Is Nebulized Aerosol Treatment Necessary in the Pediatric Emergency Department?*

Comparison With a Metal Spacer Device for Metered-Dose Inhaler

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Background: **Infants and small children admitted to the pediatric emergency department (PED) with acute wheezing episodes (AWE) are currently treated with nebulized wet aerosol (NWA).**
Objective: **To determine the efficacy of MDI with Nebuchamber (Astra AB; Lund, Sweden), a nonelectrostatic spacer device (NESD), as compared to NWA in the treatment of an unselected population of babies and small children with AWE.**
Design: **Randomized, double-blind, placebo-controlled trial. Forty-two children referred to the PED (median age ± SD, 16 ± 15 months) with AWE received either placebo MDI through a NESD (four puffs) and salbutamol 0.5 mL (2.5 mg) as a NWA (group I, n = 19), or salbutamol MDI and 0.5 mL of saline solution administered in the same manner as above (group II, n = 23). This treatment was repeated three times every 20 min.**
Results: **The respiratory rates (RRs) at baseline were as follows: group I, 45 ± 11.2 breaths/min; and group II, 52.3 ± 11.3 breaths/min (p = not significant [NS]). After the first, second, and third interventions, the percent fall from baseline of the RR were as follows: group I, 8.9, 13.1, and 17.9%, respectively; group II, 8.6, 14.6, and 18.6%, respectively. There was no significant difference at any time in the results between the two groups. The clinical scores (CSs) at baseline were as follows: group I, 6.6 ± 1.3; group II, 6.8 ± 1.49 (p = NS). After the first, second, and third interventions, the percent fall from baseline of the CS were as follows: group I, 9.1, 17.9, and 23.2%, respectively; group II, 8.6, 18.9, and 24.7%, respectively. These results, also, did not differ significantly at any time between the two groups. Hospitalization rate and side effects did not differ between the two groups.**
Conclusions: **We conclude that even in the group of unselected very young children (mean age < 2 years) with AWE, the use of MDI with NESD is at least as effective as the use of NWA. As opposed to data from an adult population, no plateau was reached in the dose-response curve using the above doses over time.** ***(CHEST 2000; 117:1309–1313)***

Key words: β_2-agonist; metered-dose inhaler; salbutamol; spacer device

Abbreviations: AWE = acute wheezing episodes; CS = clinical score; MDI = metered-dose inhaler; MDI-S = metered-dose inhaler with a spacer device; NS = not significant; NWA = nebulized wet aerosol; PC = percent change; PED = pediatric emergency department; RR = respiratory rate

Nebulized wet aerosol (NWA) delivery of salbutamol is still considered the main therapeutic option in the management of wheezing episodes in children in the emergency department.[1] However, wet aerosol therapy is expensive.[2] An electric compressor or compressed gas source is needed, generally requiring much higher doses of bronchodilators (10 times), as compared with the use of a metered-dose inhaler (MDI) with a spacer device (MDI-S) to obtain the same effect.[2–13] Wet inhalation equipment is at risk of contamination if meticulous maintenance is not applied. The common

For editorial comment see page 1226

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belief that wet inhalation is more effective is seemingly based more on faith and tradition than on solid evidence.[2–13] Several articles published mainly in the last decade have demonstrated that the use of an MDI-S with a large spacer is at least as effective as nebulized therapy in adults with asthma,[5–8,10–16] and also in pediatric asthmatic patients.[1]

The continuing use of wet aerosol inhalation of bronchodilators for children admitted to the department of emergency medicine with acute wheezing episodes (AWE) is probably based on the belief that these children are either too young or too sick to comply with the use of MDI-S.

Many articles examining the efficacy of MDI-S looked at selected populations of young adults and older children with mild to moderate airflow obstruction.[15–20] These populations may not be representative of children presenting to the emergency department with AWE. The attack may be quite severe; the child may be small or an infant. One article compared salbutamol delivery through wet aerosol to MDI-S in an unselected population of adults with severe airflow limitation.[16] The clinical and the objective bronchodilator responses to the administration of salbutamol were found to be independent of the method of delivery: MDI-S vs aerosol nebulization.

With regard to small children and infants, little information exists in the literature about the efficacy of bronchodilators delivered through MDI-S in the pediatric emergency department (PED) during AWE. We are aware of only one controlled study comparing wet inhalation with MDI-S performed in infants seen in PED for acute wheezing.[21]

We hypothesized that bronchodilator delivery through MDI-S in the PED during AWE is as effective in small children and infants as wet aerosol nebulization, and may therefore serve as an alternative method.

Materials and Methods

Devices

The MDI was discharged into a pear-shaped, nonelectrostatic, commercially available metal spacer with a volume of 250 mL and equipped with integrated inlet and outlet valves for inspiration and expiration (Nebuchamber; Astra AB, Lund, Sweden), and a rounded face mask (K.T.R. mask for Nebuchamber; Silicon; Degania, Israel; Fig 1). The pressure drop required to open the valve is 1.02 to 1.27 cm H_2O at a flow rate of 15 L/min. Instruction for use and coaching were provided according to the pamphlet provided by the manufacturer.

We utilized a nebulizer (Aeromist Nebulizer Set 61400; B&F Medical by Allied; Toledo, OH) that is routinely available in our PED, connected to a source of pressurized oxygen, from the wall, set to a flow rate of 5 L/min. This device has an output of 3 mL in 6 min, an aerodynamic diameter mass medium of 0.5- to 4-μm range, and a geometric SD of 96% of all liquid nebulized.

Figure 1. The metal spacer device used in the study.

Study Design

The study design was a randomized, double-blinded, double-dummy, placebo-controlled trial. Signed informed consent was obtained from the parents of each child, and the human ethics committee (Helsinki) of our hospital approved the study. Forty-two children of both genders who visited the PED of the Edith Wolfson Medical Center for acute wheezing during the winter of 1997–98 were selected. Their median age was 16 ± 15 months (range, 10 months to 4 years). Most of the children (30 of 42) were referred by their primary physician or by the regional walk-in clinics because of the severity of their attacks. The following exclusion criteria were used: cardiac illness, chronic respiratory disease other than asthma, and obtunded consciousness and/or progressive respiratory failure requiring mechanical ventilation.

The patients were selected (in a double-blind, randomized fashion) in permuted blocks of four patients. To ensure that age would be balanced in the two study groups, separate selection was performed for children < 24 months old and > 24 months old. All eligible patients were randomly assigned according to order of arrival to one of two groups: group I received wet aerosol inhalation of salbutamol, 2.5 mg (0.5 mL) with 1.5 mL saline solution and four puffs of placebo MDI delivered through a spacer with face mask; group II received wet aerosol inhalation of 2 mL saline solution and four puffs of salbutamol MDI-S with face mask (400 μg). Patients in each group received three treatments, delivered at intervals of 20 min.

At entry time and 20 min after the beginning of each treatment session (15 min after each treatment ended), the following parameters were measured and recorded using a clinical score (CS): (1) objective measures, respiratory rate (RR), pulse rate, and pulse oximetry data; and (2) subjective measures, (wheezing, reduced intensity of breath sounds, and retractions). This scoring system (based on Williams et al[1]) assigns a number from 1 to 4 to each variable, with increased severity receiving a higher score. We modified this for small children and infants by omitting the subject dyspnea symptom.

After randomization, the intended therapy was begun. The principal investigator repeated the clinical assessment 20 min after the beginning of each treatment. Neither the investigator nor the treatment personnel were aware of the therapy the patient had received.

Every child with oxyhemoglobin saturation $< 92\%$ received oxygen therapy. The combination of the therapeutic package

(salbutamol vs saline solution, and placebo MDI vs salbutamol MDI) was not available to the investigator; the code was deposited with the statistician.

Safety Criteria: Salbutamol is a frequently used medication with an excellent safety profile.[21] The investigator planned to cease therapy on observation of side effects (*ie*, restlessness, tachycardia, and tremor).

Statistical Methods

Two major outcomes of interest were considered: RR and CS. Other minor outcomes were pulse rate, oxyhemoglobin saturation on room air, tremor, and other adverse effects. These parameters were measured at four points of time (0, 20, 40, and 60 min).

This doubly multivariate repeated measure design was estimated and tested by the SPSS (SPSS; Chicago, IL) corresponding general linear model to evaluate changes in time. Model assumption was checked, and when deviation was found, the p value was corrected by the Greenhouse-Geisser epsilon. Means of the RRs and CSs at baseline, although not statistically different, were not equivalent for the two groups. Therefore, the percent change (PC) from baseline was calculated. PC is calculated as follows: at baseline, PC = 0; and posttreatment, PC = 100 (posttreatment/baseline)/baseline. Specific contrasts were tested by *post hoc* paired or unpaired *t* test and Fisher Exact Test when appropriate. The mean ± SD expresses the central tendency of the data. Mean ± SE was used in Figures 1, 2.

Based on a preliminary sample, 1.3 points and a 5% change were assumed to be a clinically significant change for the CS and RR, respectively. An appropriate sample size was calculated assuming 95% confidence and a 90% statistical power.

Power Calculation: Using the method based on two independent means, our results show that the use of 42 subjects (≥ 19 patients in each group) was sufficiently sensitive to detect differences of 0.8 points in CS and of 6 breaths/min with 80% power, and to detect differences of 1.3 points in CS and 10 breaths/min with 90% power, assuming an a error of 0.05.

Results

Of the 42 children who took part in the study, 19 were enrolled to receive placebo MDI through a nonelectrostatic spacer device (four puffs) and salbutamol, 0.5 mL (2.5 mg) as a NWA (group I), and 23 to receive salbutamol MDI and 0.5 mL saline solution administered in the same manner as above (group II). The two groups had similar clinical characteristics and variables at baseline (Table 1).

The RRs at baseline were 45 ± 11.2 in group I and 52.3 ± 11.3 in group II, (p = not significant [NS]). After the first, second, and third interventions, the percent fall of the RR from baseline was as follows: group I, 8.9, 13.1, and 17.9%, respectively; group II, 8.6, 14.6, and 18.6%, respectively (Fig 2). The results did not differ significantly at any time between the two groups.

The CSs at baseline were 6.6 ± 1.3 in group I and 6.8 ± 1.49 in-group II (p = NS). After the first, second and third interventions, the percent fall from baseline of the CS was as follows: group I, 9.1, 17.9, and 23.2%, respectively; group II, 8.6, 18.9, and 24.7%, respectively (Fig 3). These results did not differ significantly at any time between the two groups. There were no adverse effects in either group. Thirteen of 42 patients (31%) had to be admitted; the hospitalization rate did not differ significantly between the two groups. The pulse rate and the room air saturation of oxyhemoglobin did not differ at any time between the two groups.

Discussion

Our study shows that with an unselected group of infants and small children referred to the PED for episodes of moderate to severe airflow limitation, the clinical effects of the administration of salbutamol are independent of the method of delivery: MDI-S vs aerosol nebulization.

As opposed to some data from adults,[16] the dose-response curve for both treatments groups did not reach a plateau using three inhalations every 20 min (Fig 1, 2). This observation may lead to the possible conclusion that more inhalations must be tried before assuming a maximal dilatation dose/effect of salbutamol in infants and small babies.

A current consensus conference concluded that in adults, an MDI with reservoir chamber is the preferred mode of aerosol therapy for patients outside of the hospital.[22] We have recently reported that even in an unselected adult group of patients referred to the department of emergency medicine for

Table 1—*Clinical Characteristics

Characteristics	MDI-S, Group II (n = 23)	Wet-INH, Group I (n = 19)	p Value
Age, mo	24.1	23.5	NS
Female/male, No.	15/8	14/5	NS
First wheezing episode	19 (82.6)	16 (84.2)	NS
Passive smoking	13 (56.2)	11 (57.9)	NS
Bronchodilator treatment within 4 h before presentation	16 (69.5)	11 (57.8)	NS
Steroid treatment within 1 wk before presentation, No.	6	5	NS

*Data are presented as No. (%) unless otherwise indicated; INH = inhaler.

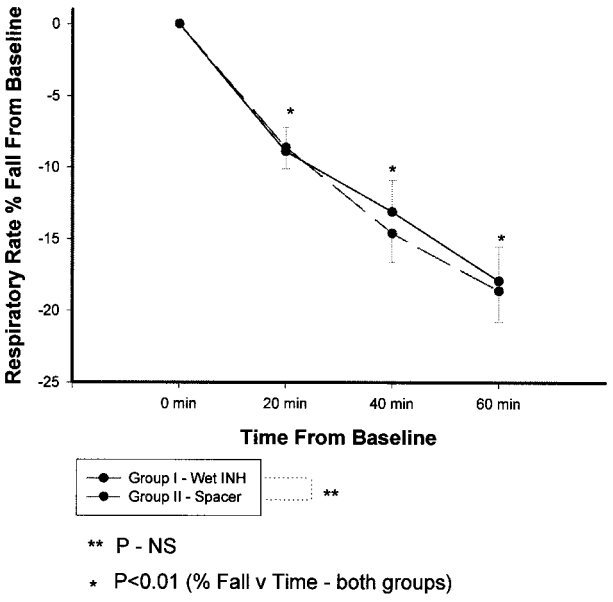

FIGURE 2. Percent fall of RR from baseline. v = vs; see Table 1 for abbreviation.

episodes of severe airflow limitation, salbutamol delivered through MDI with spacer is at least equivalent to NWA salbutamol inhalation therapy.[16]

The pediatric literature considering MDI-S is scanty and deals with children > 4 years old and with selected populations, mostly mild to moderate AWE.[1,15,23,24] Our patient population, mostly infants and small children (median age, 16 ± 15 months), also included severe cases, 13 of 42 patients (31%)

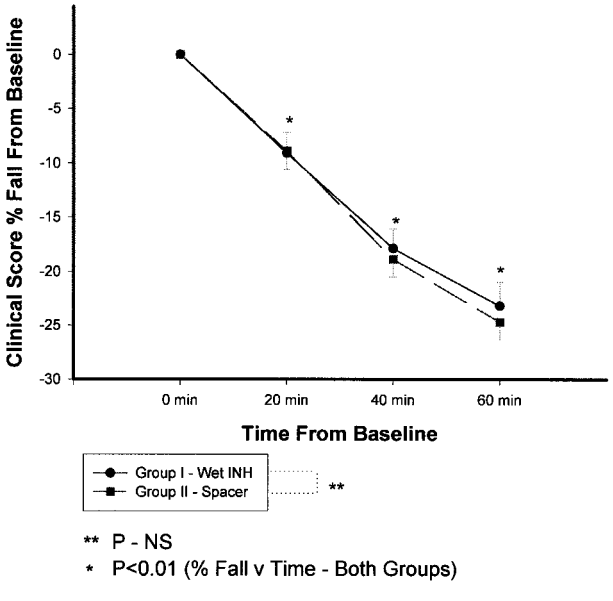

FIGURE 3. Percent fall in CS from baseline. See Figure 2 and Table 1 for abbreviations.

needing hospitalization. In the study by Closa et al,[21] only 8 of 34 subjects (24%) were hospitalized.

We used the small volume Nebuchamber in order to compensate for the small tidal volume of the infants and small children we studied. A smaller holding chamber contains a higher concentration of aerosol and requires less time to empty, but the total dose contained in airborne droplets is reduced as a result of impaction, absorption, sedimentation, and coagulation of aerosol.[24] Therefore we chose this nonelectrostatic spacer, which has a prolonged and a more predictable half-life of the available drug, as compared to other spacers available.[24,25]

The only work that compared the efficacy of MDI-S vs NWA in the delivery of β-agonists in babies and small children with acute wheezing attack has been published recently.[21] In this study using terbutaline, Closa et al[21] also conclude that, using their doses and techniques, MDI-S and nebulizer are equally effective in administering inhaled β-agonists to infants and young children. However, our study differs from this study in several regards: (1) we used placebo MDI and placebo wet inhalation as well to ensure a full double-dummy design, so that no one was aware of the therapy the patients had received. In contrast, in the study by Closa et al,[21] the treating personnel were aware of the treatment choice since no placebo was used; (2) all the assessments in our study were performed by a single principal investigator, presumably resulting in less interpersonal variability; (3) we repeated the compared treatment three times as opposed to only two times in the other study, so that we could appreciate a dose-response curve using more than two points in time. We chose three inhalations every 20 min because in adults this seemed to be the usual maximal dilatation dose and plateau point; (4) Closa et al[21] also used a small spacer device (Aerochamber; Trudell Medical Group; London, Ontario, Canada). They did not mention if priming was done before delivery. The Aerochamber (which, in its own right, is a useful delivery device for the treatment of young children) is an electrostatic chamber made of plastic and therefore highly dependent on priming and washing. Its dose delivery is less constant than the Nebuchamber, a difference that is mostly pronounced in small children and infants.[24,25] The small volume, nonelectrostatic spacer made of steel (Nebuchamber) has a higher dose delivery that is stable and independent of priming and washing. Indeed, the estimated dose delivery in small droplets from the nonelectrostatic spacer was shown to be approximately double that of the delivery from the Aerochamber (even after priming).[25] We believe that these facts increase the strength of our study supporting the idea that MDI-S can be used instead of

wet inhalation in the delivery of β-agonists, even in a relatively unselected population of wheezy infants and small children.

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