

Randomized Trial of Salbutamol via Metered-Dose Inhaler With Spacer Versus Nebulizer for Acute Wheezing in Children Less Than 2 Years of Age

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Summary. The aim of this study was to compare the efficacy of salbutamol delivered via a metered-dose inhaler with a spacer and facial mask (MDI-S) vs. a nebulizer (NEB) for the treatment of acute exacerbations of wheezing in children. In a single-blind, prospective, randomized clinical trial, 123 outpatients (1–24 months of age), presenting with “moderate to severe” wheezing, were seen in the emergency department. Children were randomly assigned to one of two salbutamol treatment groups. In the first hour, the MDI-S group received 2 puffs (100 µg/puff) every 10 min for 5 doses, and the NEB group received 0.25 mg/kg every 13 min for 3 doses. If the clinical score was >5 at the end of the first hour, the patients received another hour of the same treatment and also betamethasone (0.5 mg/kg intramuscular). On enrollment and after the first and the second hour of treatment each child had a validated clinical score assigned by a blinded investigator.

There were no differences at the time of admission to the emergency department between groups in clinical score or demographic data. Success (clinical score ≤5) after the first hour of treatment was 90% (56/62) in the MDI-S group and 71% (43/61) in the NEB group (odds ratio 3.9, 95% confidence interval 1.5–10.4, $P = 0.01$). After the second hour, the success was 100% in the MDI-S and 94% in the NEB ($P > 0.05$).

We conclude that in this study population, children less than 2 years of age with moderate-severe exacerbations of wheezing responded faster to salbutamol delivered by MDI with a spacer and facial mask than to salbutamol delivered by nebulizer. **Pediatr Pulmonol.** 2000;29:264–269. © 2000 Wiley-Liss, Inc.

Key words: wheezing; metered-dose inhalers; spacers; nebulizers; salbutamol; children; randomized clinical trial.

INTRODUCTION

In Chile, acute respiratory diseases account for nearly 80% of children’s visits to health centers during the winter.¹ Moreover, approximately 25% of infants under 1 year of age living in Santiago (capital of Chile) have at least one wheezing episode per year. In addition, wheezing illnesses together with pneumonia are the leading cause of hospitalization for children in Chile.²

Previous studies using a clinical score have demonstrated the utility of beta-2-agonists administered by metered-dose inhaler (MDI) with a spacer and a face mask in the treatment of acute exacerbations of wheezing in infants^{3,4} and children.⁵ Furthermore, studies in adults⁶ and children over 2 years of age^{7–11} have shown that beta-2-agonists administered by MDI with a spacer device and a face mask are as effective as nebulization in the treatment of asthma or acute exacerbations of wheezing and result in fewer adverse effects (tachycardia, vomiting, and oxygen desaturation) than when salbutamol is delivered by nebulizer. To our knowledge, only one ran-

domized, not placebo controlled clinical trial has been reported in an infant population, and it demonstrated that MDIs with a spacer were as effective a delivery method for salbutamol as nebulization.¹² Another consideration which may be an important factor in the ambulatory management of this common problem is the fact that beta-2-

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TABLE 1—Clinical Score¹

Score	Respiratory rate (breaths/min)		Wheezing	Cyanosis	Accessory respiratory muscle utilization
	<6 months	≥6 months			
0	≤40	≤30	None*	None	None
1	41–55	31–45	Terminal expiration with stethoscope only	Circumoral on crying only	+
2	56–70	46–60	Entire expiration and inspiration with stethoscope only	Circumoral at rest	++
3	>70	>60	Expiration and inspiration without stethoscope	Generalized cyanosis at rest	+++

¹Validated clinical score.¹³ If no wheezing is audible due to minimal air entry, score 3*. Score: “mild” (1–5), “moderate” (6–7), “severe” (8–10), “very severe” (11–12). +(low), ++(medium), +++(high).

agonists administered by MDI with a spacer and face mask require less time and cost less than drug delivery by nebulization.^{11,12}

The aim of the present study was to compare the relative efficacy of salbutamol administered by nebulizer vs. an MDI with a spacer and a face mask in the management of “moderate to severe” acute exacerbations of wheezing in children less than 2 years of age treated in the emergency department.

MATERIALS AND METHODS

Study Population

This study was conducted in the Emergency Department, Exequiel Gonzalez Cortes Children’s Hospital, Santiago, Chile, an inner-city facility with approximately 90,000 patient visits per year. Nearly 65% of the visits are for acute exacerbations of wheezing during the winter months.

Children 1–24 months of age who came to the emergency department with “moderate to severe” wheezing (clinical score from 6–10¹³) were eligible for the study. A validated clinical score¹³ (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.¹³ We did not distinguish between infantile asthma and bronchiolitis, and did not assess the specific etiologic agents responsible for the illness. Exclusion criteria included clinical or radiologic pneumonia; pulmonary and/or cardiac congenital malformations; chronic pulmonary disease (bronchopulmonary

dysplasia, cystic fibrosis, or antecedent adenovirus pneumonia); foreign body aspiration; neurological alteration; and “very severe” wheezing attack (clinical score from 11–12).

During the winter and the beginning of spring (from June to November in the Southern Hemisphere), 132 children who satisfied the inclusion criteria were enrolled in the study. All had a chest roentgenogram performed. In this open study, one investigator (L.R.) blindly enrolled and evaluated all patients without knowledge of which treatment modality they would receive. Baseline demographic data were collected from the parents of all eligible children. Patients were randomly allocated to either group, using a table of random numbers, i.e., salbutamol by nebulizer (NEB), or salbutamol by metered-dose inhaler with a spacer and a face mask (MDI-S). The present study did not include a control group, as the standard of care in our hospital for “moderate to severe” acute exacerbation of wheezing in children is the use of beta-2-agonists. It was felt to be 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.

Dosage and Administration

The NEB group received a 0.5% salbutamol aerosol solution (0.25 mg/kg weight, up to a maximum of 5 mg, Butotal®, Danes-Grünenthal, Santiago, Chile) in 3.5 mL of normal saline solution. Aerosols were generated by jet nebulizer (Hudson UP Draft II, model 1730, Hudson Oxygen Sales Co., Temecula, CA) powered by either compressed-air (if the clinical score was between 6 and 7) or oxygen (if the clinical score was between 8 and 10) and delivered via a face mask for 7 min every 20 min during the first hour (a total of three nebulizations/hr). A flow rate of 7 L/min was used as measured by a rotameter (Thorpe 1-15 L/min, model 2562, Hudson).

Children in the MDI-S group received 2 puffs of sal-

Abbreviations

MDI	Metered-dose inhaler
MDI-S	Salbutamol delivered via metered-dose inhaler with a spacer and facial mask
NEB	Salbutamol delivered via nebulizer

butamol MDI (100 µg/puff, Butotal®, Danes-Grünenthal) every 10 min 5 times over 1 hr (a total of 10 puffs/hr), using a spacer device with a face mask (volume of 500 mL, 15 cm long and with a one-way valve; Aero-cell®, Danes-Grünenthal). Following each puff the children took eight breaths from the spacer device held in place.¹⁴ Most of the children cried when the spacer was applied, but there were no problems in administering the complete dose. Oxygen was administered by nasal cannulae whenever the clinical score was between 8 and 10.

The doses used in the NEB and MDI-S groups were similar to those recommended by Chile's Acute Respiratory Infection National Program.¹⁴ In both groups, therapy and oxygen were administered by a certified registered chest physiotherapist (M.M.) without informing the enrolling physician of which treatment modality was used.

Assessment

After the first hour of treatment, the patients were reevaluated. We considered the therapy a success when the clinical score was ≤ 5 . If the clinical score was >5 , the children received another hour of the same treatment and also betamethasone (0.5 mg/kg intramuscular) and oxygen therapy. When the clinical score was still >5 after the second hour of treatment we considered the treatment a failure, and the children were hospitalized. The scoring system and the indications for hospitalization were previously validated;¹⁴ Chile's Acute Respiratory Infection National Program uses the same protocol throughout the country. Figure 1 provides the flowchart of the treatment protocol and patient assessment. In addition, during the first hour of treatment, all patients received one session of chest therapy with vibration and compression-decompression techniques (without clapping) executed by the same chest physiotherapist.

Statistical Analysis

To evaluate differences between groups, the Chi-square test was used for categorical variables and Student *t*-test for continuous variables. The sample size of 60 patients in each group provided greater than 90% power to detect a difference in the clinical score of 1, given a standard deviation (SD) of 1.5 with an α level of 0.05 and assuming a two-tailed test.

RESULTS

One hundred thirty-two patients were initially enrolled. The parents of two children declined to participate in the study. Seven children were excluded from the study because of radiologic evidence of pneumonia. Of those remaining, 61 were in the NEB group and 62 in the

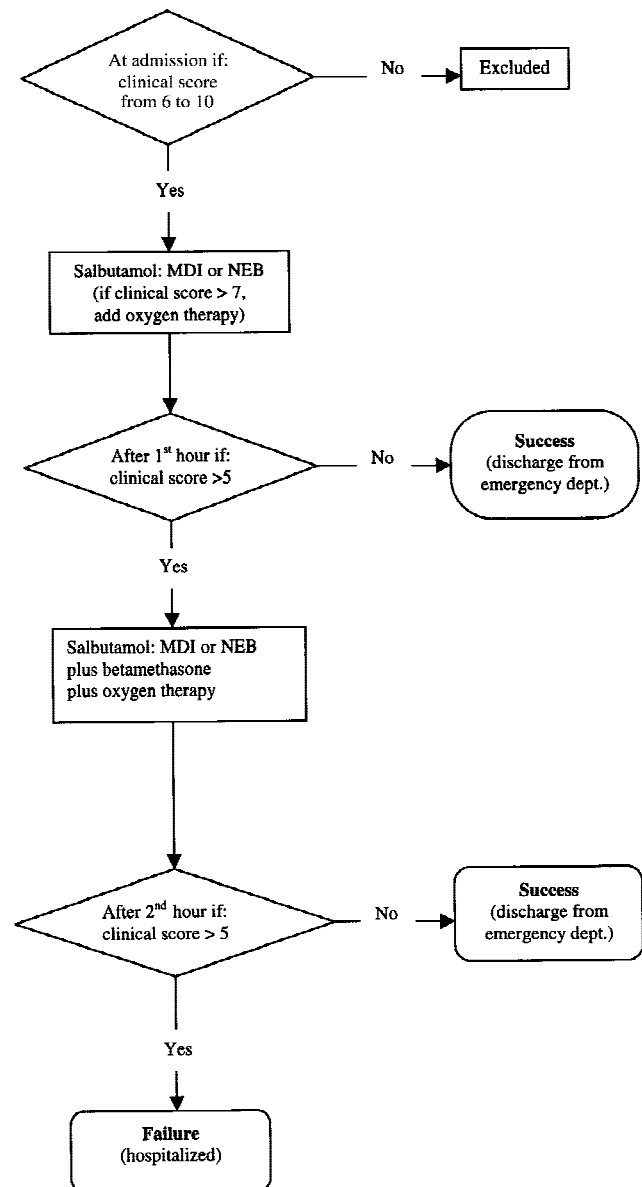


Fig. 1. Flowchart of treatment.

MDI-S group. All patients completed the study, and none were studied twice. Most of the children were under 1 year of age (mean \pm SD, 8.5 ± 5.4 months for the NEB group and 7.2 ± 4.7 months the MDI-S group, $P > 0.5$; Table 2). The distribution of children under 6 months of age was also similar: 22 in the NEB and 27 in the MDI-S groups.

The groups did not differ significantly in demographic characteristics, exposure to indoor pollution, or a history of asthma and atopy in first-degree relatives (Table 2). There were no significant differences between groups in terms of age at first wheezing episode, percentage of prior hospitalizations for wheezing, or number of previous wheezing episodes (Table 2). The number of first-time wheezing children was 17 in the NEB group and 19

TABLE 2—Demographic and Historical Characteristics of the Two Study Groups*

	NEB (n = 61)	MDI-S (n = 62)
Gender (M/F)	41/20	42/20
Age (months) ¹	8.5 ± 5.4	7.2 ± 4.7
Birth weight (g) ¹	3,420 ± 684	3,511 ± 823
Asthma and atopy in first-degree relative (%)	18	20
Indoor pollution		
Parental smoking (%)	67	52
Kerosene stove (%)	70	58
History of wheezing		
Age at first attack (months) ¹	4.0 ± 2.5	3.6 ± 0.8
Previous attacks (no.) ¹	3.3 ± 3.2	2.6 ± 2.0
Previous hospitalizations (%)	33	32

¹Mean ± SD.**P* > 0.5 (no significance), for all comparisons between the two groups.

in the MDI-S group. The percentage of children who received antiasthmatic medications in the previous 48 hr was 24.6% in the NEB group and 27.4% in the MDI-S groups. Moreover, the duration of symptoms prior to the current wheezing episode was similar in both groups (mean ± SD, 3.7 ± 2.0 vs. 3.6 ± 3.0 days, NEB vs. MDI-S, respectively, *P* > 0.5).

Children in both groups had similar clinical scores on entry (mean ± SD, 7.4 ± 0.9 in the NEB group vs. 7.1 ± 1.0 in the MDI-S, *P* > 0.5; Table 3). However, after the first hour of treatment, 90% (56/62) of patients in the MDI-S group had clinical score ≤5 (success) vs. only 71% (43/61) in the NEB group (odds ratio (OR) 3.9, 95% confidence interval (CI) 1.5–10.4, *P* = 0.01). Also, the mean ± SD of the clinical score was significantly different between groups (mean SD, 3.3 ± 1.4 in the MDI-S group vs. 4.4 ± 1.5 in the NEB group, *P* = 0.01; Table 3). At the end of the second hour of treatment, the success was 100% in the MDI-S group vs. 94.4% in the NEB group (*P* > 0.5; Table 3). Changes in clinical score from admission to 1 hour after treatment also showed a significant difference between children in the NEB group vs. MDI-S group (mean ± SD, 2.9 ± 1.2 vs. 3.8 ± 1.0, respectively, *P* < 0.0001); changes from admission to the second hour after treatment were 4.0 ± 0.8 in the NEB group vs. 5.3 ± 0.8 in the MDI-S group (*P* = 0.002). Finally, one patient in the NEB group was hospitalized due to treatment failure. Transitory tremor was found in 3 children in the NEB group and in 1 in the MDI-S group; no children worsened following either treatment.

Results did not change in the subanalysis of children under 6 months of age (n = 22 in the NEB and n = 27 in the MDI-S group). After the first hour of treatment, the success was 72.7% in the NEB group vs. 96.0% in the MDI-S group (*P* = 0.035); after the second hour of treatment the success was 100% in both groups. The results also did not change when the population was di-

TABLE 3—Comparison of Treatments

	NEB (n = 61)	MDI-S (n = 62)	<i>P</i>
Respiratory rate (min ⁻¹)			
On admission	55.3 ± 7.8 ¹	56.2 ± 7.1	NS
After first hour	45.1 ± 6.9	38.8 ± 6.0	0.0001
After second hour	43.8 ± 3.8	37.3 ± 6.8	0.01
Clinical score: On admission			
Score from 6 to 7	37/61 (61%)	43/62 (69%)	NS
Score from 8 to 10	24/61 (39%)	19/62 (31%)	NS
Mean score ± SD	7.4 ± 0.9	7.1 ± 1.0	NS
After first hour			
Score ≤5 (success)	43/61 (71%)	56/62 (90%)	0.01
Mean score ± SD	4.4 ± 1.5	3.3 ± 1.4	0.01
After second hour			
Score ≤5 (success)	17/18 (94%)	6/6 (100%)	NS
Mean score ± SD	4.2 ± 1.0	3.5 ± 0.8	NS

¹Mean ± SD. NS, no significance.

vided into children with a first wheezing episode and those with a history of more than one wheezing episode. In the subanalysis of children with more than one wheezing episode (n = 44 in the NEB and n = 43 in the MDI-S group), the success after the first hour of treatment was 72.7% in the NEB group vs. 90.7% in the MDI-S group (*P* = 0.03); after the second hour, the success was 97.7% vs. 100%, respectively (*P* = >0.5). In the subanalysis of first-time wheezing children (n = 17 in the NEB and n = 19 in the MDI-S group), the success after the first hour of treatment was 72.7% in the NEB group vs. 89.5% in the MDI-S group (*P* = 0.07); after the second hour, the success was 100% in each group.

DISCUSSION

The results of this randomized trial suggest, for the first time to our knowledge, that delivery of salbutamol by MDI with a spacer and a face mask results in equivalent improvement, but faster symptom resolution compared to a higher dose of salbutamol delivered by nebulizer for treatment of children less than 2 years of age who present with an acute “moderate to severe” exacerbation of wheezing to the emergency department. Success after the first hour of treatment (clinical score ≤5) was 90% in the MDI-S group vs. 71% in the NEB group (*P* = 0.01); however, both methods were 99.2% successful after 2 hr of treatment. In terms of hospitalization rate, our results were similar to a previously published series.¹⁴ The present study did not include patients with “very severe” wheezing (clinical score from 11 to 12), because according to the policy of our National Program,¹⁴ those children must be hospitalized immediately; therefore, we cannot extrapolate our results to the entire spectrum of severity of illness.

To evaluate the severity of acute wheezing, we se-

lected a clinical score because this method is simpler and more reproducible than pulmonary function tests, which are cumbersome and require sedation in this age group.^{7-9,15} Although our clinical scores had subjective parameters, most of the changes in score were due to respiratory rate, which is an objective parameter with less observer bias. Moreover, our group recently demonstrated a good correlation ($r = -0.76$, 95% CI -0.68 to -0.83 , $P = 0.0001$) between this modified tal's clinical score and pulse oximetry.¹³ Pulse oximetry or pulmonary function tests were not used in this study because it is not always available in the primary care center, where most children with acute wheezing are seen in Chile.¹⁴ The use of chest therapy in acute bronchial obstruction is controversial, with one study showing no benefit in using percussion technique in infants with bronchiolitis.¹⁶ However, the present study was done in children with several clinical conditions (children with asthma or bronchiolitis) and used a different chest therapy technique that does not include percussion and is part of our Acute Respiratory Infection National Program protocol.¹⁴

In our study, the dose of nebulized salbutamol (0.25 mg/kg weight, maximum of 5 mg) was higher than in other studies (0.15 mg/kg, maximum of 5 mg).^{7,17} Previous studies showed a wide ratio of beta-2-agonist doses administered by MDI with a spacer and a face mask vs. by nebulizer (ratio from 1:1 to 1:10).^{5,6,11} In the present study, the ratio had a range from 1:3 to 1:7 (according to total doses/body weight).

Kerem et al.⁷ demonstrated in 33 children over 6 years of age that salbutamol administered by MDI with a spacer had the same efficacy (using a clinical score and spirometry) and fewer side effects (tachycardia) than salbutamol administered by nebulizer in the treatment of acute asthma exacerbation. Similarly, Chou et al.,⁸ in a randomized study with 152 children over 2 years of age with acute asthma exacerbation, found the same efficacy with shorter delivery time and fewer side effects from albuterol administered by MDI with a spacer and mouth-piece or face mask than salbutamol delivered by a nebulizer. In our study, the patients who received salbutamol by MDI with a spacer improved in a shorter time than when the drug was given by nebulizer. Moreover, Parkin et al.¹² studied 60 hospitalized children under 5 years of age (mean \pm SE, 35 ± 1.9 months) with moderate acute asthma and showed that salbutamol administered by MDI with a spacer device was as effective as when given by nebulizer. In that study the incidence of relapse was similar in both groups during 2 weeks of follow-up. In our study population, only one child given NEB treatment failed to achieve resolution of symptoms with the treatment given as part of this study and required admission. We did not follow our population after discharge from the emergency department; since our children were discharged with very low clinical scores, we expected no

relapses. Yung-Zen and Kue-Hsiung,⁹ in a randomized study with 111 children from 5 to 16 years of age with asthmatic crises, demonstrated that a beta-2-agonist administered by MDI with a spacer device and a face mask was superior (based on forced expired volume in 1 sec and peak expired flow) and was associated with fewer adverse effects (desaturation) than when delivered by nebulizer. Finally, our results are an agreement with those Closa et al.,¹⁸ who found that terbutaline administered by an MDI with a spacer had the same efficacy (using a clinical score and pulse oximeter) as when the drug was administered by nebulizer in infants with acute wheezing.

Other differences worth noting between use of a nebulizer vs. an MDI with a spacer and a face mask are that nebulizer devices are more expensive, more cumbersome to use, and require electrical power.⁷⁻⁹ It is also known that a nebulizer device is an inefficient method of drug delivery; up to 90% of the administered medication remains in the apparatus or is lost to the atmosphere.⁷ Finally, there are many factors that influence the efficiency of drug delivery by nebulizer, namely the type of nebulizer, and the volume, temperature, concentration, and osmolarity of the solutions used.¹⁹⁻²¹ An MDI with a spacer and a face mask also has advantages when large populations are treated in a primary care center.¹¹ MDIs with a spacer and a face mask are simpler to use, more compact, and more portable, and take less time to give a treatment than nebulizers.⁷⁻⁹ In addition, the spacer with a face mask is less expensive than a nebulizer, and it can be reused after sterilization in the emergency department or at home. Likewise, Bowton et al.²² found a 25% reduction in monthly costs after substitution of nebulizers with MDIs in a large adult tertiary care center. It has been demonstrated that the use of MDI systems in the pediatric emergency department and health center services helps children learn correct inhalation techniques.²³ Utilization of spacer devices with face masks eliminates young children's inability to coordinate inspiration with aerosol delivery and thereby increases aerosol deposition in the lung.²² However, recent studies have shown a substantial within-subject variability in children using MDI-S with plastic or metal spacers at home,²³ making it important to know the performance of the different inhalation devices²³ and also the correct doses of the drug²⁴ if treatment is to be optimized. Therefore, when dealing with a common symptom like wheezing, all of these concerns are important factors and need to be taken into consideration.¹⁴

In conclusion, this study suggests that children less than 2 years of age who were treated in the emergency department with a standardized protocol for "moderate to severe" acute wheezing responded faster to salbutamol delivered by an MDI and a spacer and a face mask than when delivered by nebulizer.

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