

Repeated doses of salbutamol and aeroallergen sensitisation both increased salbutamol-induced hypoxia in children and adolescents with acute asthma

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Abstract

Aim: We aimed to identify the frequency, magnitude and risk factors of salbutamol-induced hypoxia in children with acute asthma.

Methods: This study was conducted at Hacettepe University on children who presented to the paediatric allergy clinic or the paediatric emergency room with acute asthma between July 2014 and June 2015. Vital signs, pulse oximeter defined oxygen saturation and modified pulmonary index scores were evaluated before and after the first, second and third doses of nebulised salbutamol and repeated one and 10 days later.

Results: We included 304 patients (65.7% male) from median age of 5.3 years (range 1-18 years). Salbutamol-induced hypoxia was detected in 14.7%, 3.9% and 1.3%, respectively, after the first, second and third doses of salbutamol. The risk factors for hypoxia were younger age and a higher modified pulmonary index score, but the risk factors for salbutamol-induced hypoxia were the number of salbutamol doses given in the last six hours and the presence of aeroallergen sensitisation. The maximum decrease in oxygen saturation after salbutamol was %5.

Conclusion: Although bronchodilators are the first-line treatment for acute asthma, they caused modest hypoxemia, especially at repeated doses and, or, in patients with aeroallergen sensitisation.

Keywords: asthma; children; hypoxia; modified pulmonary index score; salbutamol

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Keynotes:

- This study aimed to identify the frequency, magnitude and risk factors of salbutamol-induced hypoxia in 304 children aged 1-18 years with acute asthma.
- Salbutamol-induced hypoxia was found 14.7%, 3.9% and 1.3% of the children after the first, second and third doses of salbutamol.
- Although bronchodilators are the first-line treatment for acute asthma, we found that they caused modest hypoxemia, especially at repeated doses and, or, in patients with aeroallergen sensitisation.

INTRODUCTION

Inhaled bronchodilators are the first-line treatment in acute asthma, but they may also cause hypoxemia by worsening the ventilation/perfusion (V/Q) mismatch. A relatively greater increase in perfusion than ventilation is thought to be the reason for the V/Q mismatch. It has been suggested that this increase in perfusion may arise from beta2 adrenergic pulmonary vasodilation effects and, or, beta1 adrenergic effects that increase cardiac output (1-3). Hence, the increase in the perfusion of low ventilated areas may lead to a further decrease in oxygenation.

Arterial blood gases can be accurately measured by arterial blood gas analysis in patients with acute asthma, but this is a painful and invasive procedure and its use is limited outside paediatric intensive care. Non-invasive surrogates for arterial oxygen, such as pulse oximetry, are helpful in estimating oxygen saturation and their common use in emergency rooms has decreased the need to obtain arterial blood gas analysis, as they are trusted by physicians (4,5).

This study aimed to investigate the frequency, magnitude and risk factors of pulse oximetry defined hypoxia that were triggered by salbutamol in children with acute asthma.

MATERIALS AND METHODS

This prospective study was performed in the Ihsan Dogramaci Children's Hospital at the Hacettepe University between 1 July 2014 and 30 June 2015. Children who presented to the paediatric allergy clinic or the paediatric emergency room with acute asthma were invited to participate in the study.

We included children who were 1-18 years of age, had physician diagnosed asthma or had experienced at least wheezing attacks in the current year and had an increase in asthma symptoms, such as cough, wheezing, shortness of breath, and, or, chest tightness. The other inclusion criteria were beta2-agonist use lasting for more than 24 hours and, or, a 25% decrease in peak expiratory flow (PEF) or forced expiratory volume in one second (FEV1), compared to their previous lung function or predicted values.

Patients with chronic pulmonary disease, lower respiratory tract infections or systemic disease were excluded. The Local Ethics Committee approved the study and informed consent was obtained from the patients and, or, their parents.

Study design

The data collected on admission included demographics and asthma specific characteristics. The patients' vital signs, peripheral capillary oxygen saturation (SpO₂) measurements and modified pulmonary index scores (MPIS) were evaluated before and after the first, second and third doses of salbutamol. Subsequent control visits were scheduled for 24 hours and 10 days. During these control visits, the same evaluations were carried out before and after they inhaled salbutamol.

Salbutamol was administered to all patients as a 0.15 mg/kg/dose every 20 minutes for the first hour with an oxygen-driven nebuliser with a face mask. Children with an SpO₂ of up to 92% during the initial evaluation were given oxygen support with a face mask. Physicians followed the recommendations of the Global Initiative for Asthma guidelines for acute asthma treatment (6). SpO₂ was measured with an NPB-290 pulse oximetry (Nellcor, Minneapolis, USA) with a finger probe after 15 minutes of breathing room air. The device has a margin of error of two units. All SpO₂ measurements were repeated at least three times with three different fingertips and the highest two values with a difference of up to two units were recorded.

Hypoxia was defined as an SpO₂ of up to 92% with a pulse oximetry. Salbutamol-induced hypoxia was defined as more than a two-unit reduction in previous SpO₂ measurements that were measured 20 minutes after salbutamol. Since the instrument has a measurement accuracy of ± 2 units, reductions of more than two units were considered significant in accordance with previous similar studies (7).

Attack severity was evaluated using the MPIS, which uses six variables: respiratory rate, heart rate, inspiratory-to-expiratory flow ratio, accessory muscle use, degree of wheezing and oxygen saturation in room air. Each variable is given a score between zero and three depending on its presence and, or, severity (8,9). Aeroallergen sensitisation was defined as having at least one positive test response to one of the common aeroallergens tested by either specific immunoglobulin E measurement or the skin prick test as detailed previously (10).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows 22.0 (IBM Corporation, Armonk, New York, United States). The descriptive data for categorical variables were expressed as frequencies and percentages for continuous variables and as
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means and standard deviations (SD) or medians and interquartile ranges, according to the distribution of variables, as appropriate. For categorical variables, the chi-square test was used to compare groups, McNemar and Cochran Q tests were used for dependent variables. Group comparisons for variables that were not distributed, normally were carried out with the Mann-Whitney U Test or Kruskal-Wallis Test and the Wilcoxon-Signed-Ranks Test and Friedman tests were used for dependent variables. Although comparing the groups found a statistically significant difference, it did not show which groups led to a significant difference. For that reason, pairwise comparisons were performed using Dunn's test to determine the groups that were responsible for that difference. Univariate and multivariate regression analyses were performed to determine risk factors for hypoxia and salbutamol-induced hypoxia. Variables that were associated with the outcomes in the univariate analysis, at a p value of <0.25, were entered into multivariate logistic regression models using the stepwise selection technique. The results of the logistic regression analysis were expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). A p value of less than 0.05 was considered statistically significant.

RESULTS

We enrolled 304 children up to the age of 18 years into the study and 273 (89.8%) participated in the second visit 24 hours later and 285 (93.7%) in the third visit 10 days later. The median (interquartile range) age was 5.3 (3.3-8.0) years and 65.7% were male (Table 1). The subjects were broken down into three age groups: 1-5 years (47.0%), 6-11 years (40.5%) and 12-18 years (12.5%).

All the children were evaluated at initial presentation, and after each of the three doses of salbutamol administration (Table 2). At admission, the SpO₂ values were measured as ≥95% in 142 (46.7%) patients and as 93-94% in 53 (17.1%) patients. Hypoxia (SpO₂

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≤92%) was found in 36.2%, 41.7%, 37.8% and 24.4% of the patients, respectively, at the time of admission, and after the first, second and third doses of salbutamol ($p<0.001$) (Table 2).

Salbutamol-induced hypoxia, defined as an absolute decrease in SpO_2 of two units, was detected in 14.7%, 3.9% and 1.3% respectively, after the first, second and third doses of salbutamol ($p<0.001$) (Table 2). After 24 hours and 10 days, salbutamol-induced hypoxia was detected 0.7% and 3.5%, respectively. The maximum observed decrease in SpO_2 after salbutamol was 5%.

As for MPIS, the score was eight (6-11) on admission. After each of the three doses of salbutamol treatment the MPIS was eight (5.75-11), seven (5-10) and six (4-9), respectively ($p<0.001$) (Table 2), reflecting the gradual improvement in respiratory distress.

The multivariate regression analysis that was performed to determine the risk factors for salbutamol-induced hypoxia were the number of salbutamol doses given in the last six hours, with an odds ratio (OR) of 3.241 and 95% CI of 1.246-8.430 and presence of aeroallergen sensitisation (OR 11.823, 95% CI 1.325-105.489) (Table 3). Furthermore, the risk factors for hypoxia at admission revealed that age (OR 0.82, 95% CI 0.707-0.952) and MPIS (OR 1.509, 95% CI 1.301-1.751) were significant risk factors.

On day 10, when the children had no asthma symptoms, the risk factor for salbutamol-induced hypoxia was found to be the presence of aeroallergen sensitisation (OR 12.581, 95% CI 1.573-100.611) (Table 3).

Moreover, we reanalysed the children according to the three age groups, namely 143 aged 1-5 years, 123 aged 6-11 years and 38 aged 12-18 years. This showed that the salbutamol-induced hypoxia was 23.7% at 12-18 years, 13% at 6-11 years and 14% at 1-5 years, respectively, after the first dose of salbutamol ($p=0.251$) (Figure 1). In addition, when the subjects were grouped together based on their oxygen saturation at admission, salbutamol-induced hypoxia did not differ between the groups (Figure 2).

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DISCUSSION

Our data indicated that salbutamol may cause or aggravate modest hypoxia and this was mainly related to the use of repeated doses of salbutamol and, or, the presence of aeroallergen sensitisation.

Although it is known that hypoxia can be seen in acute asthma, there are very few studies on this subject, particularly on children (5,11). Adult studies have demonstrated that the decrease in ventilation is associated with the severity of the exacerbation and that the hypoxia shows a similar increase (12). We also found that high MPIS values were more frequently associated with hypoxia and that during the observation period in the emergency department the hypoxia rates gradually decreased, while the MPIS values increased, indicating a close relationship between attack severity and hypoxia. Furthermore, the multivariate analysis at a young age appeared to be a significant risk factor for the presence of hypoxia. There are many potential reasons for the easy development of hypoxia at an early age, as the airways are smaller and more prone to collapse with greater peripheral airway resistance, the chest wall is more compliant and the collateral ventilation is not completely developed (13). It has previously been shown that young age was associated with frequent exacerbations and hospitalisation (14,15). When we evaluated all of these factors together, our findings highlighted that more attention and care should be given to preschool children aged 1-5 years with asthma.

Salbutamol and other beta2-agonists are the first choice drugs in the treatment of acute asthma. However, they may decrease SpO₂ by causing a V/Q mismatch (16,17). The salbutamol-induced hypoxia rate in our study was 14.7% after the first salbutamol administration, 3.9% after the second and 1.3% after the third. It was noticeable that the decrease in rates was parallel to the decrease in MPIS. There have been very few studies of salbutamol-induced hypoxia and those that do exist have tended to focus on a small number of paediatric subjects (1,2,7,11). A paediatric study that reported a 2-6 unit decrease in SpO₂

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during or after salbutamol treatment in 10 of the 27 patients with acute asthma, noted higher rates in young children (18). Another study that investigated 43 patients under the age of two years who received nebulised salbutamol, only found a decrease in oxygen saturation of more than two units (19). The results from our study contribute to these existing findings, as our large cohort demonstrated that the number of salbutamol doses administered in the last six hours and the presence of aeroallergen sensitisation were main determinants of salbutamol-induced hypoxia. The results of several studies carried out on paediatric populations indicate that using a pressurised metered dose inhaler with a holding chamber was as effective as a nebuliser in treating mild and moderate acute asthma. It also provided additional advantages, such as ease of use, shorter administration time, fewer side effects and decreased cost (20-22). Another study reported that some centres routinely used pressurised metered dose inhalers in their paediatric emergency departments, but that most centres continued using nebulisers (23,24). Most of the paediatric emergency departments in Turkey do not use pressurised metered dose inhaler techniques as standard treatment and our finding of high rates of salbutamol-induced hypoxia suggest that there needs to be a change of policy in clinical practice.

Our study found that salbutamol-induced hypoxia also occurred when patients were asymptomatic for asthma and not just during exacerbation. We also found that the presence of aeroallergen sensitisation was a risk factor in both situations. Since we could not find any similar previous data to confirm our results, it is difficult to explain why salbutamol-induced hypoxia, namely a V/Q mismatch, was seen more commonly in patients with aeroallergen sensitisation. An explanation may be that a V/Q mismatch can develop based on certain secreted substances in patients with atopic asthma where T helper 2 inflammation is more prominent. For example, vascular endothelial growth factor causes vascular proliferation and therefore vasodilatation can cause an increase in perfusion more than ventilation after salbutamol and may increase the V/Q mismatch (25,26).

The size and magnitude of salbutamol-induced hypoxia was previously investigated in a study with just 18 subjects with acute asthma and reported a decrease of more than 5% in oxygen saturation in nine (50%) of these subjects (1). This effect emerged within the first 15 minutes and lasted for less than 30 minutes. However, our large cohort observation showed that salbutamol-induced hypoxia occurred at a lower and more limited level: it only affected 14.7% of the children and did not exceed 5% in any of the patients.

Our study had certain limitations and this included the fact that we did not measure blood gases. Some may argue that the definition of hypoxia was based on SpO₂ levels instead of the partial pressure of oxygen in arterial blood, but this study was based on the real-life practice of hypoxia evaluation. It was assessed by pulse oximetry, except in those patients who had critical illnesses or required hospitalisation. In addition, a mild to moderate asthma exacerbation was seen in most patients included in this study, which differs from emergency clinics in developed countries where most asthma cases are expected to have moderate to severe exacerbations.

Noteworthy strengths of our study were that we included patients over a one-year period, which meant that we could evaluate patients during different seasonal conditions, including summer and winter when they were exposed to different triggers. Our study also featured a larger patient population and age range (1-18 years) than similar studies. This was also the first study to show a high rate of pulse oximetry defined hypoxia during asthma attacks, and following salbutamol treatment, and the causative risk factors.

CONCLUSION

Although bronchodilators are the first-line treatment for acute asthma, they can cause modest hypoxemia, especially when repeated doses are provided and, or, patients have

aeroallergen sensitisation. Supplemental oxygen administration, when needed, should be considered as an appropriate method of managing acute asthma.

ABBREVIATIONS

SpO₂: Peripheral capillary oxygen saturation

MPIS: Modified pulmonary index score

V/Q mismatch: Ventilation perfusion mismatch

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TABLES

Table 1. Characteristics of the patients

	n=304
Gender n, M/F (%)	200 (65.7%) / 104 (34.3%)
Age in years, median (IQR)*	5.3 (3.3-8.0)
Age groups, n (%)	
1-5 years	143 (47.0%)
6-11 years	123 (40.5%)
12-18 years	38 (12.5%)
Atopic dermatitis, n (%)	72 (23.6%)
Allergic rhinitis, n (%)	52 (17.1%)
Aeroallergen sensitisation, n (%)	139 (45.7%)
1-5 years (n=143)	60 (41.9%)
6-11 years (n=123)	57 (46.3%)
12-18 years (n=38)	22 (57.8%)
Family history of atopy, n (%)	42 (13.8%)
Mother's education level (high school-university), n %	144 (47.3%)
Father's education level (high school-university), n %	189 (62.1%)
Controller medication use, n (%)	201 (66.1%)
ICS [†]	129 (42.4%)
LTRA [‡]	26 (8.5%)
ICS+LTRA	24 (7.9%)
ICS+LABA [§]	22 (7.2%)
Total IgE (IU/L)*	100 (31-194)
Eosinophil %	1.8 (0.5-3.8)
Eosinophil number*	200 (100-400)
MPIS at initial presentation*	8 (6-11)

*Median (interquartile range 25%-75%), [†]ICS: Inhaled corticosteroids, [‡]LTRA: Leukotriene receptor antagonist, [§]LABA: Long-acting beta-agonist, ^{||}MPIS: Modified pulmonary index score

Table 2. Evaluation of children at admission and after the first, second, and third doses of salbutamol (n=304)

	Admission	After first dose of salbutamol	After second dose of salbutamol	After third dose of salbutamol	p (Comparison of all groups)
SpO2 %*	94 (92-96) ^{a, b}	94 (90-97) ^a	94 (90-98) ^b	95 (93-98)	<0.001
MPIS* [†]	8 (6-11) ^c	8 (5.75-11) ^c	7 (5-10)	6 (4-9)	<0.001
Hypoxia (SpO2≤92%), n (%)	110 (36.2)	127 (41.7)	115 (37.8)	74 (24.4)	<0.001 [‡]
Salbutamol-induced hypoxia, n (%)	-	45 (14.7)	12 (3.9) ^a	4 (1.3) ^a	<0.001

*Median (interquartile range), [†]MPIS: Modified Pulmonary Index Score [‡]For hypoxia (SpO2≤92%): Only the p value between first dose and third dose of salbutamol is significantly different, the other pairwise comparisons are not different.

^{a, b, c}: There was no difference between the groups with the same letter on each line, but there was a statistically significant difference between the other groups (p<0.001).

Table 3. Logistic regression analysis for predicting salbutamol-induced hypoxia following the first dose during an asthma attack and salbutamol-induced hypoxia after 10 days later of asthma attack

(a)	Univariate			Multivariate		
	OR [*]	% 95 CI [†]	p	OR	% 95 CI	p
Total immunoglobulin E	1.002	1-1.004	0.041			
Allergic rhinitis	1.802	0.909-3.57	0.092			
Eosinophil %	1.128	0.969-1.314	0.119			
Salbutamol doses in the last 6 hours	2.876	1.657-4.991	<0.001	3.241	1.246-8.43	0.016
Acute exacerbation (in the last 4 weeks)	0.345	0.084-1.419	0.14			
Aeroallergen sensitisation	15.48	5.374-44.587	<0.001	11.823	1.325-105.489	0.027
(b)						
Aeroallergen sensitisation	11.382	1.436-90.188	0.021	12.581	1.573-100.611	0.017

*OR: Odds ratio, [†]CI: Confidence interval, [‡]MPIS: Modified pulmonary index score, [§]OCS: oral corticosteroids

Figure Legends

Figure 1. Frequency of salbutamol-induced hypoxia and median MPIS values according to age groups after first dose of salbutamol (MPIS, Modified pulmonary index score)

Figure 2. Frequency of salbutamol-induced hypoxia and median MPIS values according to SpO₂ values at admission (MPIS, Modified pulmonary index score)

