

TREATMENT

Inhaled Salbutamol Plus Ipratropium in Moderate and Severe Asthma Crises in Children

RICARDO IRAMAIN, PH.D., M.D.,¹ JESÚS LÓPEZ-HERCE, PH.D., M.D.,^{2,*} JULIA CORONEL, M.D.,¹ CRISTOPHER SPITTERS, PH.D., M.D.,³ JAIME GUGGIARI, M.D.,¹ AND NORMA BOGADO, M.D.,¹

¹*Emergency Unit, Emergency Department, Maternity-Children's Hospital, Asunción National University Asunción, Paraguay.*

²*Pediatric Intensive Care Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain.*

³*University of Washington Schools of Medicine and Public Health & Community Medicine, Seattle, WA, USA.*

Background. The combination of inhaled β_2 agonists and anticholinergics is recommended for children with acute asthma, although there are few randomized controlled trials. The aim of the study was to determine whether salbutamol plus ipratropium bromide improves oxygenation and lung function and reduces the frequency of hospitalization in children with asthma crises. **Methods.** A prospective, randomized, double-blind study of children aged 2–18 years with moderate to severe asthma crises. Patients were evaluated using the asthma score and spirometry. They received six nebulizations of salbutamol plus placebo or salbutamol plus ipratropium and were reevaluated at 30, 60, 90, 120, and 240 minutes, at which time it was decided whether they were to be admitted. **Results.** A total of 97 patients completed the study, 49 in the salbutamol plus ipratropium group and 48 in the salbutamol-only group. There were no differences in the status at baseline between the two groups. Children treated with salbutamol plus ipratropium presented a greater improvement in clinical state and lung function and required hospitalization less frequently (18.4%) than children in the salbutamol group (43.8%) ($p = .007$). Improvement was more marked in children with severe asthma crises than in those with moderate crises. The effect of salbutamol plus ipratropium was similar in children over 8 years of age and in younger children. **Conclusions.** Salbutamol plus ipratropium bromide improves lung function in asthmatic children with moderate to severe asthma crises, independently of age. The effect is greater in children with severe crises, with a substantial reduction in the need for hospitalization.

Keywords asthma, ipratropium bromide, pulmonary score, salbutamol, children

INTRODUCTION

The administration of β_2 agonists by inhalation of salbutamol is a standard treatment for mild to moderate asthma crises in emergency departments (1, 2). Current guidelines recommend the use of a combination of inhaled β_2 agonists plus anticholinergics for pediatric patients with acute severe or life-threatening asthma in the emergency setting (1–4). However, there are a relatively small number of randomized controlled trials, and few of them have classified patients according to age or clinical severity. Furthermore not all studies have reported positive results (5–22).

The objective of our study was to analyze whether the combination of salbutamol plus ipratropium bromide administered by nebulizer in the emergency department improved oxygenation and lung function and reduced the frequency of hospital admission among children with asthma crises, compared with salbutamol alone, with a differential analysis according to age and severity of the asthma crisis.

METHODS

A prospective, randomized, double-blind clinical trial was performed in the hospital emergency department between

the months of January 2005 and January 2008. The study was previously approved by the hospital ethics committee.

Children between 2 and 18 years of age who presented moderate to severe asthma crises were enrolled in the study. All the patients were treated at the same hospital emergency department. An asthma crisis was defined as an episode of respiratory difficulty and wheezing associated with the use of accessory muscles (intercostal) or subcostal retraction and a fall in the peak expiratory flow (PEF) and in the forced expiratory volume in the first second (FEV₁).

The primary objective of the study was to determine the efficacy of the treatment to reverse airflow obstruction and improve oxygenation, evaluated using the pulmonary asthma score, SaO₂, and FEV₁. The secondary objective of the study was to evaluate the need for hospital admission after 4 hours of nebulized treatment using salbutamol alone or in combination with ipratropium bromide.

Patients were evaluated by pediatricians using the pulmonary score (23), described in Table 1. The oxygen saturation (SaO₂) was measured using a pulse oximeter (Ohmeda N-180, Louisville, CO, USA). In children aged over 8 years, spirometry was performed using a portable device (Electronic Peak Flow/FEV₁ Meter, Ferraris Respiratory Europe Ltd. Piko-I, Hertford, UK), following the recommendations of the American Thoracic Society (24). The predicted PEF and FEV₁ were adjusted for sex and height and the percentages of the PEF and FEV₁ were calculated. Three spirometry tests were performed, selecting the highest values for the analysis (25).

*Corresponding author: Jesús López-Herce, Ph.D., M.D., Pediatric Intensive Care Department, Hospital General Universitario Gregorio Marañón, Dr Castelo 47, 28009 Madrid, Spain; Tel: +34 913145613; Fax: +34 915868018; E-mail: pielvi@ya.com

TABLE 1.—Pulmonary score.

Score	Respiratory rate (breaths/min)		Wheezing	Accessory muscle use- sternocleidomastoid
	<6 years	>6 years		
0	<30	<20	None	No apparent increase
1	31–45	21–35	Termination expiration with stethoscope	Mild increase
2	46–60	36–50	Entire expiration with stethoscope	Increased
3	>60	>50	Inspiration and expiration without stethoscope	Maximal activity

The severity of the asthma crisis was classified according to the pulmonary asthma score as mild (score 5–7) and PEF > 70% of the predicted value according to the age and sex; moderate (score 8–11) and PEF 50–70% or FEV₁ 60–80% of the predicted value; and severe (score 12–15) and PEF < 50% or FEV₁ < 60% of the predicted value. The pulmonary asthma score was the main criteria to rank severity of asthmatic crisis.

The following exclusion criteria were applied: mild asthma crisis, administration of corticosteroids in the previous 48 hours, presence of severe respiratory failure requiring immediate admission to intensive care or mechanical ventilation, history of respiratory failure requiring admission to intensive care, cardiac or pulmonary malformations, chronic lung disease (pulmonary bronchodysplasia, cystic fibrosis), stridor, foreign body aspiration, neurological alterations, or contraindications for the use of β_2 agonists or anticholinergic medication.

The hospital pharmacy department prepared two types of numbered plastic bottles. The S bottles contained 5 mg of salbutamol (Ventolin[®], GlaxoSmithKline, Madrid, Spain) in 5 mL of saline solution; the

SBI bottles contained salbutamol (5 mg, Ventolin[®], GlaxoSmithKline) plus ipratropium bromide [40 drops = 500 μ g of ipratropium bromide (Atrovent[®], Boehringer Ingelheim Pharmaceuticals, Ridgefield, CO, USA)] in 5 mL of saline solution. The two solutions had the same smell, color, and fluid level in order to prevent differentiation. Neither the investigators nor the patients knew which solution the bottles contained. The bottles were kept in the emergency department ready for immediate use. After obtaining the informed consent from the parents, patients were randomized using a computer-generated random sequence.

All patients received six nebulizer treatments (one every 20 minutes), using 2.5 mL of salbutamol solution in children weighing less than 20 kg and 5 mL in children over this weight. The aerosols were created by a jet-type nebulizer (Whisper Jet, Intec Medical Inc., Englewood, CO, USA), providing an oxygen flow of 6–7 L/min measured using a flow meter (Thorpe 1–15 L/min, model 2562, Hudson Oxygen Sales Co., Temecula, CA, USA), and released through a face mask. Each nebulizer treatment lasted 7 minutes.

The pulmonary asthma score and oxygen saturation were reevaluated at 30, 60, 90, 120, and 240 minutes after treatment and, in children over 8 years of age, the PEF and FEV₁ were measured at 30, 90, and 240 minutes.

Those children with an asthma score at 240 minutes less than 7 and an SaO₂ \geq 94% breathing air or a PEF or FEV₁ > 60% of the predicted value were discharged from the emergency department. The rest of the children were admitted to the hospital. The decision to discharge or admit patients and the treatment after discharge was made by pediatricians who did not know the treatment used. All patients requiring admission were treated with corticosteroids (dexamethasone, 0.6 mg/kg IM, or methylprednisolone, 1–2 mg/kg IV).

Treatment failure was considered to have occurred when the patient presented tachyarrhythmias, except for sinus tachycardia less than 200 bpm, marked clinical deterioration that required immediate additional treatment based on the criterion of the duty pediatrician or independent emergency department supervisor, or severe eye pain or visual disturbances.

The sample size was calculated based on the frequency of hospital admission. To achieve a minimum difference of 30% between the two groups (salbutamol plus ipratropium bromide vs. salbutamol plus placebo) with an

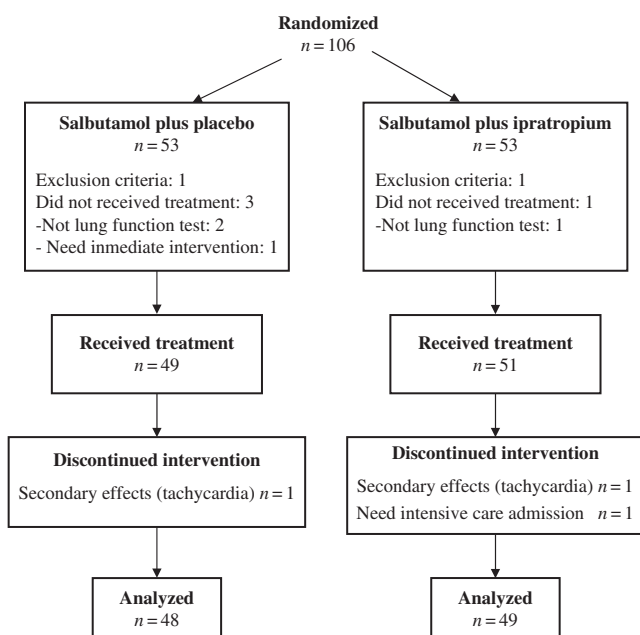


FIGURE 1.—Consort Style Diagram.

alpha error of 0.05 and power of 80%, the sample size was calculated as 45 patients per group.

The results were analyzed using the SPSS version 15.0 statistical package. Fisher's exact test and analysis of variance were used to evaluate the differences between the two groups. For all analyses, statistical significance was taken as a p -value $< .05$.

RESULTS

One hundred and six children were enrolled in the study, of whom nine were excluded: three children of 8 years of age because they could not perform lung function tests satisfactorily (two in the salbutamol plus ipratropium group and one in the salbutamol plus placebo group); one patient in the salbutamol plus placebo group required immediate intervention and another in the salbutamol plus ipratropium group developed severe respiratory failure and was admitted to the intensive care unit after the third nebulizer; two patients, one from each group, developed sinus tachycardia >200 beats/min, and two children with a history of bronchopulmonary dysplasia and cardiac malformations were enrolled in error. The protocol was completed by 97 patients (91.5%), 49 in the salbutamol plus ipratropium group and 48 in the salbutamol plus placebo group (Figure 1).

The demographic characteristics, pulmonary asthma score, SaO_2 , lung function tests (performed in 32 children in the salbutamol plus ipratropium group and 33 children in the salbutamol plus placebo group), and severity of the asthma were similar in the two groups (Table 2).

The evolution of pulmonary asthma score, SaO_2 , and lung function is showed in Figures 2–4. The children in the salbutamol plus ipratropium group presented a significantly greater improvement in the clinical parameters (pulmonary asthma score and SaO_2) and in lung function (FEV_1 and PEF) than the children in the salbutamol plus placebo group (Table 3). The need for hospitalization was significantly lower in the patients treated in the salbutamol plus ipratropium group (18.4%) than in the salbutamol plus placebo group (43.8%) [$p = .007$; relative risk (RR): 0.29, 95% CI: 0.1–0.8; number needed to treat (NNT): 3.9, 95% CI: 2–13].

In the group of 32 children with moderate acute asthma, those treated with salbutamol plus ipratropium presented a significantly greater improvement in the SaO_2 and in the FEV_1 than those in the group treated with salbutamol plus placebo, but the differences in the pulmonary asthma score and in the frequency of hospital admission did not reach statistical significance (Table 4). In contrast, in the subgroup of 65 children with severe asthma, those in the salbutamol plus ipratropium group presented not only a significantly greater improvement in the clinical parameters (SaO_2 and pulmonary asthma score) and in lung function (FEV_1 and PEF) than those in the salbutamol plus placebo group, but also a significantly lower rate of hospitalization (17.6% vs. 51.6%, $p = .004$, RR = 0.2, 95% CI: 0.1–0.7; NNT: 2.9, 95% CI: 2–8) (Table 3).

The reduction in the risk of hospitalization with treatment with salbutamol plus ipratropium was maintained when patients were divided into two age groups (over or under 8 years of age). The rate of admission in children under 8 years treated with salbutamol plus ipratropium was 11.8% compared with 53.3% in those treated with salbutamol plus placebo ($p = .03$; RR = 0.22, 95% CI: 0.0–0.8; NNT = 4.5). In children over 8 years, the admission rate in those treated with salbutamol plus ipratropium was 18.8% compared with 42.4% in those treated with salbutamol plus placebo ($p = .04$; RR = 0.44, 95% CI: 0.10–0.90; NNT: 2.27).

DISCUSSION

Ipratropium bromide is an acetylcholine antagonist that acts on the bronchial smooth muscle. Although parasympathetic fibers are only present in the large airways, ipratropium can have a generalized action throughout the lung. On the other hand, the β -adrenergic receptors are distributed more peripherally, creating an ideal situation for combined action (26). The bronchodilator effect of ipratropium is somewhat slower than that of the β_2 agonists, but combined administration can potentiate the effects of both drugs.

Although the administration of repeated doses of ipratropium is generally recommended in the first 24–48 hours, the optimal dose and frequency in children with asthma crises has still not been established (1, 2). In our study, we administered six nebulized inhalations, which is a slightly larger number than has been used in other studies (5–22). Further studies are necessary to evaluate the most appropriate interval for the administration of ipratropium in children with asthma crises.

The results of our study confirm that the addition of ipratropium bromide to standard therapy with salbutamol improves lung function and significantly reduces hospital admission in children with moderate to severe asthma crises. This benefit is observed in children under 8 years of age and older children.

In only three previous studies that analyzed the effect of salbutamol plus ipratropium were patients stratified according to clinical severity of the asthma (16–18). In our study, the clinical and functional improvement with the combination of salbutamol and ipratropium was greater in severe asthma crises than in moderate crises, coinciding with the results reported by other authors (3). This finding underlines the importance of an early initial treatment with salbutamol plus ipratropium in children with more severe asthma crises (3, 4).

Our results agree with those found by Rodrigo in their systematic review (3). Anticholinergic agents are particularly beneficial in patients with moderate to severe obstruction treated with multiple dose-fixed protocols consisting of three or more doses of an anticholinergic drug (3).

Although it is difficult to compare our results with those of other studies due to the heterogeneity of patients

TABLE 2.—Demographic characteristics and baseline clinical and lung function parameters of the two groups.

Characteristic	Salbutamol plus ipratropium bromide	Salbutamol plus placebo	P-value
Number	49	48	
Age (years)	8.3 ± 3.9	9.8 ± 4.5	.3
Male (%)	49	52	.8
Height (cm)	131.8 ± 19.2	136.0 ± 23.7	.3
Sao ₂ (%)	89.0 ± 1.9	89.2 ± 1.5	.9
Asthma score	12.3 ± 1.4	12.5 ± 1.4	.9
Children <8 years of age (%)	33.3	32.6	.9
Severe acute asthma (%)	69.4	64.6	.6
Lung function tests	n = 32	n = 33	
FEV ₁ (L)	1.4 ± 0.3	1.5 ± 0.5	.2
% of predicted FEV ₁	62 ± 7	60 ± 8	.5
PEF (L/min)	180.1 ± 46.3	186.3 ± 67	.7
% of predicted PEF	63.5 ± 7.9	60.1 ± 9.8	.12

Note: Data presented as percentages or mean ± SD.

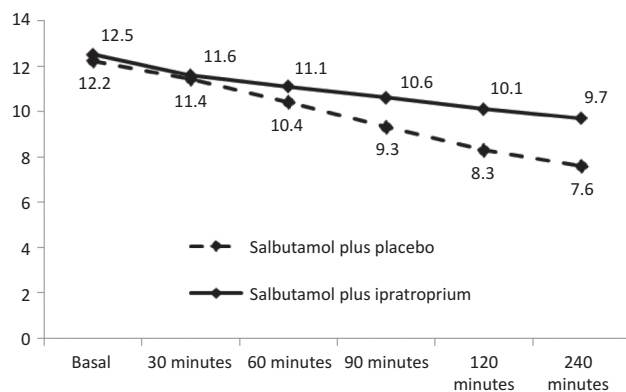


FIGURE 2.—Evolution of pulmonary asthma score.

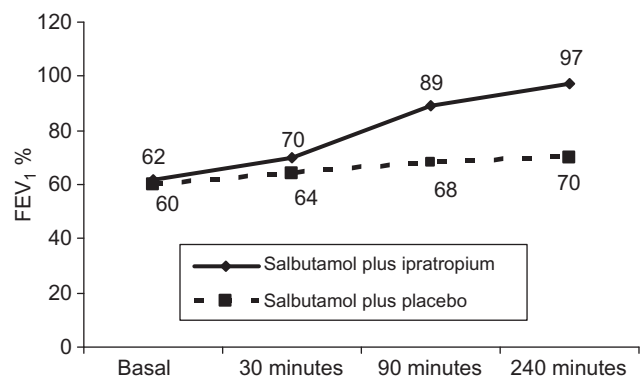


FIGURE 4.—Evolution of functional spirometric tests.

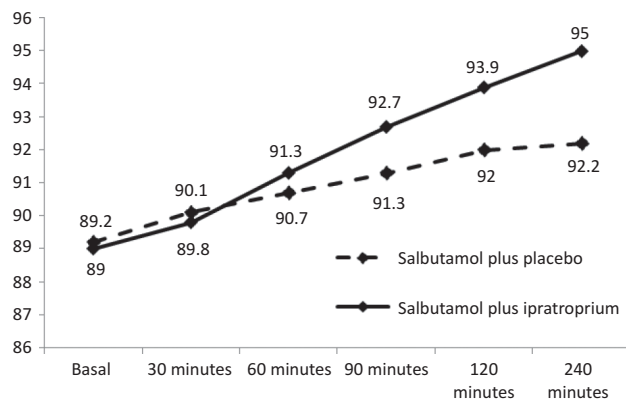


FIGURE 3.—Evolution of saturation.

and of the criteria of severity, the improvement in the FEV₁ and PEF found after the administration of salbutamol plus ipratropium in our study (over 40%) and the 25% reduction in hospital admissions were higher figures than have been reported in the majority of previous studies (3–25). In a systematic review, Rodrigo (3) found that the NNT for salbutamol plus ipratropium was 13, indicating that 13 children needed to be treated with β_2 agonists plus anticholinergics to prevent one admission, with an NNT of 7 in children with severe acute asthma. In comparison, the overall NNT in our study was 3.9, and

this fell to only 2.9 in children with severe asthma crises, highlighting the efficacy of combined treatment in these children.

This substantial reduction in the percentage of hospital admissions represents a major health benefit: on the one hand, avoiding the psychological distress of hospital admission for the child and the disturbance for the family and, on the other, significantly reducing hospital costs. These effects are even more relevant in countries with a lower socioeconomic level and those that do not have free hospital health care for the whole population.

In our study we found that the combination of salbutamol plus ipratropium produced an improvement in the clinical parameters (asthma score) and oxygen saturation, as well as in lung function tests compared with salbutamol as monotherapy. Although measurement of the FEV₁ and PEF is a good method for the objective assessment of the severity of a crisis and of the response to bronchodilator treatment, it does have certain limitations in children with acute asthma crises. In general, it can only be used in children over 6–8 years of age, as it requires good collaboration, and in children who frequently perform this test, as there is a degree of training involved. Furthermore, in patients with severe crises, forced expiration can exacerbate the bronchospasm. Clinical parameters such as the asthma score and saturation are less invasive measures to

TABLE 3.—Clinical and lung function parameters at the end of the study.

Characteristic	Salbutamol plus ipratropium bromide	Salbutamol plus placebo	P-value
Number	49	48	
Sao ₂ (%)	95.0 ± 2.4	92.2 ± 1.9	.0001
Asthma score	7.7 ± 2.1	9.7 ± 2.4	.0001
Hospital admission (%)	9 ± 18.4	21 ± 43.8	.007
Lung function (n)	32	33	
% of predicted FEV ₁	97 ± 25	69 ± 10	.0001
% of predicted PEF	93 ± 21	69 ± 12	.0001

Note: Data presented as percentages or mean ± SD.

TABLE 4.—Comparison of clinical and lung function parameters at the end of the study according to the severity of the asthma crisis.

Characteristic	Salbutamol plus ipratropium bromide	Salbutamol plus placebo	P-value
Moderate asthma crisis			
Number of patients	15	17	
Age (years)	10.9 ± 1.7	11.9 ± 3.4	.3
Sao ₂ (%)	95.1 ± 1.9	92.6 ± 1.8	.0006
Asthma score	7.0 ± 1.7	7.5 ± 1.3	.3
Hospital admission (%)	1 ± 6.7	2 ± 11.8	.6
Lung function tests	10	11	
% of predicted FEV ₁	102.5 ± 25.1	81.5 ± 5.5	.014
% of predicted PEF	94.9 ± 20.9	82.6 ± 9.3	.09
Severe asthma crisis			
Number of patients	34	31	
Age (years)	10.6 ± 1.9	10.9 ± 2.0	.5
Sao ₂ (%)	94.8 ± 2.5	92.0 ± 2.0	.0001
Asthma score	7.9 ± 2.1	10.0 ± 2.4	.0004
Hospital admission (%)	6 ± 17.6	16 ± 51.6	.004
Lung function tests	22	22	
% of predicted FEV ₁	93.9 ± 25.2	63.4 (3.7)	.0001
% of predicted PEF	92.2 ± 21.4	62.5 (4.7)	.0001

Note: Data presented as percentages or mean ± SD.

perform, can be used in all types of patients, and serve in practice to establish the treatment and hospital admission.

Although a number of adverse effects of ipratropium have been reported in adults, such as anisocoria or glaucoma (27, 28), we did not detect any of these adverse effects, confirming the safety of this drug. Only two patients had to be withdrawn from the study due to the onset of tachycardia, one in each therapeutic group, suggesting that ipratropium was not a triggering factor (21).

Our study had certain limitations. We did not register the number of previous hospitalizations due to asthma crisis nor the use of chronic medications except corticoids.

Although the number of patients included was large, their classification into moderate and severe asthma crises produced a smaller number in each subgroup: there were only 15 patients with moderate asthma crises treated with salbutamol plus ipratropium and 17 with salbutamol alone. As the need for hospitalization in moderate asthma crises is low, this small number of patients was one of the reasons that could explain the absence of statistically significant differences between these subgroups. Although the FEV₁ and Sao₂ improved significantly in this group, the improvement in the pulmonary asthma score was small. Further studies are necessary that include a larger number of patients to determine the clinical utility of the anticholinergic drugs in moderate asthma crises.

A systematic review found that the effect of salbutamol plus ipratropium was maintained independently of the administration of corticosteroids (3). Corticosteroids do not improve the initial results of salbutamol plus ipratropium in the emergency department because corticosteroids require 6–12 hours to reach its maximum effect (3). However, the current guidelines of asthma treatment recommend early administration of corticosteroids in children with moderate or severe asthma crises.

We conclude that the combination of salbutamol plus ipratropium bromide produces an improvement in lung function in asthmatic children with moderate to severe asthma crises, independently of age. The effect is greater in children with severe asthma crises with a significant reduction in the need for hospital admission in these children.

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DECLARATION OF INTEREST

The authors declare no conflicts of interest.

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