial OSI had a significantly greater improvement in oxygenation after a furosemide bolus compared with those children with a lower initial OSI (−0.30 [−1.06 to 0.44] vs. 0.00 [−0.15 to 0.43], $p = 0.04$). However, when patients were stratified by severity of pARDS, there was no significant difference in the change in OSI between patients who were at risk for pARDS, those with mild pARDS, and those with moderate or severe pARDS (0.02 [−0.14 to 0.51] vs. 0.04 [−0.46 to 0.44] vs. −0.34 [−1.47 to 0.42], $p = 0.123$).

Discussion

In this retrospective study of 65 patients with bronchiolitis on MV, we observed that the initial bolus of furosemide was not associated with a significant improvement in oxygenation, despite the expected changes in urine output and fluid balance. These results do not support the idea that

Table 1 Demographics and clinical characteristics

Clinical characteristic	$n = 65$
Age (mo)	2 (1–6)
Female (%)	32 (49.2%)
Race (%)	
Caucasian	30 (46.1%)
African American	28 (43.1%)
Other	7 (10.8%)
PIM2 ROM score	0.22 (0.18–0.71)
Comorbid conditions (%)	
No comorbidities	33 (50.8%)
Prior surgery/cardiac catheterization	2 (3.1%)
Gestational age < 37 wk	21 (32.3%)
Chromosomal abnormalities	2 (3.1%)
Developmental delay	1 (1.5%)
Home medications other than vitamins or antibiotics	16 (24.6%)
Respiratory syncytial virus status (%)	
Yes	46 (70.8%)
No	19 (29.2%)
PICU length of stay (d)	12 (9.5–15)
Duration of MV (d)	7.96 (5.65–10.72)
Pre-furosemide MV (d)	1.83 (1.12–2.91)
Pre-furosemide OSI	6.25 (5.01–7.92)
Acute kidney injury (%)	
No	54 (83.1%)
At risk	11 (16.9%)
pARDS criteria (%)	
At risk	17 (26.2%)
Mild	30 (46.2%)
Moderate/Severe	18 (27.7%)

Abbreviations: MV, mechanical ventilation; OSI, oxygen saturation index; pARDS, pediatric acute respiratory distress syndrome; PICU, pediatric intensive care unit; PIM2 ROM, pediatric index of mortality 2 risk of mortality.
Note: Values are reported as *n* (%) or median (interquartile range).

furosemide has acute benefits on oxygenation in children with bronchiolitis on MV. However, our secondary analyses suggest that children with more severe lung disease may have had a more favorable response to furosemide. Coupled with the limitations inherent in a retrospective observational investigation, these results suggest the need for further study of the effects of furosemide in children on MV, especially those with more severe hypoxemic respiratory failure.

In a recent survey of pediatric intensivists, more than 80% of respondents reported that they prescribe furosemide to children on MV if aiming for a negative fluid balance.[14] Despite the apparent pervasiveness of this practice, there are surprisingly scant published data on the physiologic effects of furosemide in children undergoing MV. Initiation of a continuous infusion of furosemide was associated with improved oxygenation, as measured by PaO_2/FiO_2 ratio, in children with dengue fever who were described as having ARDS.[15] However, none of those 46 children received invasive MV and the second assessment of oxygenation occurred 48 hours following initiation of furosemide, limiting comparability to our data. It is possible that we may have observed improved oxygenation had we evaluated later time points, but prolonging the sampling interval would have conferred an increased risk of confounding variables, including the natural history of critical bronchiolitis in which the vast majority of subjects improve over time.

Our results more closely align with a recent interventional trial in children presenting to an emergency department with bronchiolitis.[10] In that randomized controlled trial of 46 children, a single dose of furosemide did not improve oxygenation or clinical outcomes. Though the study may have been underpowered, those data and ours suggest that furosemide may not acutely improve oxygenation in children with bronchiolitis. This may be due to the multifactorial etiology of respiratory embarrassment in children with bronchiolitis, in which multiple pathways unlikely to respond to furosemide may contribute, such as airway obstruction from mucus and sloughed epithelium, inflammation, and bronchospasm.[16] It is also possible that we did not observe improved oxygenation due to limitations inherent in our methods. Furosemide prescription was not standardized, and so it may have been prescribed to children in whom oxygenation was progressively worsening. In such an instance, the lack of continued worsening in oxygenation could be interpreted as showing that furosemide actually had a beneficial effect. Only a prospective randomized trial can truly determine if furosemide has salutary effects in children with bronchiolitis on MV.

While we believe this to be the most comprehensive description of furosemide administration in children with bronchiolitis on MV to date, there are several additional limitations to consider in our study. First, our retrospective study design makes our data susceptible to variations in EMR charting and recording. However, since our patients were in the ICU, they all had hourly vitals and oxygen saturations which ensured that multiple data points could be evaluated for each epoch. Second, we did not include a control group, choosing instead to compare two epochs for the same patient. Due to heterogeneity in the dosage and timing of the initial furosemide bolus, choosing appropriate times at which OSI should be measured in control patients is not feasible. Therefore, we cannot compare "no therapy" to a furosemide bolus in its effect on oxygenation. However, our results do indicate that providers should not assume an acute physiologic benefit of furosemide boluses in children on MV without further studies. Future prospective studies should consider using a protocol to administer furosemide to enable comparisons to nontreated control patients. Third, our sample size may have been underpowered to detect improvements in oxygenation after furosemide administration. Without a prospective trial with an adequately large sample

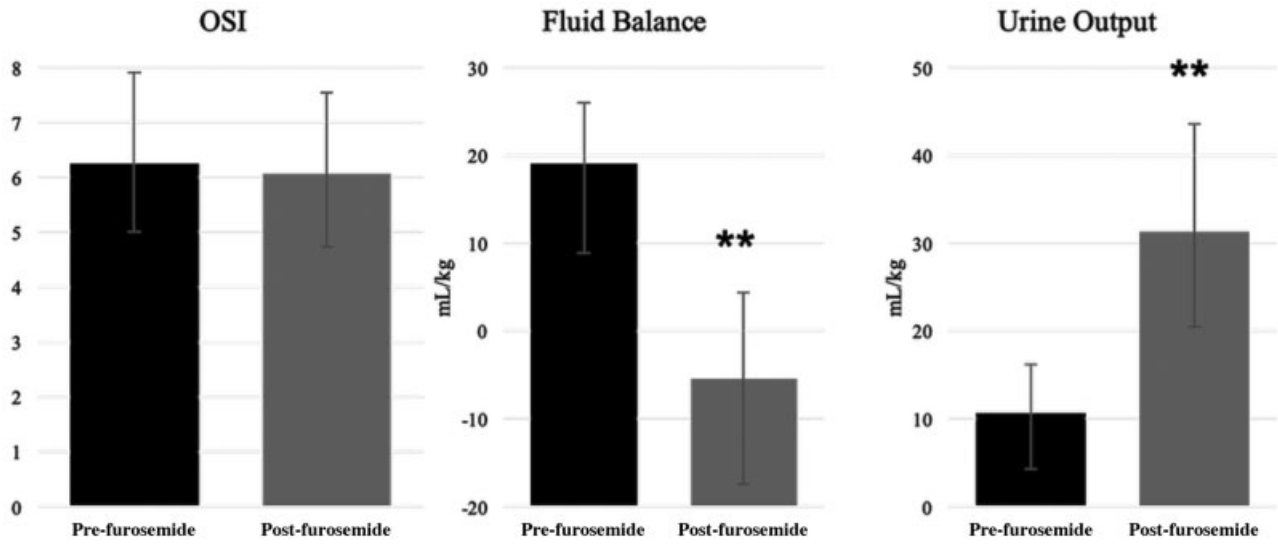

Fig. 1 Measures of oxygenation and fluid balance before and after furosemide. Bars represent median values. Error bars represent interquartile ranges. OSI, oxygen saturation index. ** indicates a result that is significantly different from its corresponding pre-furosemide value as calculated by Wilcoxon signed-rank.

Table 2 Vital signs and ventilator settings before and after the initial dose of furosemide

Outcome	Pre-furosemide ($n = 65$)	Post-furosemide ($n = 65$)	*p*-Value
Heart rate (bpm)	145.2 (129.1–158.5)	145.2 (130.8–163.2)	0.43
Blood pressure (mm Hg)			
Systolic	91.0 (84.4–101.4)	91.0 (83.8–99)	0.56
Diastolic	47.2 (40.7–51.8)	46.8 (41.3–54.5)	0.81
Tidal volume (mL/kg)	7.0 (6.2–7.5)	7.0 (6.3–7.4)	0.58
PEEP (mm Hg)	7.0 (6.0–8.0)	7.0 (6.0–8.0)	0.43
PIP (mm Hg)	27.0 (22.3–30.4)	25.5 (22.5–28.8)	0.08

Abbreviations: bpm, beats per minute; mm Hg, millimeters of mercury; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.
Note: Median values are reported. Ranges in parentheses indicate the interquartile range.

Table 3 Variables associated with the change in oxygenation

Independent variable	ρ (Change in OSI)	*p*-Value
Age (mo)	−0.15	0.24
Pre-furosemide OSI	−0.29	0.02
Pre-furosemide duration of mechanical ventilation	0.07	0.56
Pre-furosemide fluid balance (mL/kg)	0.02	0.86
Post-furosemide fluid balance (mL/kg)	0.15	0.23
Post-furosemide urine output (mL/kg)	−0.13	0.31
Furosemide dose (mg/kg)	0.09	0.48

Abbreviation: OSI, oxygen saturation index.
Note: Spearman's correlation coefficient (ρ) is shown.

size, we cannot conclusively say that furosemide has no acute benefit on oxygenation in critically ill children. However, our cohort is still the largest to date in a study of furosemide therapy in critically ill children on MV. Moreover, our analyses were able to detect some effects of furosemide, such as the expected changes in fluid balance and urine output. Fourth, we only studied children with bronchiolitis, and children receiving MV for other indications may have different responses to furosemide administration. Additionally, furosemide is not listed as a conventional or nonconventional therapy for acute bronchiolitis in recent expert guidelines.[17] However, the majority of patients in our study met criteria for pARDS, in which diuretics have been used as therapy as reported by pediatric intensivists.[14] Additionally, children with bronchiolitis tend to have fewer comorbidities and may be a more homogenous population, which decreases the likelihood of other confounding variables affecting our results. Fifth, as stated before, we may have observed improved oxygenation past 6 hours of furosemide administration. However, prolonging the sampling interval would increase the risk of confounding intervals, including the natural history of bronchiolitis. Lastly, our cohort mainly consisted of patients who had fairly modest hypoxemia and thus some patients had to be excluded because their

Table 4 Changes in oxygenation and lung compliance in subgroups

Strata	Change in OSI	*p*-Value
RSV status		
Positive ($n = 46$)	−0.09 (−0.65 to 0.26)	0.18
Negative ($n = 19$)	0.02 (−0.38 to 0.73)	
Furosemide dose (mg/kg)		
≤ 0.5 ($n = 31$)	−0.01 (−0.79 to 0.22)	0.60
> 0.5 ($n = 34$)	−0.15 (−0.42 to 0.63)	
Pre-furosemide OSI		
$\leq$ Median ($n = 33$)	0.00 (−0.15 to 0.43)	0.04
$>$ Median ($n = 32$)	−0.30 (−1.06 to 0.44)	
Pre-furosemide OSI by pARDS classification		
At risk: OSI < 5 ($n = 16$)	0.02 (−0.14 to 0.51)	0.123
Mild: $5 \leq$ OSI < 7.5 ($n = 31$)	−0.04 (−0.46 to 0.44)	
Moderate/Severe: OSI ≥ 7.5 ($n = 18$)	−0.34 (−1.47 to 0.42)	
Pre-furosemide duration of MV		
$\leq$ Median ($n = 33$)	0.00 (−0.15 to 0.43)	0.44
$>$ Median ($n = 32$)	−0.30 (−1.06 to 0.44)	
PIM2 ROM score		
$\leq$ Median ($n = 33$)	0.00 (−0.15 to 0.43)	0.80
$>$ Median ($n = 32$)	−0.30 (−1.06 to 0.44)	

Abbreviations: MV, mechanical ventilation; OSI, oxygen saturation index; pARDS, pediatric acute respiratory distress syndrome; PIM-2, pediatric index of mortality-2; ROM, risk of mortality; RSV, respiratory syncytial virus.
Note: Median values are reported. Values in parentheses indicate the interquartile range. Children with unknown RSV status were considered "negative."

saturations rose above 98% and thus could not be used to calculate OSI. Future prospective studies should focus on patients with more severe hypoxemia to better determine if furosemide has different effects on oxygenation in those patients.

Conclusion

In this study, we did not observe an association between furosemide and an acute improvement in oxygenation in children with bronchiolitis receiving invasive MV. The reported common use of furosemide by pediatric intensivists obligates further study to better establish its efficacy, or lack thereof, in critically ill children. Additional observational studies in children with other indications for MV could be informative, particularly in patients with more severe hypoxemia, but prospective randomized trials are needed to definitively evaluate if furosemide improves gas exchange in children with acute respiratory failure.

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Conflict of Interest
A.T.R. reports personal fees from Vapotherm, Inc, and royalties from Elsevier, outside the submitted work.

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