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Salbutamol and ipratropium by inhaler is superior to nebulizer in children with severe acute asthma exacerbation: Randomized clinical trial

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Abstract

Introduction: In moderate-severe asthma exacerbation, salbutamol by inhaler (MDI) is superior to salbutamol delivered by nebulizer (NEB); however, to our knowledge, no studies in children with exclusively severe exacerbations were performed.

Objective: To compare the efficacy of salbutamol and ipratropium bromide by MDI versus by NEB in severe asthma exacerbations.

Methods: We performed a clinical trial enrolling 103 children (2-14 years of age) with severe asthma exacerbations (defined by the Pulmonary Score ≥ 7) seen at the emergency room in Asuncion, Paraguay. One group received salbutamol and ipratropium (two puff every 10 min for 2 h and then every 30 min for 2 h more) by MDI with a valved-holding chamber and mask along with oxygen by a cannula separately (MDI-SIB); and the other received nebulization with oxygen (NEB-SIB) of salbutamol and ipratropium (1 every 20 min for 2 h and then every 30 min for 2 h more). Primary outcome was the rate of hospitalization (Pulmonary Score ≥ 7) after 4 h and secondary outcome was oxygen saturation.

Results: Fifty two children received MDI-SIB and 51 NEB-SIB. After the 4th hour, children on MDI-SIB had significantly ($P = 0.003$) lower rate of hospital admission than on NEB-SIB (5.8% vs 27.5%, RR: 0.21 [0.06-0.69], respectively). Similarly, a significant improved clinical score after 60 min and increase in oxygen saturation after 90 min of treatment was observed in MDI-SIB versus NEB-SIB group (4.46 ± 0.7 vs 5.76 ± 0.65, $P < 0.00001$; and 90.5 ± 1.7 vs 88.43 1 ± 1, $P < 0.00001$, respectively).

Conclusion: Even in severe asthma exacerbations administration of salbutamol and ipratropium by MDI with valved-holding chamber and mask along with oxygen by a cannula separately was more effective than by a nebulizer.

KEYWORDS
children, ipratropium, MDI, nebulizer, salbutamol, severe acute asthma

1 | INTRODUCTION

In the United States, 2.1 and 10.7% of children with asthma (ages 0-17 years) have been reported at least one hospitalization and at least one emergency room (ER) visit in the previous year, respectively.[1] In 2008, there were 10.5 million missed school days due to asthma among American schoolchildren.[1] Moreover, severe exacerbations are risk markers of both subsequent exacerbations and mortality from asthma.[2] Severe exacerbations negatively impact the quality of life and education of children with asthma, while also causing enormous health care costs. Without including prescriptions, costs related to exacerbations accounted for $9.8B (63.2%) of the estimated $15.5B total asthma costs in the U.S. in 2002.[3]

Meta-analysis showed that using salbutamol (or albuterol) by meter doses inhaler (MDI) with a valved holding chamber (VHC) in children with moderate-severe acute asthma exacerbation was more effective, that is, fewer hospital admissions, more clinical improvement, and had fewer adverse effects (tremor and tachycardia) than salbutamol by nebulizer.[4,5] For children with more severe asthma exacerbation adding ipratropium bromide to salbutamol results in a better response (less hospital admission, improvement in lung function, and clinical score) with less adverse effects (less nausea and tremor) than salbutamol alone.[6,7]

Therefore, several international guidelines recommend the use of salbutamol by MDI rather than by nebulizer for moderate-severe asthma exacerbations.[8–10] These findings result in changing the practice of acute asthma exacerbation in ERs replacing the nebulizers with MDIs, in addition, decreases the costs.[11]

However, no studies were performed in the subgroup of children exclusively with more severe acute asthma exacerbation comparing salbutamol and ipratropium bromide administrated by MDI versus by nebulizer. For this reason we conducted a randomized clinical trial comparing salbutamol and ipratropium bromide by MDI with VHC versus by nebulizer in severe acute asthma exacerbations in children attending in the ER. We hypothesize that using MDI will be more successful and with less adverse effects than by nebulizer.

2 | METHODS

This randomized clinical trial was conduct in the ERs of the Hospital Clinicas and the Instituto Privado del Niño, Asunción, Paraguay (mean: 133 meters above sea level). Children 2-18 years of age who came to the ER with severe acute asthma exacerbation (defined by the Pulmonary Score ≥ 7)[12] were eligible for the study. The Pulmonary Score[12] (Table 1) was taken after a period of adjustment of at least 5 min and with the child quiet, not crying, without fever, and breathing room air. Respiratory rate was determined by observation of the thoracic movement over a full minute. The degree of accessory muscle use was based on the degree of intercostal or subcostal retraction. The Pulmonary Score was usually used in our institutions. Exclusion criteria included clinical or radiologic pneumonia (chest X-ray was indicated according with a doctor's decision); pulmonary and/or cardiac congenital malformations; chronic pulmonary disease (bronchopulmonary dysplasia, cystic fibrosis, or post infectious bronchiolitis obliterans); foreign body aspiration; neurological alteration; or very severe acute asthma exacerbation with cardiopulmonary failure imminent or mechanical ventilation indication.

During the period from January 2013 to January 2017, 103 children who satisfied the inclusion criteria were enrolled in the study. In this single study, the investigators (R.I., A.J., N.B., and L.C.) blindly enrolled and evaluated all patients without knowledge of which treatment protocol they would receive. The study nurse/ER doctor collected the baseline demographic data from the parents of all eligible children and administered the treatment (without telling it to the investigators). Patients were randomly allocated using a computer random numbers table and a sealed envelope technique for allocation concealment, to either group, that is, salbutamol and ipratropium bromide by nebulizer (NEB-SIB), or salbutamol and ipratropium bromide by metered dose inhaler with valved holding chamber and mask along with oxygen by a cannula separately (MDI-SIB). The present study did not include a control group since the standard care in the hospital for children with severe acute asthma exacerbation is the use of beta-2-agonists. We felt it is unethical to withhold beta-2-agonists treatment from these children.

The Ethics Committee of the hospital reviewed and approved the protocol. Informed consent for participation in the study was obtained from the parents.

2.1 | Dosage and administration

Children in the NEB-SIB group received a 0.5% salbutamol aerosol solution (0.15 mg/kg weight, up to a maximum of 5 mg, Ventolin® GlaxoSmithKline, London, UK) in 5 mL of normal saline solution for 7 min every 20 min for 2 h, and then every 30 min for two more hours. Aerosol was generated by micro-nebulizer (Inhalar Compact, NS-Omron Co. Sao Paulo, Brazil) powered by compressed-air (5 L/min) with Y-connection with oxygen (3 L/min) and delivered via a face mask (Nanjing Winice Trade Co., Nanjing, China). In order to maintain a FiO2 between 35 and 40% a flow rate of oxygen used was 3 L/min by nasal cannula and saturation more or equal to 92%.

Children in the MDI-SIB group received two puffs of salbutamol MDI (100 mcg/puff, Ventolin® GlaxoSmithKline) every 10 min for 2 h, and then every 30 min for two more hours. MDI was administrated using a valved holding chamber and mask along with oxygen by a cannula separately (Mather Pharma® Asunción, Paraguay, volume of 350 mL, 15 cm long). After each puff the child performed eight inhalations. In order to maintain a FiO2 between 35 and 40% a flow rate of oxygen used was 3 L/min by nasal cannula and a saturation more or equal to 92%.

Both groups received ipratropium bromide between salbutamol administrated. Children in the NEB-SIB group received ipratropium bromide solution (250 mcg in children <20 kilos weight or 500 mcg in children >20 kg, Atrovent® Boehringer Ing., Ingelheim am Rhein, Germany) every 20 min for the first 2 h then every 30 min for 2 h more.

TABLE 1 Pulmonary score[12]

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

The Pulmonary Score ranges from 0 (no or very mild exacerbation) to 9 (severe exacerbation).

Those in the MDI-SIB group received two puffs of ipratropium bromide (20 mcg/puff, Aerotrop® Cassara Lab., Buenos Aires, Argentina) every 20 min for the first 2 h and then every 30 min for 2 h more. Additionally, children in both groups also received methylprednisolone 1 mg/kg EV and magnesium sulfate 50 mg/kg EV during the 1st hour of treatment.

2.2 | Assessment

Pulmonary Score [12] (Table 1), oxygen saturation (measured by GE Healthcare Dash 2500 Monitor, Milwaukee, WI) was recorded by the study nurse/ER fellow at baseline, 30, 60, 90, 120, and at 240 min (4th hour). After the end of the treatment (4th hour) a patient's success of treatment was determined if the patient had a pulmonary score ≤ 6; those with a higher score were admitted to the hospital (primary outcome). Oxygen saturation was the secondary outcome, and tachycardia was considered as an adverse effect of the therapy. Until this moment the investigators were blinded to the treatment received in each of the children. The children with a successful treatment were sent home with an asthma treatment plan prescribed by the attending pediatrician.

2.3 | Statistical analysis

To evaluate differences between NEB-SIB and MDI-SIB groups, the Chis square test was used for categorical variables. For continuous variables with normal distribution the Student *t*-test was used, otherwise Mann-Whitney test was used for those with non-normal distribution. A survival analysis by log rank test (Mantel-Cox) was performed for pulmonary score ≤ 6 between groups. The sample size of 40 patients in each group provided 90% power to detect a difference in hospitalization rate of 20% with a level of 0.05 and assuming a two-tailed test. Epi-Info® (CDC, Atlanta, GA) software was used for the analysis and $P < 0.05$ was consider as statistically significant.

3 | RESULTS

During the study period, 112 were initially enrolled (see CONSORT flow diagram on Figure 1). Nine children were excluded. The parents of three patients declined to participate; three children were excluded because of radiologic evidence of pneumonia; and, three had failure of treatment during the first 30 min of treatment (two belong to NEB-SIB and one to MDI-SIB). Of those 103 remaining children, 51 were in the NEB-SIB group and 52 in the MDI-SIB group, (Figure 1). All patients completed the study, and none were studied twice. The median [IQR] age was 5.0 [3-10] years, and 55% were males.

The groups did not differ significantly in gender, age, atopy (dermatitis or rhinitis), exposure to tobacco, and history of parental asthma (Table 2). Only, around 30% of the children in both groups were diagnosed with asthma, and there was found no difference in their treatment in the last 3 months (Table 2).

At baseline, there were no differences in Pulmonary Score and oxygen saturation between treatment groups (Table 3). The mean Pulmonary Score was 7 and the oxygen saturation was ~85% reflecting the severity of the acute exacerbation. From 60 min of treatment and until the 4th hour, children in the MDI-SIB group had significantly better pulmonary score index than those in the NEB-SIB group (Table 3). In the survival analysis, children in the NEB-SIB group had a significantly ($P < 0.0001$) higher chance to not have a pulmonary score ≤ 6 than those on MDI-SIB (Figure 2).

Also, the oxygen saturation (secondary outcome) was significantly higher from the 90th minutes of treatment and until the 4th hour in the MDI-SIB group than NEB-SIB group (Table 3 and Figure 3). In terms of the primary outcome, the necessity of hospitalization at the end of the 4th hour of treatment (Pulmonary Score ≥ 7), was significantly higher in the NEB-SIB versus the MDI-SIB group (RR: 0.21 [0.06-0.69], $P = 0.003$). Those children who failed the treatment were sent to the pediatric intensive care unit for non-invasive mechanical ventilation and more aggressive treatment. In relation to adverse effects, heart rate was significantly higher in the NEB-SBI than MDI-SIB group from the 30 min of treatment until the end of the study (Table 3).

4 | DISCUSSION

This randomized trial demonstrates that, in children with severe asthma exacerbations, the use of salbutamol and ipratropium bromide administrated by MDI and valved holding chamber was more effective than by nebulizer in decreasing hospital admission (~80% decrease),

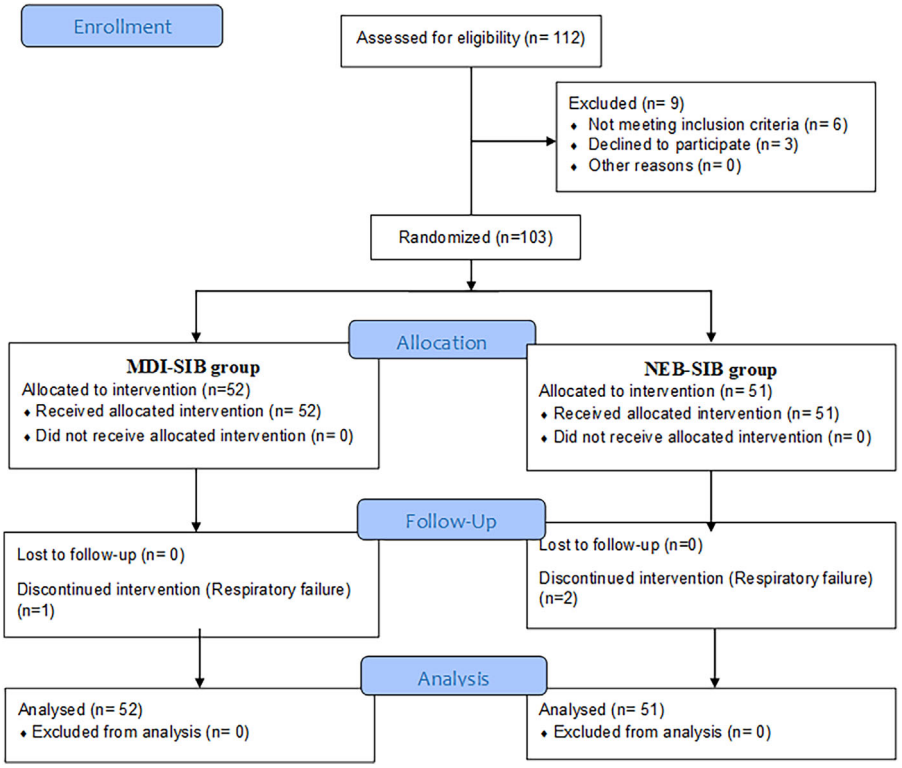

FIGURE 1 CONSORT flow diagram

clinical score and oxygen saturation, and fewer tachycardia. To our knowledge, this is the first trial done exclusively in children with severe asthma exacerbations, that is, at baseline the mean of oxygen saturation was ~85% and pulmonary score was ~7 out of 9.

Most guidelines[8–10] and recent reviews[13,14] recommend the use of salbutamol by MDI instead of by nebulizer for moderate-severe asthma exacerbation, but for severe acute asthma exacerbation when oxygen is needed the guidelines recommend the use of a nebulizer. The main reason is the necessity to use oxygen by nebulizer to avoid hypoxemia. However, in the present study adding oxygen by nasal cannula to the MDI-SIB resulted more effective than oxygen into a nebulizer in severe acute asthma exacerbation. A potential explanation for the superiority of MDI/spacer compared to nebulizer is the higher percentage of pulmonary deposition of the former.[15]

TABLE 2 Demographic characteristics of the study groups[a]

	MDI-SIB (n = 52)	NEB-SIB (n = 51)	P-value
Age (years)	5 [3-9.5]	5 [3-10]	0.67
Gender (male)	30 (57%)	27 (52.9%)	0.56
Atopy (dermatitis, rhinitis)	16 (30.8%)	18 (35.3%)	0.6
Parental asthma	15 (28.8%)	14 (27.5%)	0.8
Second hand tobacco exposure	17 (32.7%)	19 (37.3%)	0.7
Asthma diagnosis	16 (30.8%)	17 (33.3%)	0.7
Asthma controllers last 3 months			
ICS + LABA	17 (32.7%)	18 (35.3%)	0.7
ICS	16 (30.8%)	14 (27.5%)	0.7
Montelukast	17 (32.7%)	16 (41.4%)	0.8

MDI-SIB, MDI plus valved holding chamber; NEB-SIB, nebulizer.
[a]Numbers were expressed as (%), mean ± SD, or median [25-75 percentile] when correspond.

We found no improvement in clinical score at 30 min nor saturation at 60 min. These results are in accordance with a local study[16] and systematic reviews,[6,7] showing that only after repeated doses of salbutamol and ipratropium bromide a clinical effect is reached.

The administration of beta-2 agonists by MDI compared to the use of nebulizer is cheaper,[11] and since our study shows that it requires less hospitalization, we can expect an additional contribution using MDI to decrease the indirect costs associated to acute severe exacerbation asthma management in children. The exacerbations account for the majority of asthma-related costs and had a negative impact in the quality of life and education in children with asthma.[1–3] Also, many studies showed that the use of MDIs with spacers instead of nebulizers to deliver beta-2 agonist to treat children with mild-to-moderate asthma exacerbations in the ED could yield significant cost savings for hospitals and, by extension, to both the health care system and families of children with asthma.[17–19]

Children with moderate-severe asthma exacerbations receiving salbutamol and ipratropium by nebulizer had more frequent adverse

TABLE 3 Comparison of treatment between the two study groups

	MDI-SIB (n = 52)	NEB-SIB (n = 51)	P-value
Pulmonary score			
Basal	7.04 ± 0.19	7.06 ± 0.37	0.73
30 min	7.04 ± 0.19	7.00 ± 0.28	0.42
60 min	4.46 ± 0.7	5.76 ± 0.65	<0.00001
90 min	4.02 ± 0.83	5.08 ± 0.77	<0.00001
120 min	3.32 ± 0.83	4.49 ± 0.73	<0.00001
4 h	2.5 ± 1.0	4.15 ± 0.9	<0.00001
Oxygen saturation (%)			
Basal	85.0 ± 1.3	85.15 ± 0.8	0.59
30 min	85.3 ± 1.5	85.4 ± 1.4	0.57
60 min	87.8 ± 1.3	87.09 ± 0.8	0.097
90 min	90.5 ± 1.7	88.4 ± 1.1	<0.00001
120 min	92.8 ± 1.9	90.0 ± 1.8	<0.00001
4 h	95.3 ± 2.0	91.9 ± 1.9	<0.00001
Heart rate (beat/min)			
Basal	156.63 ± 1.84	156.54 ± 1.77	0.8
30 min	156.76 ± 4.88	160.17 ± 4.77	0.003
60 min	159.67 ± 7.29	166.84 ± 6.67	<0.00001
90 min	158.46 ± 8.24	166.84 ± 6.67	<0.00001
120 min	158.34 ± 5.10	173.05 ± 8.58	<0.00001
4 h	144.7692 ± 6.50	172.20 ± 9.52	<0.00001
Hospital admission at 4 h[a]	3 (5.76%)	14 (27.45%)	0.003

[a]Primary outcome.

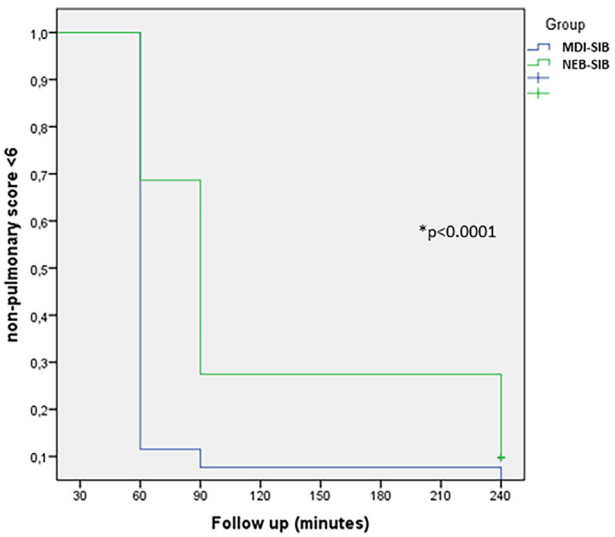

FIGURE 2 Survival analysis for non-pulmonary score <6 during the treatment between groups (*P < 0.0001, log rank test Mantel-Cox)

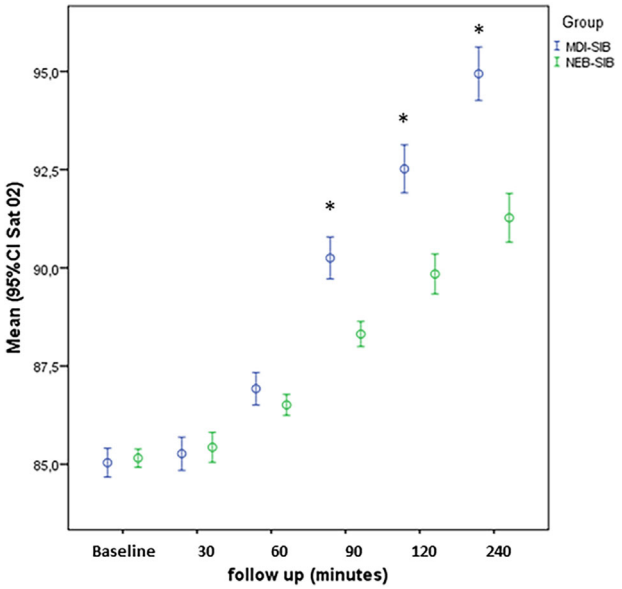

FIGURE 3 Oxygen saturation (mean and 95%CI) during the treatment between groups (*P < 0.0001)

effects than using MDI.[7] Moreover, our study showed that children with severe asthma exacerbation treated by nebulizer had a significantly higher heart rate starting 30 min of treatment compared to those with MDI. The explanation would be that nebulizers use higher doses of drugs, higher oral pharyngeal deposit, and more systemic absorption of the drug compared to MDI.[4,20] A recent meta-analysis done in adults/children with acute asthma in either the ED or in the community setting reported a lower incidence of side effects (eg, tremor, tachycardia, desaturations) with beta-agonist administrated by MDI compared to nebulizer.[17]

The present study has some limitations. First, no lung function (spirometry or PEF) was evaluated. However, an objective measurement, that is, oxygen saturation and pulmonary score was used. Second, we did not follow up on our patients after the ER discharge. However, at the end of the 4th hour of treatment the Pulmonary Score was very low and the saturation high enough expecting a very low chance of relapse. Third, no data on the age of asthma onset, and previous severe exacerbations and hospitalization, were recorded. Fourth, no other adverse effects (eg, vomiting, tremor) were evaluated.

In conclusion, even in children with severe asthma exacerbations that required oxygen use of salbutamol and ipratropium bromide administrated by MDI with valved holding chamber and mask along with oxygen by a cannula separately was more effective than by nebulizer in decreasing hospital admission (~80% decrease), improved clinical score and oxygen saturation. More trials need to be done to corroborate these new findings.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest to disclose relevant to this article.

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