

BRIEF RESEARCH REPORT

Pediatrics

Nebulized albuterol delivery is associated with decreased skeletal muscle strength in comparison with metered-dose inhaler delivery among children with acute asthma exacerbations

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Abstract

Objective: Albuterol is a β_2 -agonist and causes an intracellular shift of potassium from the interstitium. Whole-body hypokalemia is known to cause skeletal muscle weakness, but whether this occurs as a result of hypokalemia from the intracellular shift during albuterol treatment is unknown. We sought to determine if albuterol total dose or route of administration (nebulization and/or metered-dose inhaler) is associated with skeletal muscle weakness.

Methods: This was a prospective observational study using convenience sampling. Skeletal muscle strength was measured before and after 1 hour of albuterol treatment using a hand-grip dynamometer in participants aged 5–17 years with acute asthma exacerbation in the emergency department. We examined associations of albuterol dose and route of administration with changes in grip strength.

Results: Among 50 participants, 10 received continuous albuterol by nebulizer and 40 received albuterol by metered-dose inhaler. The median (interquartile range) in change of grip was -7.8% (interquartile range, -23.3, +5.1) for those treated with a nebulizer and +2.4% (interquartile range, -5%, +12.7%) for those treated with a metered-dose inhaler ($P = 0.036$ for the difference). In a multiple linear regression model adjusted for the pretreatment Acute Asthma Intensity Research Score and age, participants treated with a nebulizer had a 12.9% decrease in skeletal muscle strength compared with those treated with a metered-dose inhaler.

Conclusion: Higher doses of albuterol administered via nebulization result in decreased skeletal muscle strength in patients with acute asthma; whereas, albuterol administration via metered-dose inhalers showed no effect on skeletal muscle strength.

KEYWORDS

acute asthma exacerbation, albuterol, emergency medicine, hypokalemia, metered-dose inhaler, nebulizer, pediatrics, skeletal muscle strength

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1 | INTRODUCTION

Asthma is the most common chronic childhood disease in the United States with approximately 1 in 12 children aged 0–17 years diagnosed in 2016.¹ This results in >540,000 pediatric acute asthma emergency department (ED) visits per year. A US nationwide analysis in 2010 estimated the yearly state Medicaid costs for pediatric asthma-related ED visits to be >\$272 million.² Even with medical and public health progress, acute asthma exacerbations remain a common and costly cause for pediatric ED visits in the United States.

For many years, albuterol has been a mainstay treatment for asthma exacerbation and has been shown to quickly improve respiratory symptoms and forced expiratory volume in one second (FEV₁) in symptomatic children. Albuterol acts on β_2 adrenergic receptors to relax the bronchial smooth muscle. It also inhibits the release of immediate hypersensitivity mediators from mast cells. Nebulization, continuous or intermittent, and a metered-dose inhaler are the most commonly used administration routes for albuterol treatment. Although dosing recommendations vary, nebulizers are often used to deliver 2.5–15 mg of albuterol over an hour, whereas metered-dose inhalers have been recommended up to maximum dose of 24 puffs in 1 hour (at 90 mcg albuterol per puff) equaling a maximum total dose of 2.16 mg over an hour.³ Some studies have shown metered-dose inhaler albuterol delivery to be non-inferior to nebulized albuterol delivery in the treatment of acute asthma exacerbation.⁴ Both delivery methods appear to be effective in the treatment of children with asthma exacerbations, and optimal dosing appears to depend on symptom severity and responsiveness to treatment.

Although a landmark advancement, albuterol is not without adverse effects. The most common adverse drug reactions experienced by children are tremor and tachycardia; however, electrolyte shifts also can be significant. Albuterol-induced β_2 activation stimulates the Na⁺/K⁺ pump, leading to intracellular transport of potassium and temporary extracellular hypokalemia. Significant hypokalemia has been seen after albuterol administration in patients with acute asthma exacerbation.⁵ One case series of accidental pediatric albuterol overdoses ranging from 1.1–3.7 mg/kg resulted in subsequent hypokalemia of 2.3–2.8 mmol/L.⁶ Even albuterol doses as low as 2.5 mg nebulized over 10 minutes given to healthy adults has been shown to lead to significant serum potassium reduction.⁷ The hypokalemic effect does not appear to be predictable in severity or duration, with some studies showing a continued reduction in serum potassium levels 6 hours after albuterol administration.⁸ Although the albuterol-induced hypokalemia does not appear to lead to dangerous arrhythmias or vital sign disturbances in otherwise healthy pediatric patients, it is unknown if it may affect other organ systems.

1.1 | Importance

Studies have shown that significant muscle weakness occurs at serum potassium levels <2.5 mmol/L but can occur at higher levels if the onset is acute. This can include the respiratory muscles with extremely

The Bottom Line

Albuterol can cause significant hypokalemia and in turn significant muscle weaknesses, including respiratory, in severe cases. In this preliminary study, 50 children aged 5–17 years with acute asthma exacerbation underwent standard dynamometer assessment before and after albuterol treatment. Nebulizer use was associated with a 13% decrease in muscle strength. Metered-dose inhalers or lower doses of albuterol may be beneficial over nebulizers to minimize muscle weakness.

severe cases, leading to respiratory failure.⁹ Although it is known that asthma-related albuterol treatment in children leads to hypokalemia, it is unknown if albuterol treatment may also lead to muscle weakness in this population.

1.2 | Goals of this investigation

Given that albuterol doses administered via nebulizer are much higher than those administered via a metered-dose inhaler, we sought to determine if treatment with nebulized albuterol is associated with decreased skeletal muscle strength when compared with treatment with a metered-dose inhaler.

2 | METHODS

2.1 | Study design and setting

We designed a prospective observational study using convenience sampling to test the hypothesis that treatment with nebulized albuterol is associated with a greater decrease in skeletal muscle strength when compared with treatment with a metered-dose inhaler during the first hour of care for children presenting to the ED with an acute asthma exacerbation. Our institutional review board approved this study.

2.2 | Selection of participants

Inclusion criteria included children aged 5–17 years with a past medical history of primary care provider-diagnosed asthma who presented to the ED with mild, moderate, or severe acute asthma exacerbation and for whom the care team planned to deliver inhaled albuterol treatment. Exclusion criteria included children with muscular dystrophy or current injury or anatomic abnormality of the dominant upper extremity. We recruited a prospective convenience sample of subjects. When investigators were available in the ED, all patients triaged with

TABLE 1 Acute Asthma Intensity Research Score

Component	Component values			
	0	1	2	3
Retractions ^a				
Suprasternal-SCM	No		Yes	
Intercostal	No		Yes	
Subcostal	No		Yes	
Air entry	Normal	Decreased at bases	Widespread decrease	Absent or minimal
Wheezing	Absent	Expiratory	Inspiratory and expiratory	Audible without stethoscope
SpO ₂ (on room air)	≥95%	92%–94%	<92%	
Expiratory phase	Normal	Prolonged	Severely prolonged	
Add component values	()	+()	+()	= (AAIRS score)

Possible score range is 0–16. AAIRS, Acute Asthma Intensity Research Score. Severity levels: mild, 1–6; moderate, 7–11; severe, 12–16.

^aAny visible use of accessory muscle group (yes/no).

respiratory complaints were evaluated for inclusion and exclusion criteria and approached for consent if the criteria were met. We obtained written informed consent from a parent and assent from each participant.

2.3 | Exposures

We recorded participant demographic information and asthma characteristics, including age, sex, race, medications in use, medications received before ED admission, weight, and albuterol treatments applied in the ED. In addition, values for the validated Acute Asthma Intensity Research Score (AAIRS; see Table 1) at the time of ED admission were recorded.^{10–12} The clinical team determined the mode of albuterol administration and was not advised of the grip strength measurement results.

2.4 | Measurements

Skeletal muscle strength was measured using a Lafayette Instrument digital hand dynamometer (model 5030D1), the design of which is also referred to as a Lode dynamometer. A previous study analyzed the accuracy of the hand Lode dynamometer, where it was noted that mean values using the dominant hand were 119 Newtons (N) for ages 7–9 years ($n = 39$; SEM, 12.2) and 175 N for ages 10–12 years.¹³ The accuracy of the Lafayette model 5030D1 over this force range is $\pm 1\%$, or < 2 N, and, thus, was expected to provide similarly accurate measurements for our study.

In accordance with prior investigations of dynamometer accuracy in children, each participant was studied in a sitting position in a chair or sitting up in bed, with the shoulder abducted, the elbow at 90° flexion, and the wrist in the neutral position.¹⁴ Each participant was verbally instructed to make each measurement with the words “Squeeze as hard as you can!” with their dominant hand. Three measurements were made at each time point, and the mean of 3 voluntary

contractions were used as the measure of skeletal muscle strength at that time point. These measurements were taken before treatment with albuterol and then repeated using the same method 1 hour after the initiation of albuterol treatment.

2.5 | Outcomes

The primary outcome measurement was the percentage of change in skeletal muscle strength in the first hour of albuterol treatment in the ED for each participant.

2.6 | Analysis

Planned data analyses included a paired *t* test, or Wilcoxon rank-sum test if non-parametric, to examine the percent differences between skeletal muscle strength before and after 1 hour of treatment. We used multivariable linear regression models to examine adjusted associations between the metered-dose inhaler and nebulized albuterol with change of skeletal muscle strength and included the covariates albuterol dose, age, sex, race, and acute exacerbation severity measured using the AAIRS.

3 | RESULTS

3.1 | Characteristics of study participants

A total of 50 children were enrolled in the study, with asthma and demographic characteristics presented in Table 2. Of these children, 10 received albuterol via continuous nebulization and 40 received albuterol via metered-dose inhalers during treatment in the ED, reflecting our institutional asthma clinical practice guideline that recommends the metered-dose inhaler as the preferred mode of albuterol

TABLE 2 Characteristics of 50 children with acute asthma exacerbations treated with inhaled albuterol

Characteristics	Mode of inhaled albuterol		P value
	Metered-dose inhaler	Nebulized	
n (%)	40 (80)	10 (20)	
Median age, y	9.4 (7.4–12.3)	10.1 (7.9–11.7)	0.68 ^a
Weight, kg	34.5 (27–55.5)	35 (30–52)	0.86 ^a
Sex, male, %	42	30	0.65 ^b
Race, n (%) ^c			
Black	25 (63.5)		
White	14 (35)		
>1 race	1 (2.5)		
Pretreatment AAIRS	4 (2.5–7)	7 (6–8)	0.13 ^a

Values are median (interquartile range) unless otherwise specified. AAIRS, Acute Asthma Intensity Research Score.

^aWilcoxon rank-sum test.

^bChi-square test.

^cParent-designated racial categories.

delivery. There was a trend toward greater pretreatment AAIRS in participants receiving albuterol by nebulizer. All patients were recorded as having perceived good effort at strength measurements according to research personnel collecting data. Of the 10 participants in the nebulizer group, 9 received albuterol within the 4 hours before ED presentation, whereas 32 of the 40 patients in the metered-dose inhaler group received albuterol within the 4 hours before ED arrival.

3.2 | Main results

In the initial hour of treatment, the average albuterol dose delivered was 10 mg to those treated with a nebulizer and 0.72 mg to those treated with a metered-dose inhaler. The median decrease in measured skeletal muscle strength for those undergoing treatment with a nebulizer was -7.8% (interquartile range, $-23.3, +5.1$), whereas those treated with a metered-dose inhaler had a median measured skeletal muscle strength increase of 2.4% (interquartile range, $-5\%, +12.7\%$), with $P = 0.036$ for the difference using the Wilcoxon rank-sum test. In a multiple linear regression model adjusted for pretreatment AAIRS and age, the β coefficient was -12.9% (95% confidence interval, -27.6 to -0.2). Thus, after adjusting for age and pretreatment AAIRS, the participants treated with a nebulizer had a 12.9% decrease in skeletal muscle strength compared with those treated with a metered-dose inhaler.

3.3 | Limitations

Limitations of our study include small sample size, although differences in change of muscle strength were statistically significant between participants receiving nebulized and metered-dose inhaler delivered

albuterol. In addition, it is unknown what degree of skeletal muscle strength decrease is clinically significant, although any decrease of respiratory muscle strength is of concern in a child with an acute asthma exacerbation. Further study could help reveal the relationship between albuterol delivery and dose with percent-predicted FEV₁. An additional limitation is that serum potassium levels were not obtained, which could have been used to examine the associations of muscle strength and serum potassium values at the time of strength measurement.

4 | DISCUSSION

Asthma exacerbation treated with albuterol is one of the most common clinical scenarios found in the pediatric ED. Our study results show that nebulized albuterol is associated with decreased skeletal muscle strength during asthma exacerbations; whereas, albuterol administration via a metered-dose inhaler is not. Prior studies have shown that albuterol use leads to hypokalemia, and separate studies have shown that hypokalemia can cause skeletal muscle weakness. Extrapolating these results to our study, we postulate that the weakness seen after nebulizer use is secondary to the hypokalemia caused by the significantly higher doses of albuterol given in the nebulizer group. Given our results, treatment with metered-dose inhalers, or lower doses of albuterol, over nebulization may be beneficial when either route is deemed clinically appropriate.

In the univariate analyses, there also was notable variability of skeletal muscle strength change after nebulization with a lower interquartile range of -23.3% highlighting that some patients experience greater weakness than others. In children with greater decreases this may be clinically meaningful. We suspect that the slight overall increase in median strength seen with the metered-dose inhaler use ($+2.4\%$) may represent these participants feeling better overall after treatment.

Future studies are needed to further evaluate the clinical significance of our findings. It remains unclear how well respiratory muscle strength correlates with hand grip strength or how long these strength effects last in patients with acute asthma exacerbation. Even with the limitations of this study, our results offer evidence to consider treating children with lower doses of albuterol during acute asthma exacerbation in situations where either treatment strategy, metered-dose inhaler or nebulization, appears clinically appropriate.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

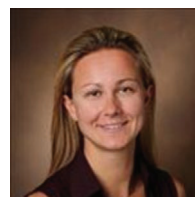
AUTHOR CONTRIBUTIONS

Donald Arnold, Danica Vendiola, and Catherine Burger conceived the study, designed the trial, collected data, and wrote the abstract. Donald Arnold and Catherine Burger wrote the article.

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