Effect of High-Dose Continuous Albuterol Nebulization on Clinical Variables in Children With Status Asthmaticus

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Objectives: Continuous albuterol nebulization is generally administered at 2.5–20 mg/hr at most centers. We examined the effect of high-dose (75 or 150 mg/hr) albuterol on clinical variables in children with status asthmaticus.

Design: Retrospective analysis of inpatient medical records and prospectively collected computerized PICU respiratory therapy database.

Setting: Twenty-five-bed multidisciplinary PICU in a tertiary care children's hospital.

Patients: Children admitted to the PICU between January 2006 and December 2007 with status asthmaticus receiving high-dose continuous albuterol nebulization. (Those with cerebral palsy, cardiac pathology, and ventilator dependence were excluded.)

Interventions: Chart review for PICU length of stay, albuterol dose, duration of nebulization, occurrence of chest pain, vomiting, tremors, hypokalemia (serum potassium < 3.0 mEq/L), and cardiac arrhythmia. Maximal heart rate, lowest diastolic blood pressure, and mean arterial pressure were compared to the variables at initiation of therapy and at hospital discharge.

Measurements and Main Results: Forty-two patients (22 boys and 20 girls) received high-dose continuous albuterol nebulization. Twenty-three received 75 mg/hr and 19 received 150 mg/hr (3.7 mg/kg/hr [interquartile range, 2.4–5.8 mg/kg/hr]) for a duration of 22.3 hours (interquartile range, 6.6–31.7 hr). Heart rate increased and diastolic blood pressure and mean arterial pressure were significantly lower during nebulization compared to initiation of therapy or at hospital discharge ($p < 0.05$). No patient required fluid resuscitation or inotropic support, and one had self-limited premature ventricular contractions. Hypokalemia occurred in five of 33 patients who had serum electrolytes measured but did not require supplementation. One patient required endotracheal intubation after initiation of nebulization, and seven patients (16.7%) received noninvasive ventilation. PICU length of stay was 2.3 ± 1.7 days; there were no deaths.

Conclusions: High-dose continuous albuterol nebulization is associated with a low rate of subsequent mechanical ventilation and fairly short PICU length of stay without significant toxicity. Prospective studies comparing conventional and high-dose albuterol nebulization are needed to determine the optimum dose providing maximum efficacy with the least adverse effects. (*Pediatr Crit Care Med* 2014; XX:00–00)

Key Words: continuous albuterol; efficacy; pediatric intensive care; safety; side effects; status asthmaticus

Asthma is a chronic illness with several major consequences, including school absence, decreased quality of life, emergency department (ED) visits, hospitalizations, and deaths. Although the quality of outpatient care for patients with asthma has steadily improved, severity of acute exacerbations and the mortality related to status asthmaticus remain unchanged (1). Consequently, critical care physicians encounter patients with status asthmaticus who have failed initial urgent medical treatment and are admitted to the PICU for intensive therapy and monitoring. These patients frequently have impending or actual respiratory failure. According to national and international pediatric asthma guidelines, β-adrenergic receptor agonists and corticosteroids are the mainstay of therapy for status asthmaticus (2, 3). Although β-agonists are widely used during asthma exacerbations, there are many variations in terms of frequency, dosing, and route of administration (4–6).

Albuterol is a β-agonist approved for nebulized therapy in children and is commonly used for treating asthma exacerbations in hospitals across the United States. Continuous nebulized albuterol delivered at 5–15 mg/hr has been shown to be

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superior to intermittent nebulization in children admitted to the ICU for status asthmaticus (7). Even though continuous nebulization treatment is beneficial and widely used, the dose of albuterol remains variable in the absence of evidence directly comparing different doses. Most published studies describe fairly low doses for continuous albuterol nebulization (4–10 mg/hr). Among various expert opinions, the doses of albuterol recommended vary from 40 to 80 mg/hr, although dosing up to 150 mg/hr has been reported anecdotally (8–10). The potential toxicity of higher albuterol doses has not been previously examined systematically.

At Loma Linda University Children's Hospital, continuous high-dose albuterol nebulization can be used to treat status asthmaticus in children. In children with significant respiratory distress, we initiate a dose of either 75 mg/hr (half diluted 5 mg/mL) albuterol solution delivered via a HEART nebulizer (High-output Extended Aerosol Respiratory Therapy, Westmed, Tucson, AZ, at 10 L/min oxygen flow) or undiluted albuterol at 150 mg/hr delivered in a similar manner based on the severity of the patients' presentation. Because the albuterol dose we use is considerably higher than that generally described in the published literature, the objective of this study is to examine the efficacy and safety of high-dose continuous albuterol in children admitted to our PICU with status asthmaticus.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board at Loma Linda University. Eligible subjects included all children admitted with status asthmaticus to our 25-bed multidisciplinary PICU over a 2-year period from January 2006 through December 2007. We included patients referred from outlying hospitals and EDs transported to our PICU by a dedicated PICU transport team, admissions originating from our own ED as well as patients transferred into the PICU from our step-down unit or pediatric ward. We screened all patients with a diagnosis of status asthmaticus and studied those who received continuous albuterol nebulization as a part of their PICU therapy in greater detail. In order to analyze a relatively homogenous population, we excluded patients with a known history of mental retardation with cerebral palsy, cardiac pathology, and tracheostomy or ventilator dependence.

Data were collected from a prospectively collected computerized database maintained by the PICU respiratory therapists and review of patient records including nursing flow sheets, physician notes, and physician orders. The length of PICU stay, the total hospital stay, and the dose and duration of continuous albuterol therapy were recorded. Variables associated with known adverse effects of β-agonists before and after treatment were also collected and included the following: chest pain; vomiting; tremor; heart rate (HR); diastolic blood pressure (DBP); mean arterial pressure (MAP); hypokalemia (defined as serum potassium < 3.0 mEq/L within 24 hr of initiation of continuous albuterol); and cardiac arrhythmia. Patient symptoms, such as vomiting, were noted as present or absent if a direct affirmative or negative recording was made in the nursing or physician notes (e.g., "patient vomited" vs "no emesis during this shift"). If there was no mention either way, we noted this as not applicable. As all patients had already received some β-agonist therapy prior to PICU admission, in order to estimate the effect of high-dose albuterol nebulization on hemodynamic variables, we recorded HR, MAP, and DBP at initiation, during continuous albuterol therapy, as well as at the time of discharge from the hospital. To enable an assessment of the maximal adverse effects resulting from high-dose continuous albuterol therapy, the discharge hemodynamic variables were treated as the patient's true "baseline" for statistical analysis. Additional therapeutic modalities used in status asthmaticus, such as terbutaline, magnesium sulfate, aminophylline, heliox, noninvasive ventilation (NIV) or intubation, and mechanical ventilation, were recorded. The assessment of patient severity and management were based on attending physicians' decision.

We used IBM SPSS version 15 (IBM, Chicago, IL) for statistical analysis. Descriptive data were expressed as frequencies (%) or as mean ± SD. A two-tailed Student's *t* test was used for comparisons of continuous variables with normal distribution, and the Mann-Whiney *U* test was used for continuous variables without normal distribution. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of forty-two patients (22 boys and 20 girls) with status asthmaticus satisfying the inclusion and exclusion criteria admitted to our PICU received continuous albuterol during the 2-year period studied. Forty-one patients were admitted specifically for continuous albuterol nebulization, and one patient who was already intubated at admission received continuous albuterol after extubation. Only one of 41 patients (2.4%) required intubation for respiratory failure after continuous albuterol nebulization was started, although seven patients (16.7%) received NIV (bilevel positive airway pressure). Overall, 23 patients received an initial albuterol dose of 75 mg/hr and 19 received 150 mg/hr. The mean PICU length of stay (LOS) of nonintubated patients was 2.3 ± 1.7 days. There were no deaths. Demographic characteristics, duration of continuous albuterol therapy, and additional treatment for patients who received continuous albuterol nebulization are summarized in **Table 1**.

Selected symptoms, vital signs, and laboratory data collected during continuous albuterol therapy are shown in **Table 2**. Most adverse symptoms that could be ascribed to continuous albuterol during treatment were not affirmatively recorded in the nursing notes. No major cardiac arrhythmia occurred, and only one patient developed premature ventricular contractions (PVCs) that resolved after the cessation of albuterol treatment. Data comparing patients who received 75 mg/hr and 150 mg/hr of albuterol treatment regarding changes in vital signs and requirement of additional treatment are demonstrated in **Tables 3** and **4**, respectively. **Figure 1** shows the changes in mean HR, mean DBP, and mean MAP before and after the treatment. HR significantly increased during high-dose albuterol nebulization when compared with the HR at

TABLE 1. Demographic Characteristics of Study Population

Characteristics	Continuous Albuterol Nebulization ($n = 42$)
Age (yr), median (IQR)	8.0 (2.0–10.0)
Weight (kg), median (IQR)	27.8 (14.8–37.4)
Male gender, *n* (%)	22 (52.4)
Dose of continuous albuterol Rx (mg/kg/hr), median (IQR)	3.7 (2.4–5.8)
Duration of continuous albuterol Rx (hr), median (IQR)	22.3 (6.6–31.7)
Source of admission, *n* (%)	
ED	10 (23.8)
Outside ED	30 (71.4)
Ward or step-down unit	2 (4.8)
Additional treatment, *n* (%)	
Terbutaline	9 (21.4)
Aminophylline	4 (9.5)
Magnesium	13 (30.9)
Heliox	14 (33.3)
Noninvasive ventilation	7 (16.7)
Intubation	2 (4.8)

IQR = interquartile range, ED = emergency department.

TABLE 2. Selected Symptoms, Vital Signs, and Pertinent Laboratory Results During High-Dose Albuterol Nebulization Compared With Initial PICU Admission and Hospital Discharge Time Points

Variables	Continuous Albuterol Nebulization ($n = 42$)
Chest pain, *n* (%)	
Yes	1 (2.4)
No	41 (97.6)
Vomiting, *n* (%)	
No	35 (83.3)
Yes	3 (7.2)
NA	4 (9.5)
Tremor, *n* (%)	
Yes	1 (2.4)
NA	41 (97.6)
Increment in HR vs initial %	12.6 ± 10.8
Increment in HR from hospital discharge, %	87.9 ± 32.1
Decrement in DBP vs initial, %	43.9 ± 15.2
Decrement in DBP vs hospital discharge, %	53.5 ± 12.0
Decrement in MAP vs initial, %	30.7 ± 11.7
Decrement in MAP vs hospital discharge, %	36.9 ± 11.9
Hypokalemia, *n* (%)	5/33 (15.2)
Arrhythmia, *n* (%)	1 (2.4)

NA = not available, HR = heart rate, DBP = diastolic blood pressure, MAP = mean arterial pressure.

the initiation of therapy or at hospital discharge ($p < 0.05$). DBP and MAP were significantly lower during therapy when compared with either initial or hospital discharge time points ($p < 0.05$). These changes were not clinically significant, and none of the patients required fluid resuscitation or inotropic support. Hypokalemia occurred in five of 33 patients (15.2%) who had serum electrolyte measured while on continuous albuterol treatment.

DISCUSSION

We examined the effect of nebulized high-dose (75 or 150 mg/hr) albuterol for status asthmaticus in children admitted to our PICU. Hemodynamic changes (tachycardia, lower MAP, and lower DBP) were the major side effects observed. These changes were not clinically significant as none of the affected patients required fluid resuscitation or vasoactive medications. Mild hypokalemia was seen in a small number of patients (15.2%). High-dose albuterol also appeared to be fairly efficacious, with a mean PICU LOS of 2.3 ± 1.7 days in this cohort.

Continuous albuterol nebulization for the management of status asthmaticus is well accepted. A systematic Cochrane Airway Group review recommended β-agonist therapy by inhalation rather than parenteral route (4). Continuous nebulization may be superior to intermittent nebulization in improving forced expiratory volume in 1 second and peak expiratory flow rate in patients presenting to the ED with status asthmaticus (5, 6). The albuterol doses used in our study were either 75 or 150 mg/hr. These are 7.5–30 times higher than the 5–10 mg/hr used in the randomized controlled trial by Papo et al (7), enabling us to examine adverse effects at the maximal dosing capabilities of the currently available HEART nebulization device.

We found a significant increase in HR and decrease in DBP and MAP on continuous albuterol compared with before treatment or at hospital discharge. This is in contrast to the findings of Papo et al (7), that is, no significant change of HR, systolic blood pressure, electrocardiogram (ECG), or creatine kinase MB (CK-MB) level from baseline with the continuous albuterol dose of 0.3 mg/kg/hr (range, 5–10 mg/hr) for a period of 12 hours. However, we did not find any hemodynamic changes between 75 mg/hr and 150 mg/hr albuterol doses. It is reassuring that no patients required fluid resuscitation or inotropic agents for hemodynamic support.

TABLE 3. Selected Vital Signs During High-Dose Albuterol Nebulization (75 mg/hr vs 150 mg/hr)

Variables	Continuous Albuterol Nebulization ($n = 42$)		p
	75 mg/hr ($n = 31$)	150 mg/hr ($n = 11$)	
Increment in HR vs initial (%), mean ± SD	12.2 ± 11.0	13.7 ± 10.4	NS
Increment in HR from hospital discharge (%), mean ± SD	88.3 ± 32.5	87.2 ± 32.3	NS
Decrement in DBP vs initial (%), mean ± SD	44.2 ± 16.1	42.9 ± 12.6	NS
Decrement in DBP vs hospital discharge (%), mean ± SD	54.6 ± 11.3	49.9 ± 14.1	NS
Decrement in MAP vs initial (%), mean ± SD	31.1 ± 11.7	29.5 ± 12.1	NS
Decrement in MAP vs hospital discharge (%), mean ± SD	38.1 ± 11.1	33.2 ± 13.8	NS

HR = heart rate, NS = nonsignificant, DBP = diastolic blood pressure, MAP = mean arterial pressure.

Our findings regarding adverse effect of continuous albuterol therapy are consistent with several prospective studies in children. Katz et al (11) reported elevated CK-MB in two of 19 patients during 3.4 ± 2.2 mg/kg/hr of albuterol therapy for 12–72 hours. However, CK-MB returned to normal, and there was no evidence of myocardial ischemia. There was no chest pain, cardiac arrhythmias, or HR changes reported. Transient CK-MB elevation without myocardial ischemia has also been documented by Craig et al (12) while using 10 mg/hr albuterol for 12 hours. No difference in HR at the beginning versus the end of treatment was noted in this study. Although none of our patients had chest pain or ECG evidence of ischemia, we did not measure CK-MB values. A prospective study, including CK-MB or troponin measurements, would be needed to better understand the effects of high-dose albuterol on myocardial ischemia. Montgomery and Eid (13) found no hypokalemia; however,

TABLE 4. Requirement of Additional Treatment During High-Dose Albuterol Nebulization (75 mg/hr vs 150 mg/hr)

	Terbutaline, n (%)			
Factor $n = 42$	No	Yes	OR (95% CI)	p
CAN 75 mg/hr	27 (87.1)	4 (12.9)	1	
CAN 150 mg/hr	6 (54.5)	5 (45.5)	5.6 (1.1–27.4)	0.033
Factor $n = 42$	**Aminophylline, n (%)**		**OR (95% CI)**	**p**
	No	**Yes**		
CAN 75 mg/hr	28 (90.3)	3 (9.7)	1	
CAN 150 mg/hr	10 (90.9)	1 (9.1)	0.9 (0.1–10.0)	NS
	Magnesium, n (%)			
Factor $n = 42$	No	Yes	OR (95% CI)	p
CAN 75 mg/hr	22 (71.0)	9 (29.0)	1	
CAN 150 mg/hr	7 (63.6)	4 (36.4)	1.4 (0.3–5.9)	NS
	Heliox, n (%)			
Factor $n = 42$	No	Yes	OR (95% CI)	p
CAN 75 mg/hr	19 (61.3)	12 (38.7)	1	
CAN 150 mg/hr	8 (72.7)	3 (27.3)	0.6 (0.1–2.7)	NS
	Noninvasive ventilation, n (%)			
Factor $n = 42$	No	Yes	OR (95% CI)	p
CAN 75 mg/hr	28 (90.3)	3 (9.7)	1	
CAN 150 mg/hr	7 (63.6)	4 (36.4)	5.3 (0.9–29.5)	0.05

OR = odds ratio, CAN = continuous albuterol nebulization, NS = nonsignificant.

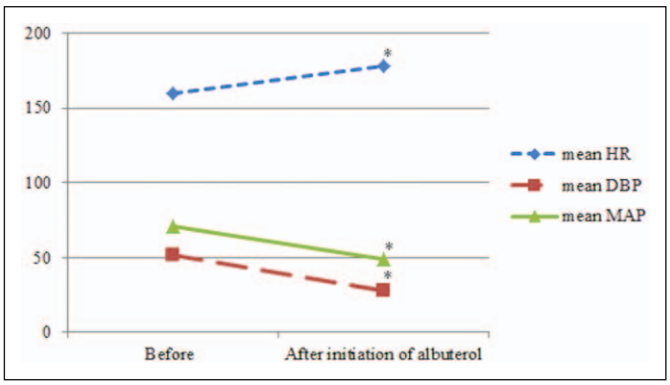

Figure 1. Maximal hemodynamic effects of continuous albuterol nebulization. *$p < 0.05$ compared to before treatment and hospital discharge. Heart rate (HR, beats/min), diastolic blood pressure (DBP, mm Hg), and mean arterial pressure (MAP, mm Hg) before (before continuous albuterol treatment) and after initiation of albuterol.

three of seven patients developed cardiac arrhythmias with albuterol given at 0.05 mg/kg/hr for 26 hours. One of our patients experienced cardiac arrhythmia (PVCs), and hypokalemia was documented in 15.2%. Therefore, the high dose of albuterol appears to be relatively safe, with minor cardiac arrhythmia in one child and hypokalemia in just a small number of patients.

It is interesting that the higher albuterol doses we used did not lead to more serious side effects. Lung deposition of aerosol is influenced by two main factors: particle size and velocity. Larger and higher velocity particles may get deposited on the upper airway mucosa and not reach the lower airways for systemic absorption. The particle size generated by HEART nebulizer at the flow rate of 10–15 L/min is around 2 μm (14). Coleman et al (15) reported more upper airway impaction and loss of aerosol in the inspiratory tubing at higher gas flows (5 vs 6.5 L/min and 5 vs 8 L/min) likely due to increased turbulence from the small diameter tubing, smaller pediatric airway, or ventilator circuit. Thus, the driving gas flow of 10–15 L/min set on the HEART nebulizer may have reduced the lung deposition of albuterol particles. Other studies also suggest that higher gas flow can decrease the particle size of aerosol (16). Although smaller particles (1.5 μm) bypass the upper airways and filter mechanism with less oropharyngeal deposition loss, these small particles were also exhaled the most (17). The particle size generated by the HEART nebulizer is relatively small. Hence, even with higher albuterol doses, the generation of smaller particles in our study could have led to decreased lung deposition. Additionally, high inspiratory flow rate (fast inhalation, > 60 L/min in patients with significant respiratory distress) increases oropharyngeal deposition compared to slower flow rates (30–60 L/min) (18). Together, these data suggest that a significant portion of any aerosol therapy is deposited in the inspiratory tubing circuit, oropharynx or upper airway, and more is wasted in the exhaled breath. This predicts a much smaller amount of drug delivered for absorption despite a high albuterol dose, which may also explain the lack of increased side effects in our patients. Which of these mechanisms predominate and explain the relatively low prevalence and magnitude of side effects observed in our patients is impossible to clarify with our study design.

Despite uncertainty about the amount of albuterol delivered to the lungs, our data suggest some benefits judging by our low intubation rate compared to previous reports. In our study, intubation was required in only one of 41 patients (2.4%) admitted for continuous albuterol nebulization treatment, whereas the study by Papo et al (7) demonstrated that intubation was needed in two of nine patients (22%) who received continuous albuterol nebulization. A short PICU LOS of 2.3 ± 1.7 days is also a measure of the effectiveness of high-dose continuous albuterol. In a study involving 271 children with uncomplicated status asthmaticus, Carroll and Zucker (19) reported PICU LOS as 2.7 ± 2.1 days. Most patients in their study were nonintubated, similar to our findings. We recognize that caution should be exercised when comparing the LOS or rates of intubation between studies. These can be influenced by many different factors such as disease severity, pharmacologic management, and clinical decisions made by treating staff. Still, our findings raise the question whether high-dose albuterol could be associated with lower LOS and intubation rates, without increasing toxicity. Although conclusions about cause and effect cannot be drawn due to our retrospective study design, even a slight reduction in LOS or intubation could be significant in a busy PICU and should be studied prospectively.

A recent Collaborative Pediatric Critical Care Research Network study in eight tertiary care PICUs focused on patients with near-fatal asthma. They reported variability in albuterol use across the study centers. Continuous albuterol was used in 35–67% of patients preintubation and in 23–58% postextubation. Seventy percent of intubations were performed in the referring hospital. No details of albuterol dosing in these intubated patients were noted, and nonintubated patients needing ICU admission were not discussed. One of the recommendations from this study was that since little information exists on the prevalence of β2-agonist toxicity by IV or inhaled route in children, further investigation would be of value (20). Our novel findings regarding the effect of high-dose nebulized albuterol add to the literature regarding this subset of patients with status asthmaticus requiring PICU admission. The low intubation rates in our patients raise the question whether more uniform use of continuous albuterol or the adoption of a higher dosing range may avert intubation.

Our study has several limitations due to its retrospective nature. The choice of 75 or 150 mg/hr albuterol was subjectively made by the attending physician on call based on their assessment of patient severity. Adjuvant therapies including noninvasive or invasive mechanical ventilation were also individualized. We relied on chart review to identify adverse effects related to high-dose albuterol and may have underestimated these events. Addition of adjuvant modalities was not standardized and may have influenced the LOS. Since we examined LOS rather than readiness for transfer from PICU, bed availability could also have influenced the PICU LOS for some patients. In future studies, readiness for PICU discharge or objective clinical respiratory scores or variables might be a better comparative endpoint than LOS. We do not routinely

measure serial blood gases in patients with status asthmaticus and are therefore unable to discern the effects of continuous albuterol on gas exchange. Despite these limitations, our data suggest that high-dose albuterol nebulization is effective and is associated with a short PICU LOS.

CONCLUSIONS

In summary, high-dose (75–150 mg/hr) continuous albuterol nebulization used at our center was associated with a fairly short PICU LOS without clinically adverse effect. This dosage of albuterol use significantly affects HR, DPB, and MAP, but these changes are temporary and did not require corrective treatment. Prospective studies comparing conventional albuterol dosage (typically ranging from 2.5 to 20 mg/hr) to high-dose albuterol (75 to 150 mg/hr) are needed to determine efficacy and safety. Cardiac enzymes and ECG monitoring may be helpful to assess cardiovascular consequences. Our data provide future investigators with information regarding potential albuterol-related side effects to anticipate and enable equipoise for randomized studies comparing various doses since none of the side effects were serious or life-threatening.

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