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ORIGINAL ARTICLE

The use of the association of bronchodilators in the management of moderate/severe asthma attacks in the pediatric emergency of a reference hospital in the Federal District

Keywords:
Asthma,
Ipratropium,
Pediatric Emergency Medicine,
Asthmatic State.

Abstract

Introduction: Treatment instituted in the care of the child with asthma/wheezing exacerbations may influence clinical outcome and should take the severity of condition into consideration. In moderate/severe exacerbations, residual bronchoconstriction often results in refractory high doses of beta-2-agonists, and the association of bronchodilators is indicated. **Objectives:** To analyze the clinical outcome obtained with the use of the association of bronchodilators in management of moderate to severe asthma/wheezing episodes in the pediatric emergency regarding the need for hospitalization, duration of oxygen supplementation, length of hospital stay and transfer to the ICU. **Methods:** A retrospective cross-sectional observational study was carried out by reviewing the medical records of patients with moderate to severe wheezing/asthma episodes in the pediatric emergency of the *Hospital Materno Infantil* of Brasília, from March 2017 to August 2017. Patients that used bronchodilator monotherapy with beta-2-agonists were compared with those who received the combination of bronchodilators, ipratropium bromide, and beta-2-agonists, through the chi-square independence test. **Results:** All patients selected (129 patients) were hospitalized after initial care. Three patients were transferred to the ICU and one died, with no statistical relation to the therapy. Those who used bronchodilator association generally had a shorter hospital stay and oxygen therapy, but there was no statistically significant difference between the groups (p=0.55 e 0.21, respectively). **Conclusions:** No statistical significance was observed between the therapeutic groups and the clinical outcomes analyzed, although shorter hospital stay and oxygen therapy were observed in the group that used the bronchodilator combination.

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INTRODUCTION

Asthma is a disease characterized by chronic airway inflammation[1]. According to the Global Initiative For Asthma (GINA), it is defined by a pattern of symptoms, such as wheezing, dyspnea, chest tightness and cough that vary in frequency and intensity, together with limitation in expiratory flow[1].

It is also commonly characterized as reversible airway bronchoconstriction, associated with airway inflammation and edema, with increased mucus production[2].

A combination of factors, such as environmental exposure and genetic predisposition seems to explain the etiology of the disease. Pro-allergic and pro-inflammatory genes, predominantly located on chromosome 5, have been associated with asthma, but more than 100 gene loci seem to be related to the etiopathogenesis of this comorbidity[3].

It is a common disease that affects 1 to 18% of the population in different countries[1]. All over the world, there is an increase in the prevalence of asthma, despite the greater availability of treatment and improvement in the therapies used to treat it. Studies in different countries show that this increase reaches 50% per decade[3]. The highest prevalence is found in English-speaking countries and Latin America, especially among the pediatric population (above 20%)[4].

The recurrence of the disease is closely linked to the presence of respiratory infections, especially infections by the respiratory syncytial virus, rhinovirus, influenza, adenovirus, parainfluenza and metapneumovirus. Exposure to allergens at home is strongly associated with disease intensity and persistence. In addition, passive smoking and pollutants such as ozone and sulfur dioxide have been shown to increase the severity of asthma[3,11].

Childhood asthma is one of the most common reasons for seeking emergency care, hospitalizations and school absences, according to North American data[3]. A national study showed that, in southern Brazil, 20% of school-age children have asthma, most of these children with disease beyond the control target and with high rates of physical inactivity, school absences and hospital admissions[4].

The impact of this disease on public health in our country is enormous, and hospital care is the main component of the costs of asthma in our country. In the period from 2008 to 2013, around 170 million dollars were spent on hospitalizations due to asthma in Brazil, DATASUS values, which may be underestimated[4,6]. Another study showed that the cost per patient reached $733 per year, which highlights the great economic impact of this condition on society.[4]

With regards to asthma exacerbation, also called attacks, they can be classified according to their severity as mild, moderate and severe, according to scores already well established in the literature[2]. Asthma attack duration should take the severity of the condition into account[1,7,8]. The primary objective of treatment is the relief of bronchoconstriction, and beta-2-agonist bronchodilators are proven to be most effective in achieving this objective[1-3,5-6,10].

However, in patients with moderate to severe attacks, residual bronchoconstriction often occurs, refractory to high doses of beta-2-agonists, and the association of bronchodilators is warranted[2,7-10].

Ipratropium bromide is an anticholinergic agent, a synthetic derivative of atropine, which acts locally in the airways, with low systemic absorption (less than 1%), with limited adverse effects. Its action, although slower than that of beta-2-agonists, is responsible for decreasing the cholinergic tone in the airway, reducing edema and the production of secretion in the mucosa, promoting a powerful bronchodilator action[2,8].

The use of ipratropium bromide, in combination with beta-2-agonists, improves lung function and decreases the discomfort associated with beta-adrenergic symptoms. Furthermore, it is a safe and low-cost drug[2,8].

Several studies show that the use of this medication reduces hospitalization for patients with moderate to severe attacks. Its main indication is for the initial management of the asthma spell, preferably within the first 3 hours of care, and it has more satisfactory effects in attacks triggered by infections of the upper airways[2,8].

So far, studies have not shown a reduction in length of stay or prevention of admissions to intensive care units (ICU)[2,8,11].

The primary objective of this study is to analyze the clinical outcome obtained from the use of the association of bronchodilators in the management of moderate to severe asthma attacks in the pediatric emergency service of a public reference service in the Federal District, and whether this association brings benefits to this population. It concerns the need for hospitalization, oxygen therapy, hospital stay and transfer to the ICU. As a secondary objective, describe the epidemiological profile and identify the prevalence of passive smoking in the studied population, as well as whether this factor influences the clinical outcome of this sample.

MATERIALS AND METHODS

This is a retrospective, observational, cross-sectional and descriptive study. We analyzed the medical records of patients diagnosed with wheezing/asthma attacks in the pediatric emergency service of a reference hospital in the Federal District from March 2017 to August 2017 were analyzed.

The choice of these records was made based on the description of the ICD-10 in the diagnosis of the patient registered in the TrackCare system, an electronic medical record system used by the Health Department of the Federal District. The following ICDs were used: J40 - Bronchitis not specified as acute or chronic; J45.9 - Unspecified asthma; J21.9 - Unspecified acute bronchitis; J96 - Acute respiratory failure.

Patients with the following inclusion criteria were selected for the study: Children over one year of age with a diagnosis of wheezing/moderate to severe asthma attacks (according to the PIS score – pulmonary index score)[2], with one or more previous episodes of wheezing and those who received

adequate treatment upon admission to the emergency room (corticosteroid therapy associated with bronchodilator therapy, according to the recommendations of GINA[1]).

Those with the following criteria were excluded from the analysis: children under one year of age; cardiopaths; encephalopaths, immunosuppressed; lung diseases (cystic fibrosis, bronchopulmonary dysplasia, bronchiolitis obliterans), patients diagnosed with acute viral bronchiolitis (first episode of wheezing), patients with moderate to severe asthma attacks who have not received bronchodilator therapy associated with corticosteroid therapy upon admission.

By analyzing the medical records of the patients selected for the study, a database was built in the Microsoft Excel Office 365 for Windows® 2017 software with description of epidemiological data (age group, sex, origin, age of the first episode of wheezing, number of previous hospitalizations for wheezing, access to basic sanitation, regular medical care), risk factors for asthma (family history, male gender, prematurity, low birth weight, allergic rhinitis, eczema, previous bronchiolitis, early weaning)[1] and exacerbations of the clinical signs (high short-acting beta-2-agonist (SABA), mode of use of inhaled corticosteroids [poor compliance, incorrect inhalation technique, not in use or under regular use], passive smoking, exposure to allergens, confirmed food allergy , eosinophilia),[1] and the clinical outcome of each patient (discharge, hospital stay, length of stay, time on oxygen therapy, transfer to the intensive care unit, death).

The sample was broken down into two groups, those who received only beta-2-agonist bronchodilator therapy in the first visit (control group) and those who received the association of ipratropium bromide bronchodilators and beta-2-agonists at the time of initial care. These groups were compared using the Chi-Square independence test, identified by the $\chi 2$ symbol, using the R statistical software, version 3.4.3, with the aid of the RStudio and Microsoft Office Excel tools. A statistically significant value was set at $p < 0.05$.

The study was approved by the ESCS/FEPECS Research Ethics Committee under CAAE 03532918.3.0000.5553 and embodied opinion under number 3.125.876.

RESULTS

The sample consisted of 538 patients treated in the pediatric emergency service of a reference service in the Federal District, from March to August 2017. Of these, applying the exclusion criteria, 409 were excluded from the research. Thus, 129 patients participated in the study, meeting the inclusion criteria.

Of the valid patients, most are males (61%) and in preschool age (41%). We found out that 92% of the patients had complete basic sanitation in their homes. In the case of regular medical follow-up (with or without a specialist), 70% did not have it.

Regarding the age of the first wheezing episode, 47% of the patients started the condition before 1 year of age, 42% between 1 and 6 years of age, and 11% at 6 years or more.

Regarding the number of previous hospitalizations for asthma/wheezing, 56% of the patients had never been hospitalized for this reason; 17% had a previous hospitalization; 8% two hospitalizations; 4.5% three hospitalizations and 14.5% already had more of 3 hospitalizations for asthma/wheezing.

Table 1 shows the analysis of age groups in relation to the number of previous hospitalizations for wheezing.

In all age groups, there is a predominance of patients with no previous hospitalization for wheezing, whereas in the ranges of 1 to 2 years and over 10 years, there is a relevant concentration in patients with 1 hospitalization, which is statistically significant ($p < 0.05$).

Table 2 shows, the frequency of risk factors for asthma and factors for asthma exacerbations, respectively. The total column will not add the sample size in all cases, as each variable might not have information in the medical record.

Regarding the way of using inhaled corticosteroids in the population studied, 93% did not use the medication, 4% used it regularly and 3% reported low compliance to treatment.

As for the classification of asthma/wheezing severity, 95 patients, corresponding to 74% of the cases, had a mod-

Table 1. Distribution of Age Group by Number of Previous Hospitalizations for Wheezing.

Age Group	None	1	two	3	more than 3
1 to 2 years	62.2%	24.3%	5.4%	0.0%	8.1%
3 to 5 years	57.1%	16.7%	11.9%	11.9%	2.4%
6 to 10 years	46.6%	6.7%	6.7%	0.0%	40.0%
Over 10 years old	66.7%	33.3%	0.0%	0.0%	0.0%

Table 2. Frequency Distribution of Risk Factors for Asthma and Asthma Exacerbations.

Feature	Yea	No	Total
Family history	70 (58%)	50 (42%)	120 (100%)
Prematurity	13 (12%)	100 (88%)	113 (100%)
Low weight at birth	12 (14%)	74 (86%)	86 (100%)
Allergic Rhinitis	12 (12$)	86 (88%)	98 (100%)
Eczema	5 (11%)	42 (89%)	47 (100%)
previous bronchiolitis	30 (57%)	23 (43%)	53 (100%)
early weaning	3 (6%)	47 (94%)	50 (100%)
eosinophilia	7 (16%)	38 (84%)	45 (100%)
High use of SABA*	38 (47%)	43 (53%)	81 (100%)
passive smoking	31 (30%)	74 (70%)	105 (100%)
Allergen Exposure	55 (53%)	49 (47%)	104 (100%)
Food allergy	6 (5%)	111 (95%)	117 (100%)

SABA = salbutamol.

erate crisis and the remaining 34, equivalent to 26%, had a severe attack.

As for the applied therapy, in 25 cases we used the association between salbutamol and ipratropium bromide (SABA + BI), corresponding to 19% of the cases. In 104 (81%) cases we used bronchodilator monotherapy with albuterol (SABA).

Regarding the analyzed outcomes, all the patients in the study population were hospitalized after initial care. Of these, 3 patients were transferred to the Intensive Care Unit (ICU) and 1 died. It was not possible to establish a relationship between the therapy used and these clinical outcomes.

Concerning length of stay, there was no statistically significant difference after using the Chi-Square Independence Test ($\chi 2$) between the two treatment groups ($p = 0.55$), as shown in table 3. The relationship was also demonstrated between the two treatment groups and the duration of oxygen therapy. There was no statistically significant difference ($p = 0.21$).

Next, we investigated the distribution of length of stay and oxygen therapy among the age groups (Table 4). The relationships found were not statistically significant ($p = 0.39$ and 0.91 respectively).

Analyzing the relationship between the age group and the therapy used, we noticed that as the age group increased, the use of SABA+BI therapy also increased gradually. In infants, combination therapy was used in 7.3%, in preschoolers in 17.6%, in schoolchildren 29.4% and in adolescents it was prescribed in 100% of cases. After the Chi-Square test, $p = 0.0003$ was obtained, demonstrating that the use of therapy varied significantly in relation to the patient's age group.

Finally, observing the prevalence of passive smoking in the study population, the length of stay and oxygen therapy were correlated with this variable, with no statistically significant difference between the two cases ($p = 0.49$ and 0.5 respectively).

DISCUSSION

The study population had a higher prevalence of males and preschoolers, like the data in the national literature[13]. The male gender is also predominant in data from the world literature[3], while the most prevalent age group is schoolchildren and adolescents[14].

Attention is drawn to the low prevalence of medical follow-up in the population studied and the lack of maintenance medication (inhaled corticosteroids) in a large part of the sample, generating a reflection on the quality of care provided to these patients. The literature shows that uncontrolled asthma increases the costs of hospitalizations and medications for hospital use, in addition to impairing the quality of life of the patient, responsible for absenteeism from activities of daily living[1]. The absence of treatment implies an increases in the number of attacks, their severity and increased mortality from asthma, in addition to other aspects such as morbidity resulting from bronchial remodeling[1,18].

Table 3. Distribution of Hospitalization Time and Oxygen Therapy Time given the Therapeutics used and Crisis Severity.

		Moderate		Serious	
		SABA	**SABA+BI**	**SABA**	**SABA+BI**
Length of stay	Until 12h	1,30%	0,00%	0,00%	0,00%
	Between 12h and 24h	18,2%			
	0,00%	0,00%	7,1%		
	Between 24h and 12h	26%	33,3%	26,3%	28,6%
	Greater than 48 hours	54,5%	66,7%	73,7%	64,3%
Oxygen Therapy Time	Until 12h	2,6%	0,00%	0,00%	7,1%
	Between 12h and 24h	20,8%	0,00%	5,3%	7,1%
	Between 24h and 12h	29,9%	77,8%	31,6%	28,6%
	Greater than 48 hours	46,7%	22,2%	63,1%	57,2%

Chi-Square independence test (?2): $p = 0.55$ between treatment groups and length of stay; $p = 0.21$ between the therapy groups and time of oxygen therapy. * SABA + BI = salbutamol and ipratropium bromide; SABA = salbutamol.

Table 4. Distribution of Age Group given the length of stay and the time of oxygen therapy.

Age Group	until 12 pm		Between 12:00 and 24:00		Between 24h and 48h		Greater than 48 hours	
	internment	0^2	internment	0^2	internment	0^2	internment	0^2
1 to 2 years	0.0%	2.6%	5.3%	10.5%	34.2%	36.8%	60.5%	50.0%
3 to 5 years	2.1%	2.1%	12.8%	14.9%	21.3%	31.9%	63.8%	51.1%
6 to 10 years	0.0%	3.1%	18.8%	18.8%	25.0%	31.3%	56.3%	46.9%
> 10 years	0.0%	0.0%	50.0%	50.0%	50%	50.0%	0.0%	0.0%

O^2 = oxygen therapy; h = hours of hospitalization.

Also noteworthy is the high prevalence of basic sanitation in the study population, perhaps serving as a reinforcement of the hygiene hypothesis postulated in 1989 by Strachan[15], who advocates the idea that early exposure to different microorganisms would be a protective factor against allergic diseases, including asthma, despite being a controversial topic in the literature[15,16].

There was an increased frequency of wheezing before the first year of life and between 1 and 6 years of age, compatible with literature data, which show that approximately 80% of asthmatic patients start the condition before 6 years of age[3] .

Regarding the number of previous hospitalizations for wheezing reported by patients, almost half of them (44%) had already been hospitalized previously. In the age group of infants between 1 and 2 years of age, 24.3% had already had 1 previous hospitalization, a statistically significant value (p = 0.0007); and 8.1% more than three, fitting into the concept of a Wheezing Infant Syndrome[17], whose main etiology is asthma. In school-aged patients, 40% already had more than 3 hospitalizations, suggesting the diagnosis of asthma in such patients.

Secondhand smoking in our population was present in 30% of the cases. There was no statistical significance regarding the clinical outcomes analyzed. The fact that this information is not present in 24 medical records may have changed the statistics.

As for the presence of risk factors for the development of asthma, a positive family history is highlighted in 58% of cases, in agreement with the literature[1,3]. The frequency of previous diagnosis of bronchiolitis in 57% of cases also stands out, which is another risk factor for persistent asthma in children[1,3,18].

About risk factors for asthma exacerbation, high frequency use of rescue medication, an important factor related to morbidity and mortality[1], and exposure to allergens. Only 5% had food allergy, like American data, which refer to food as a trigger for crisis in about 2% of patients diagnosed with food allergy[19].

Regarding the type of attack, 74% of the cases corresponded to moderate attack and 26%, severe crises. As for possible outcomes, three patients were transferred to the ICU and 1 died. This data does not necessarily reflect the indication for ICU in such patients, as there is a shortage of intensive care beds in the service.

All patients in this study were hospitalized for a minimum period of 12 hours, so there was no way to analyze the relationship between hospital admissions and the treatment used, as well as the reduction in the frequency of hospitalization with the use of the association of bronchodilators, suggested by some studies[2,10,11]. This limitation was due to the selection of medical records in the statistics department of the hospital in question, which provided data only on patients who were admitted to the pediatric emergency department.

As for the therapy applied, in only 19% of the sample the association between salbutamol and ipratropium bromide (SABA + BI) was used, and in the others, monotherapy with salbutamol (SABA) was used. The age group increased, the use of SABA+BI therapy also increased. We also noticed that the association of bronchodilators increased from 7.3% in the age group from 1 to 2 years, to 30% in the 6 to 10 years age group. All cases of patients older than 10 years used SABA+BI.

Analyzing the length of stay in the different groups, we noticed that for severe attacks in those who used the association of bronchodilators, 7.1% were discharged between 12 and 24 hours, and 0% were discharged from the monotherapy group. We also noticed that 73.7% of patients with severe attacks who used only SABA remained hospitalized for more than 48 hours, against 64.3% of those who used the drug combination.

However, in relation to moderate attacks, this distribution was inverted, and patients who used the association of bronchodilators remained hospitalized for longer. When looking at the length of stay and its distribution among age groups, patients over 10 years of age were entirely discharged within 48 hours and in these patients the combined therapy was used exclusively.

There was no statistically significant relationship between therapy and length of hospital stay in this study (p = 0.55), as well as their distribution by age group (p = 0.39).

As for the time in oxygen therapy; in general, in patients who used SABA, the times of oxygen therapy longer than 48 hours were predominant, while for patients with SABA+BI the oxygen therapy duration was between 24 and 48 hours. In patients with moderate attacks and those who used combined therapy, the oxygen therapy time was 77.8% of the cases, being 24 to 48 hours, while in those who used salbutamol only, 46.8% used oxygen for more than 48 hours . In those with severe attacks, there was a more uniform distribution of oxygen therapy time in both treatment groups. In this outcome, there was also no statistical significance (p = 0.21).

The use of the combination of SABA+BI is recommended in the literature for all age groups[1-2,7-10], and in this study, there was little use of this therapy in younger patients. We believe that this fact may have influenced the results, and the question remains: would we find the same results in relation to length of stay and oxygen therapy in younger patients if the association of bronchodilators had been used more frequently? And why did professionals choose this treatment for older patients?

The study has limitations because it is retrospective through a review of medical records, filled out by different professionals without standardization. Thus, due to the large amount of information that was not included in the medical records, the study statistics may not reflect the local reality. The ideal situation would also be to analyze patients who were treated in the emergency room and were released after initial therapy, without the need for hospitalization. The group that used bronchodilator monotherapy was four times larger than the group that used the association of bronchodilators,

not being homogeneous comparison groups - another factor that may have altered the study statistics.

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