



Is Seizure an Adverse Effect of Salbutamol in the Pediatric Population?

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Background: Although studies on epileptic seizures occurring during acute asthma attacks are limited, there is widespread belief among families and physicians that salbutamol causes seizures.

Aims: To investigate whether salbutamol triggers seizures in patients with epilepsy and asthma.

Study Design: A retrospective cohort study.

Methods: Epilepsy and asthma in patients aged 2–18 years who were admitted to the pediatric emergency department because of asthma attacks between January 2016 and December 2016 in a university hospital were evaluated retrospectively. The inclusion criteria were age 2–18 years, previous diagnosis of epilepsy and asthma, and admission to the pediatric emergency department due to asthma attacks.

Results: 276 medical records were evaluated. The seizure group had a longer period of diagnosis for epilepsy than the seizure absent group in the pediatric emergency department (5.4 years and 3.1, respectively). According to the logistic regression analysis, the duration of seizures in the emergency department, duration of asthma diagnosis, duration of epilepsy diagnosis, uncontrolled asthma, and severity of asthma attack in the pediatric emergency department have significantly increased the possibility of having a seizure during an asthma attack in our study population.

Conclusion: This study shows that patients using salbutamol have a lower risk of epileptic seizures than those who do not use salbutamol. This result should be verified by studies containing a large number of patients.

INTRODUCTION

Respiratory exacerbation is a frequent cause of emergency department admissions.¹ Management includes treatment and hospital discharge, hospitalization, or pediatric intensive care admissions. Salbutamol is a selective β2-adrenoceptor agonist that is commonly used to control airflow obstruction.² Its side effects include palpitations, blood pressure changes, and tachycardia. Tremor is the main dose-limiting factor and the most common side effect.³ Preclinical studies have shown that after intravenous administration, salbutamol readily crosses the blood–brain barrier, and brain concentrations increase up to 5% of plasma concentrations.⁴ Tremors are not caused by the stimulation of the central nervous system but by the imbalance between twitching muscle groups of the limbs.⁵ Seizures can occur as a drug toxicity-related complication. Studies have estimated that 6% of new-onset seizures are due to drug toxicity. Drug-induced seizures can be a result of altered excitatory or inhibitory transmitters and

neural pathways of receptors. Numerous drugs are associated with seizures. Antidepressants, diphenhydramine, stimulants, tramadol, and isoniazid account for the majority of cases.⁶ Fortunately, many drug-induced seizures are brief and uncomplicated.

Epidemiological data supporting the association between epilepsy and asthma are insufficient. In addition, despite the common belief among families and healthcare providers that seizures are triggered by salbutamol use during treatment of asthma attacks in patients with epilepsy and asthma, the study on this issue is extremely limited. Although studies on acute asthma-induced epilepsy seizures are limited, there are widespread beliefs among families and physicians about salbutamol usage and epilepsy. There are concerns in both practical applications and patient reports from various online sources. Suspicion of adverse drug reactions might result in intentional salbutamol nonadherence. Thus, this study aimed to investigate whether salbutamol triggers seizures in patients with epilepsy and asthma.



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Received: March 25, 2022, Accepted: June 9, 2022 Available Online Date: September 09, 2022 • DOI: 10.4274/balkanmedj.galenos.2022.2022-3-103

Available at www.balkanmedicaljournal.org

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Cite this article as:

Uysalol M, Yıldız R, Özünal ZG. Is Seizure an Adverse Effect of Salbutamol in the Pediatric Population?. *Balkan Med J*; 2022; 39(5):340-4.

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MATERIALS AND METHODS

Patients' Population

Patients with epilepsy and asthma aged 2–18 years who were admitted to the pediatric emergency department (PED) due to respiratory distress between January 2016 and December 2016 in a university hospital were evaluated retrospectively. Demographic characteristics of the patients compliant with the inclusion criteria, their history of salbutamol use, history of salbutamol use associated with an increase in convulsions, and history of convulsion when salbutamol was administered during hospitalization were assessed. Short-acting beta-agonists, ipratropium bromide, and corticosteroids were given as the first-line treatment of asthma attacks. According to the Global Initiative for Asthma (GINA) management and prevention report, short-acting beta-agonists are administered by the inhaler at 20-min intervals in the first hour at an appropriate dose.⁷ Seizure states were recorded after the completion of the attack treatment.

For this study, the inclusion criteria were age 2–18 years, previous diagnosis of epilepsy and asthma, and admission to the PED due to asthma attack.

Asthma was diagnosed according to the definition specified in the GINA management and prevention report.⁷ Asthma severity was also evaluated according to this report. Moreover, response to first-line treatment for asthma attack was made according to the evaluation made at the first hour of the treatment.⁷

According to the 2014 official report of the International League Against Epilepsy, epilepsy is defined as a disease of the brain characterized by any of the following conditions.⁸

1. At least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome.

Drug-resistant epilepsy was defined as a failure of adequate trials of two appropriately selected AEDs (as monotherapies or in combination) to achieve sustained seizure control.⁹

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). Continuous variables mean standard deviation is given as minimum and maximum. Discrete variables are given as frequency and percentage. Logistic regression analyses were used to predict seizures. In analytical statistics, Student's t-test, chi-square test, and Fisher's exact test were used. Statistical significance is accepted as $p < 0.05$.

RESULTS

The medical records of 276 patients were evaluated. Demographics and clinical characteristics of patients with epilepsy who were grouped according to the presence of seizures in the PED are given in Table 1. Age and sex ratio were comparable between the two groups ($p > 0.05$). The duration of epilepsy diagnosis was significant between the two groups ($p < 0.001$). The seizure group had a longer period of diagnosis for epilepsy than the seizure absent group in the PED (5.4 and 3.1 years, respectively). The duration of asthma diagnosis was significantly different between the two groups ($p < 0.001$). The seizure group had a longer period of diagnosis for asthma than the seizure absent group in the PED (3.56 and 2.23 years, respectively). The number of admissions of epileptic seizures to the PED was significantly higher in those who had seizures during an asthma attack ($p < 0.001$). The number of seizures during an asthma attack was significantly higher in the group that had seizures while receiving asthma attack treatment in the PED than in the group that did not have seizures (1.31 and 0.19, respectively; $p < 0.001$). When the number of seizures with salbutamol treatment in the history was evaluated, those who had seizures in the PED during asthma attack treatment were significantly higher ($p < 0.001$). When the relationship between the number of antiepileptic drugs used and seizures following the treatment of asthma attacks in the PED was evaluated, the number of drugs used by those who had seizures was higher ($p < 0.001$). The presence of a history of status epilepticus was significantly higher in the seizure group while receiving asthma attack treatment in the PED ($p < 0.001$). When evaluated according to asthma control status, patients with uncontrolled asthma had significantly more frequent seizures during asthma attack treatment in the PED ($p < 0.001$). Those with severe asthma were significantly more likely to have seizures during asthma attack treatment ($p < 0.001$). Of the 55 patients with epilepsy who came to the PED with the complaint of asthma attack and seizures, 40% had seizures regardless of the use of salbutamol. In addition, the rate of nonresponse to first-line treatment in the seizure group was significantly higher than that in the seizure-free group.

The frequency of drug-resistant epilepsy among those who had seizures during asthma treatment was significantly higher than those who did not have seizures (85% vs 65%, respectively; $p < 0.05$). Within 37 patients who have a history of status epilepticus, 36 did not have seizures during asthma attack treatment. Only one experienced a seizure.

Patients who are not using salbutamol even if it is indicated were also evaluated, and 58 (33.3%) patients were not using salbutamol due to their history of seizures with salbutamol use. Moreover, 116 (66.7%) patients were not using salbutamol even in the absence of seizure history with salbutamol use.

In the PED, the number of seizures during salbutamol treatment in history was higher in patients who did not use salbutamol in the treatment of asthma attacks than in those who used salbutamol ($p < 0.001$). In addition, the number of admissions to the emergency department because of epileptic seizures was significantly lower in those using salbutamol ($p < 0.001$).

When adjusted for age and sex, independent predictors of having a seizure during an asthma attack are provided in Table 2. According to logistic regression analysis, the duration of seizures in the emergency department, duration of asthma diagnosis, duration of epilepsy diagnosis, previous uncontrolled asthma, and severity of asthma attack in the PED have significantly increased the possibility of having a seizure during an asthmatic attack in our study population ($p < 0.05$).

TABLE 1. Demographics and Clinical Characteristics of Patients with Epilepsy Grouped According to Having Seizures During Treatment of an Asthma Attack in the Pediatric Emergency Department

	Seizure (+) (n = 55)	Seizure (-) (n = 221)	p-value
Age (years)	8.67 ± 3.043	8.66 ± 2.901	0.97*
Sex			
Female	28 (50.9%)	108 (48.9%)	0.78**
Male	27 (49.1%)	113 (51.1%)	
Duration of epilepsy diagnosis (year)	5.40 ± 2.385	3.18 ± 1.640	<0.001*
Duration of asthma diagnosis (year)	3.56 ± 1.960	2.23 ± 1.410	<0.001*
Number of admissions to the pediatric emergency department due to epileptic seizures	3.40 ± 1.882	2.60 ± 2.059	<0.001*
Number of seizures during asthma attack	1.31 ± 1.245	0.19 ± 0.545	<0.001*
Number of seizures during salbutamol treatment in history	0.87 ± 0.771	0.14 ± 0.419	<0.001*
Presence of drug-resistant epilepsy	47 (85.5%)	144 (65.2%)	0.01**
Number of antiepileptic drugs used	2.73 ± 1.254	1.99 ± 0.934	<0.001*
History of status epilepticus	36 (65.5%)	1 (0.05%)	<0.001***
Asthma control levels			
Under control	9 (16.4%)	136 (61.5%)	<0.001**
Partially controlled	22 (40%)	82 (37.1%)	
Not controlled	24 (43.3%)	3 (1.4%)	
Asthma severity			
Mild to moderate	22 (40%)	185 (83.7%)	<0.001**
Severe, life-threatening	33 (60%)	36 (16.3%)	
First treatment of an asthma attack			
Salbutamol was used	31 (56.4%)	212 (95.9%)	<0.001**
Salbutamol was not used	24 (44.6%)	9 (4.1%)	
Response category of first-line treatment of asthma attack			
Good	20 (36.4%)	202 (91.4%)	<0.001**
Partial	19 (34.5%)	9 (4.1%)	
Not responding	16 (29.1%)	10 (4.5%)	

Seizure (+): seizures are present after salbutamol administration. *Student's t-test. ** Chi-square test. *** Fisher's exact test.

DISCUSSION

The relationship between asthma and seizures has been studied for a long time, and various hypotheses have been proposed about their relationship. However, no clear results have been obtained.

There have been reported cases of tonic-clonic seizures that resolved after the discontinuation of excessive use of salbutamol for treatment. A 16-year-old patient with newly diagnosed asthma

TABLE 2. Age- and Sex-adjusted Independent Correlates of Having a Seizure During an Asthma Attack.

	Significance	exp(B)	95% CI
Age (years)	0.001	0.109	0.035; 0.339
Sex	0.450	2.055	0.317; 13.329
Duration of seizures in the pediatric emergency department	0.001	1.708	1.229; 2.373
Duration of asthma diagnosis	<0.001	16.087	3.654; 70.813
Duration of epilepsy diagnosis	0.007	2.578	1.290; 5.151
Asthma control (uncontrolled/partially/under control)	0.001	20.610	4.461; 95.224
Severity of asthma attack in the pediatric emergency department (mild/moderate vs severe)	0.02	6.061	1.302; 28.227
Drug-resistant epilepsy	0.516	0.482	0.530; 4.354

who was receiving inhaled salbutamol at appropriate doses was reported to have periodic muscle contractions and intermittent myoclonic jerking in arms and legs, and symptoms disappeared within 48 h after lorazepam treatment.¹⁰ Micheli et al.¹¹ reported myoclonus in three adults, which was associated with salbutamol treatment, but no similar case was found in children. In three published cases, the onset and remission of myoclonus were thought to be closely correlated with high-dose salbutamol intake and withdrawal, although accompanying factors such as hypoxia, subdural hematoma, and malignancy might have contributed.

Castaneda et al.¹² reported that many factors related to anti-asthma drugs and severe asthma attacks might cause seizures. In our study, not salbutamol as an anti-asthma drug but asthma severity is shown to be related to seizures. A study reported that respiratory alkalosis as a result of hyperventilation in acute asthma exacerbation may cause cerebral vasoconstriction, hypocapnia, neuronal stimulation, and increased epileptogenic activity, thus increasing the risk of convulsions.¹³

Our study shows that the duration of asthma diagnosis, uncontrolled asthma, and severity of asthma attack in the emergency department increase the occurrence of seizures with salbutamol use. Better asthma treatment is found to be related to lower rates of seizures. When asthma is severe, children may be at risk of seizures. Nellhaus et al.¹⁴ reported that they have seen cases progressing from cyanosis, syncope, spell, and loss of consciousness to subsequent asthma attack-independent convulsions during severe asthma attacks in many children. Researchers have reported that most of these cases do not have abnormal electroencephalogram (EEG) findings, and they associated this situation with severe cyanotic asthma attacks. Accordingly, they concluded that serious anti-asthma treatment that prevents hypoxic brain injury was the best precaution for seizures that can develop in asthma attacks (14). Other studies have reported children very rarely develop anoxic brain injury after an acute asthma attack. A retrospective study from Denmark evaluated sudden death in patients aged 1-35 years with uncontrolled asthma.¹⁵ Seizures were counted within overall symptoms and were found to occur in 12% of patients before death. The cause of death was predominantly sudden cardiac death followed by a fatal asthma attack. Uncontrolled asthma is an important condition that may result in sudden death. Therefore, efficacious asthma treatment including short-acting beta-agonists is essential. Contrary to perception, beta-agonists may be important for decreasing seizure occurrence. Our results reveal that seizures and uncontrolled asthma attacks also support the importance of controlling respiratory distress.

According to Issakainen et al.¹⁶, EEG should be conducted for differential diagnosis of seizures, although they occur after very severe asthma attacks. A study reported an association between pseudo seizures and asthma.¹⁷ Pseudo seizures may resemble epileptic seizures, and pseudo seizures seen during bronchodilator therapy can be misleading.

Singh et al.¹⁸ presented a 65-year-old male patient treated with ipratropium and salbutamol combination for chronic obstructive pulmonary disease. The patient had a seizure history and experienced

a seizure after nebulization. To determine the relationship between salbutamol use and seizures, a discussion between the patient's relatives and health personnel is important to examine the potential role of respiratory drugs and various agents on the onset of seizures. In this study, we found that salbutamol-induced seizures may play a role in only a small proportion of patients presenting with asthma attacks. Salbutamol use and absence of seizure history are related to lower risk of seizure occurrence in the PED. Patients who experienced a seizure after salbutamol use may not experience seizures in later treatment with salbutamol. Furthermore, the lack of salbutamol use and seizure occurrence is not a guarantee for the absence of seizures with later salbutamol treatment. β_2 -agonists are crucial in severe asthma exacerbation, as they have rapid efficacy, dose flexibility, and good clinical-effect-to-adverse-effect ratio.

In the study, drugs other than antiepileptics are not shown to be different between the groups. The number of prior antiepileptic drug use and presence of drug-resistant epilepsy were higher in the seizure group. This result might suggest the severity of epilepsy and antiepileptic drugs as causes of seizures. In the literature, antiepileptic drugs are known to paradoxically induce seizures.¹⁹ Different factors determine possible seizure aggravation.

Drug-drug interaction with salbutamol and antiepileptic drug use might be a concern. Results of a preclinical study showed that one-day salbutamol use did not alter the seizure threshold.²⁰

Patients who are not using salbutamol even if it is indicated were evaluated, and 58 (33.3%) patients were not using salbutamol because of their history of salbutamol-induced seizures. Moreover, 116 (66.7%) patients were not using salbutamol even in the absence of salbutamol-induced seizures. In our study, salbutamol adherence was low, and the reason for the nonadherence included seizure history with salbutamol use (33.3%). Parents should be informed about the importance of asthma attack treatment. When patients treated for asthma were compared, asthma severity was related to seizure occurrence. The diagnosis of severe life-threatening asthma was significant in children admitted with seizures. We thought that this situation could explain why both families and healthcare workers perceive a causal relationship between salbutamol use and seizures. In the treatment of chronic asthma, overuse of short-acting β_2 -agonists was also reported to be associated with increased risk of exacerbation and mortality in a nationwide cohort study of the global SABINA program.²¹ Rational pharmacotherapy is crucial. GINA, the international guideline for asthma management and prevention, emphasizes that the initial pharmacotherapy with salbutamol in the emergency room should not be delayed and started before the full assessment is completed.⁷

In conclusion, our study shows that the seizure rate was higher when salbutamol was not used. Our results support the lack of correlation between seizures and salbutamol use in a pediatric age group admitted to the PED. The duration of seizure in the PED, duration of asthma diagnosis, duration of epilepsy diagnosis, uncontrolled asthma, and severity of asthma attack in the PED increased the probability of having a seizure during an asthma attack in patients with epilepsy and asthma. Patients who have asthma attacks should be treated based on evidence-based guidelines. We believe

that this study may shed light on the beliefs related to salbutamol-induced seizures and, if possible, contribute to timely diagnosis and treatment.

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee (10/11/2017-8).

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- M.U., R.Y., Z.G.Ö.; Design- M.U., R.Y., Z.G.Ö.; Data Collection or Processing- M.U., R.Y., Z.G.Ö.; Analysis or Interpretation- M.U., R.Y., Z.G.Ö.; Literature Search- M.U., R.Y., Z.G.Ö.; Writing- M.U., R.Y., Z.G.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Funding: The authors declared that this study received no financial support.

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