

Different inhaler devices in acute asthma attacks: a randomized, double-blind, placebo-controlled study

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Abstract

Objective: To verify the efficacy, side effects, and cost of treatment of acute asthma attacks, using different inhaler devices.

Methods: This is a randomized, double-blind, placebo-controlled study. Salbutamol was administered via a nebulizer, a metered-dose inhaler (attached to a commercially available spacer device), a homemade non-valved spacer device, or a dry powder inhaler. Assessments were made at zero, 20, 40 and 60 minutes, followed by the application of salbutamol and placebo with another device. Forty children (mean age of 11 ± 3.5 years) with acute asthma attacks, were evaluated. Clinical score, forced expiratory volume in one second and side effects were analyzed. The costs for medication and spacer devices were calculated.

Results: There is no difference between groups regarding clinical score and variation of forced expiratory volume in one second. There was a major variation in the heart rate response to the nebulizer (35%) compared to the commercially available spacer and dry powder inhaler (15 and 17%) and between the homemade spacer and the commercially available spacer (28 and 15%) ($p = 0.004$). The nebulizer and homemade spacer caused more tremor ($p = 0.02$). The cost of treatment was higher for the nebulizer and commercially available spacer ($p = 0.0001$).

Conclusions: The nebulizer was more expensive and used more medicine, showing the same efficiency. The homemade spacer was cheaper, but presented more side effects. The commercially available spacer was as expensive as the nebulizer, although safer. The dry powder inhaler was cheaper, but, just as the homemade spacer, it also caused tachycardia.

J Pediatr (Rio J). 2005;81(4):298-304: Nebulizers, metered-dose inhalers, inhalation spacers, homemade spacer, child.

Introduction

Short-acting beta-2 adrenergic agonists are the major drugs used to treat acute asthma attacks, and inhalation is the best way to use these medications. The selection of the appropriate inhaler device in emergency rooms depends on

the child's age, economic factors and ability of the patient and health team to use them. Inhaled bronchodilators can be administered via a jet nebulizer, metered-dose inhalers with spacer devices, or dry-powder inhalers.

Nebulizers are expensive and their preparation and use are time-consuming, they require electric power, and are less frequently accepted by children and families. Dose-metered inhalers with spacers are more inexpensive, easy to use, do not require electric power, and deliver bronchodilators to the lower airways as efficiently as do nebulizers. Currently, powder bronchodilators have been made available. These bronchodilators are more expensive, easy to use, and have similar efficiency to other types of bronchodilators, but they require coordination and minimum inspiratory flow for delivery of the drug, and therefore, are recommended for children older than 4 or 5 years.^{1,2}

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Homemade spacers made out of soft drink or mineral water bottles and even out of empty saline bottles have been used as an alternative to the purchase of commercially available spacers, with as great efficiency as other devices, but more inexpensive. However, these studies were either open-labeled or not placebo-controlled.³⁻⁵

The aim of this study was to check the efficiency, adverse effects, and the cost of treatment of acute asthma, using bronchodilators administered via nebulizers, dose-metered inhalers with homemade and commercially available spacers, and dry-powder inhalers.

Methods

This was a randomized, double-blind, placebo-controlled study. We assessed patients with acute asthma attacks, aged ≥ 6 years and < 18 years (mean = 11 ± 3.5 years), who sought medical care at a 24-hour emergency health unit affiliated with the City Hall of Curitiba, between 01/01/2004 and 09/30/2004. The following exclusion criteria were used: history of cardiac and pulmonary diseases other than asthma, clinical score < 3 , forced expiratory flow in the first second (FEV_1) less than 20% and greater than 80% of the predicted value. Smokers (> 10 packs of cigarettes/year), and children treated with short-acting and long-acting beta-2 agonists in the last 24 hours, corticosteroids on the last seven days, and also those receiving xanthines, were also excluded. All selected patients showed dexterity for pulmonary function maneuvers and correct use of inhaler devices. The study protocol was approved by the Research and Ethics Committee of the Institute of Biology and Health of PUC-PR, and an informed consent form was obtained from the patients. The patients were randomly selected and placed in four groups. Children were asked to draw a slip of paper containing the numbers 1, 2, 3 and 4 (which would determine their group) out of a non-translucent jar. The assessments were performed by a researcher blinded to the treatment groups, and randomizations and the administration of drugs and placebo were performed in a different room by another researcher, who was able to handle the inhaler devices properly.

Salbutamol was used in different devices according to each group (1, 2, 3 or 4), as follows:

- 1) Nebulizer group (NEB): inhaled salbutamol (Aerolin™, Glaxo Smithkline do Brasil) 0.15 mg/kg (max 5 mg), saline 0.9% complemented with 3 ml of solution, in a Proneb Ultra compressor with Pari jet™ (Pari Inc, EUA) nebulizer, followed by four jets of placebo via a metered-dose inhaler (MDI) (Glaxo Smithkline do Brasil) + commercially available spacer - Aerochamber™ (Monaghan Medical Corporation, New York, EUA). Total of three nebulizations, one of them at T0-T20, T20-T40 and T40-T60.
- 2) Metered-dose inhaler group + Commercially available spacer (CAS): four jets of salbutamol (Aerolin™, Glaxo Smithkline do Brasil) 100 μ g/jet with slow and deep inspiration, followed by apnea during 10 seconds and 30-second intervals, combined with the use of a 145-ml

CAS (Aerochamber™), followed by two aspirations with Pulvinal™ placebo (Farmalab – Chiesi do Brasil). Total of 1,200 μ g, of which 400 μ g were at T0-T20, T20-T40 and T40-T60.

- 3) Metered-dose inhaler group + Non-valved homemade spacer (HMS): four jets of salbutamol (Aerolin™, Glaxo Smithkline do Brasil) 100 μ g/jet with slow and deep inspiration, followed by apnea during 10 seconds and 30-second intervals, using a spacer made out of a plastic 500-ml mineral water bottle coupled to the MDI, and sealed with epoxy resin (Araldite™ - Brascola LTDA. São Paulo, Brazil) and tested by immersion in water, to make sure there was no air leakage, followed by two aspirations with Pulvinal™ placebo (Farmalab – Chiesi do Brasil). Total of 1,200 μ g, of which 400 μ g were at T0-T20, T20-T40 and T40-T60.
- 4) Dry-powder inhaler group (DPI): two aspirations of salbutamol Butovent Pulvinal™ (Farmalab – Chiesi do Brasil) 200 μ g/aspiration with slow and deep inspiration, followed by apnea during 10 seconds and 30-second intervals, followed by four jets of MDI placebo (Glaxo Smithkline do Brasil) + CAS Aerochamber™. Total of 1,200 μ g, of which 400 μ g were at T0-T20, T20-T40 and T40-T60.

The study design is shown in Figure 1.

All patients wore a noseclip during the administration of the active drug/placebo to make sure there was no leakage.

The spacers were used prior to the study with jets of Aerolin™ and were washed with neutral detergent for reduction of the electrostatic charge. They were sterilized with 1% sodium hypochlorite and water diluted 1:3 for 30 minutes.

The clinical score used by Tal *et al.*, which consists of the assessment of respiratory frequency, presence of wheezing, cyanosis, chest retractions and transcutaneous oxygen saturation, was evaluated at zero, 20, 40 and 60 minutes, ranging between 0 and 15.⁶

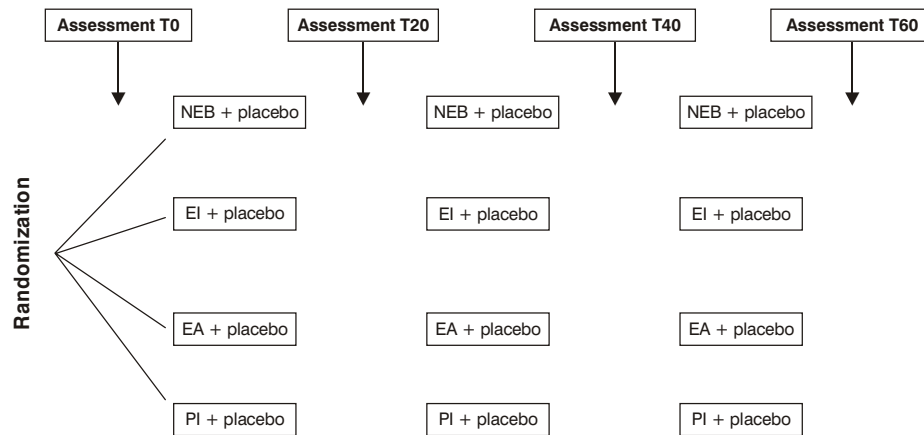
An Airwatch™ (Enatec Health Management Systems Inc., USA) portable digital monitor was used for FEV_1 analysis. The highest value of three consecutive attempts of forced expiration was observed at zero, 20, 40 and 60 minutes. The percentage of variation of the predicted FEV_1 value was used to avoid the influence of other variables.

The following adverse effects were assessed: tachycardia, tremors, nausea and/or vomiting and hypokalemia after 60 minutes.

A formula was developed to calculate direct costs, according to the resources of the local health system, since all the material was purchased by researchers. The formula is expressed as follows: cost = (number of doses *versus* dose cost) + cost of the device/number of patients.

Statistical analysis

Based on a previous pilot study with 20 children, we determined that the sample size necessary to establish significant differences ($p < 0.05$) between the four treatments

**Figure 1** - Study design

NEB = nebulizers; EA = metered-dose inhalers + homemade non-valved spacer device;
EI = metered-dose inhalers + commercially available spacer device; PI = dry powder inhaler.

proposed, for a 15% increase in FEV_1 at 60 minutes, with a power of 80%, should be 40. The quantitative variables were expressed as means and standard deviations, and the categorical variables were expressed as frequency and percentage. The comparison of groups in each stage of the treatment was made by using ANOVA, variance homogeneity was assessed by Cochran's test, and normality condition was evaluated by Shapiro-Wilks' test. Multiple comparisons were made using the LSD test. In comparisons in which ANOVA could not be performed, we used the nonparametric Kruskal-Wallis test. A p value of < 0.05 was considered statistically significant for all tests.

Results

Forty children with an acute attack of mild and moderate asthma participated in the study and completed it. The sample was homogeneous in terms of age, gender, race, weight, height and severity of the acute asthma attack at the beginning of the study. Demographic data, clinical score and percentage of the predicted FEV_1 value at the beginning of the study are shown in Table 1.

There was remarkable improvement in the clinical score and in the percentage of FEV_1 variation in all treatments and at all assessment times, with no difference between the groups (Figures 2 and 3). No patient had to be hospitalized

Table 1 - Demographic data, clinical score and percentage of the predicted FEV_1 value at the beginning of the study (mean values and standard deviation)

	NEB (n = 10)	EA (n = 10)	EI (n = 10)	PI (n = 10)	p
Age (years)	10.74±3.64	11.95±3.23	10.17±3.60	11.18±3.78	0.72
Gender (M/F)	5/5	6/4	5/5	6/4	1
Race (Black/Caucasian)	2/8	3/7	3/7	2/8	1
Height (cm)	143.70±16.02	145.30±16.44	136.80±15.76	141.20±18.32	0.68
Weight (kg)	38.85±12.19	39.88±15.79	32.75±14.02	36.06±16.31	0.70
Score T0	4.10±0.57	4.20±0.42	4.30±0.67	4.30±0.82	0.94
FEV_1 T0 (% of the value expected)	55.90±8.72	53.60±11.82	56.20±9.70	50.70±10.39	0.60

EB = nebulizers; EA = metered-dose inhalers + homemade non-valved spacer device; EI = metered-dose inhalers + commercially available spacer device; PI = dry powder inhaler.

and all of them were discharged with beta-2 agonists and anticholinergics for inhalation.

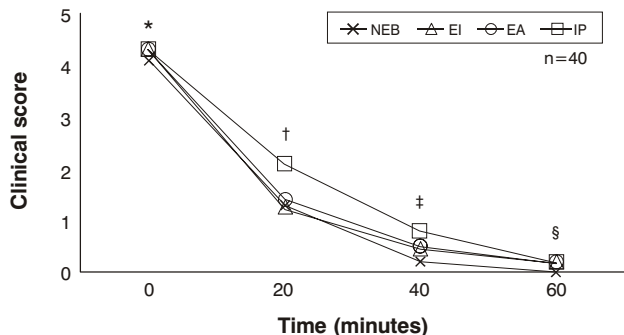


Figure 2 - Mean of clinical scores among groups at 0, 20, 40 and 60 minutes
 * p = 0.94; † p = 0.33; ‡ p = 0.49; § p = 0.51
 NEB = nebulizers; EA = metered-dose inhalers + homemade non-valved spacer device; EI = metered-dose inhalers + commercially available spacer device; PI = dry powder inhaler.

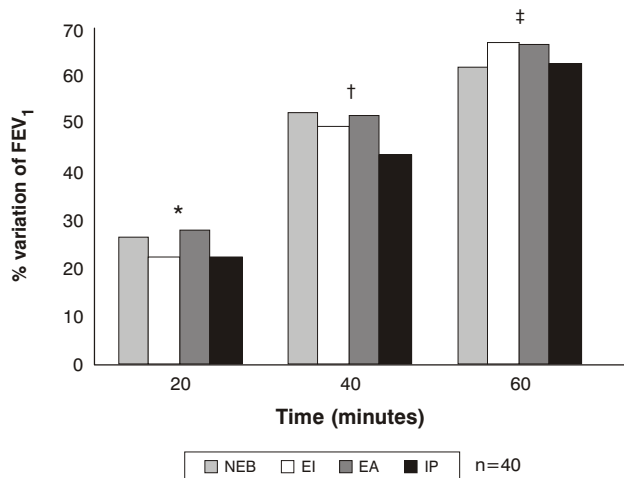


Figure 3 - Mean of FEV1 variation (% of expected) among groups at 20, 40 and 60 minutes
 * p = 0.98; † p = 0.75; ‡ p = 0.96
 NEB = nebulizers; EA = metered-dose inhalers + homemade non-valved spacer device; EI = metered-dose inhalers + commercially available spacer device; PI = dry powder inhaler.

Nebulizers caused a greater variation in heart rate than did the commercially available spacers and dry-powder inhalers. Homemade spacers produced more tachycardia than commercially available spacers, and there were higher chances of tachycardia with the use of homemade spacers compared to dry-powder inhalers (Figure 4). Tremors were more frequent with the use of nebulizers and homemade spacers, and vomiting was observed only in one child who

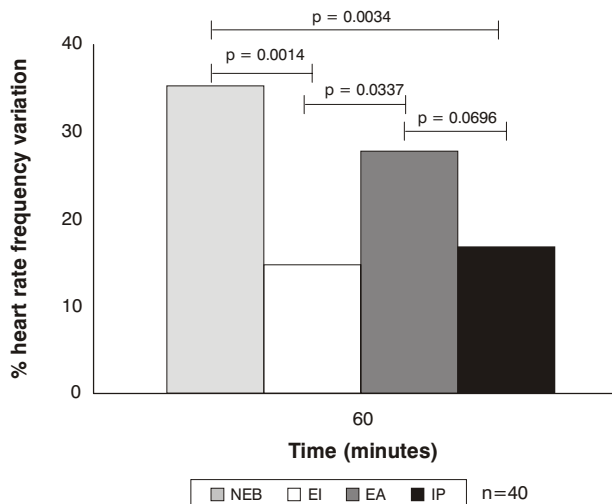


Figure 4 - Mean of heart rate frequency variation after 60 minutes
 NEB = nebulizers; EA = metered-dose inhalers + homemade non-valved spacer device; EI = metered-dose inhalers + commercially available spacer device; PI = dry powder inhaler.

used a homemade spacer. Serum potassium concentration was normal in all children after 60 minutes. The direct cost of the treatment per patient was higher with the use of nebulizers and commercially available spacers (Table 2).

Discussion

Several drugs and inhaler devices have been commercially available for the management of acute asthma attacks, and have been indicated for children of all ages by the most important national and international consensus standards. The selection of the ideal inhaler device is based on its availability, child’s age, and ability of the health team and family members to use it.^{1,2}

The health unit where the study was conducted treats, every year, approximately more than 2,000 children, aged between 0 and 14 years, with acute asthma attacks. For this reason, we decided to assess the use of inhaler devices at this health unit.

Despite the varied treatment options and all the accumulated knowledge on the topic, jet nebulizers are still prevalent in our emergency services, and little has been investigated about the benefits or not of other treatment options.^{4,5}

Schuh et al. conducted a randomized, double-blind study and assessed 90 children, aged between 5 and 17 years, with acute attack of mild asthma, and initial FEV₁ of 50 to 70%. The authors used albuterol administered via a nebulizer (0.15 mg/kg), and via a metered-dose inhaler with Aerochamber, 200 µg, and 600 to 1,000 µg. No significant difference was noted between the groups as to FEV₁ variation.⁷

Table 2 - Adverse events and cost of treatment per children

	NEB (n = 10)	EA (n = 10)	EI (n = 10)	PI (n = 10)
Tremor (yes/no)	9/1 *	9/1 *	3/7	3/7
Vomiting (yes/no)	0/10	1/9	0/10	0/10
Serum potassium (mEq/l)	4.08±0.54	4.15±0.51	4.03±0.44	4.28±0.62
Costs related to the use of salbutamol/children	Three nebulizations 22.31±0.14 †	12 jets 2.38	12 jets 16.58 †	Six aspirations 3.42

* p = 0.0198; † p = 0.0001.

NEB = nebulizers; EA = metered-dose inhalers + homemade non-valved spacer device; EI = metered-dose inhalers + commercially available spacer device; PI = dry powder inhaler.

A similar result was found by Kerem et al. in a study with 33 children, aged between 6 and 14 years, with an acute attack of severe asthma, which compared albuterol administered via a nebulizer (0.15 mg/kg) and via a metered-dose inhaler with a large commercially available spacer (750 ml), 600 to 1,000 µg.⁸

A similar efficiency (assessed by the clinical score) was obtained with albuterol administration via nebulizers and commercially available spacers in children between 2 and 24 months, and between 1 and 5 years.^{9,10}

The administration of terbutaline sulfate via a dry-powder inhaler and a metered-dose inhaler with a commercially available spacer was assessed in a randomized, double-blind study carried out by Drblik et al. The authors assessed children aged between 6 and 16 years, with an acute asthma attack. No significant difference was found between the groups in terms of FEV₁ variation and clinical score at the end of the study.¹¹

Zar et al. evaluated 88 children aged between 5 and 13 years, with moderate to severe airway obstruction. They used fenoterol via a metered-dose inhaler with Aerochamber™, a plastic 500-ml bottle sealed with glue, a plastic 500-ml non-sealed bottle and a plastic 200-ml cup. There was remarkable improvement in lung function with the use of the commercially available spacer and with the plastic bottle sealed with glue compared to the non-sealed bottle and the plastic cup.³

Duarte & Camargos carried out a study of children with acute asthma attacks in which they used salbutamol via a nebulizer and via a metered-dose inhaler with a plastic, non-valved, non-sealed mineral water bottle. The authors did not observe any difference in the assessment of clinical score and lung function in these patients.⁴

In this study, with school-aged children and adolescents presenting with acute attacks of moderate to severe asthma, the efficiency measured through the clinical score and the percentage of FEV₁ variation was similar at all assessment times with the use of nebulizer, metered-dose inhaler with commercially available and homemade spacers, and dry-powder inhalers.

Some consensus guidelines recommend using two to four jets of salbutamol via a metered-dose inhaler every 10 to 20 minutes or 0.15 mg/kg/dose in a nebulization solution every 20 minutes within the first hour of treatment of acute asthma in children.^{1,2}

Amirav & Newhouse carried out a meta-analysis of randomized studies in which they assessed the use of different inhaler devices in children with acute asthma, either hospitalized or treated at the outpatient clinic. The authors observed improvement in clinical symptoms and in lung function with the use of bronchodilators, at proportions between 1:1 and 1:6.9.¹²

Ram et al., in a systematic review of randomized and controlled studies involving the use of beta-2 agonists for the management of acute asthma attacks, found 64 studies that used salbutamol in doses of 100 µg to 4,200 µg, 15 studies with terbutaline in doses of 0.25 mg to 4 mg, and five studies with fenoterol in doses of 200 µg to 600 µg. Of these 84 studies, thirteen were carried out with children.¹³

In this study, a higher cumulative dose of salbutamol administered via a nebulizer (12.5 times) was used in relation to other devices in order to obtain the same efficiency, a fact that was not surprising, since according to the literature, bronchodilators had the same efficiency when varied proportions were used in nebulizers compared to other devices.^{12,13}

In the studies conducted by Kerem *et al.* and Schuh *et al.*, nebulizers caused a higher variation in heart rate than metered-dose inhalers with spacers.^{7,8}

In the study undertaken by Drblik *et al.*, terbutaline administered via a dry-powder inhaler produced a similar oscillation in the heart rate, but this was different when a metered-dose inhaler with spacer was used.¹¹

When comparing commercially available spacers with homemade spacers, Zar *et al.* did not find any difference in the occurrence of adverse events provoked by these devices.³

Duarte & Camargos, in a randomized but open-labeled study, observed adverse events in 17% of the children who used nebulizers and in 4% of the patients who used homemade spacers.⁴

In this assessment, children in the NEB, HMS and DPI groups had a higher variation in their heart rate than those in the CAS group. Tremors were more frequent in NEB and HMS than in the CAS and DPI groups, a finding that runs counter to the literature, probably due to the greater bronchodilator deposition in the oropharynx and in the gastrointestinal tract, with consequently higher systemic absorption.¹ Still, this could be due to the design of the other studies (open-labeled and not placebo-controlled).

No hypokalemia was detected after 60 minutes of bronchodilator administration, but we should view these results with caution, since we did not measure serum potassium levels at the beginning of the study.

Leversha *et al.* assessed the costs of medications and inhaler devices and found out that children with acute asthma attacks whose medication at the emergency room was administered via a metered-dose inhaler and spacer cost NZ\$ 30.60, while those medicated via a nebulizer cost NZ\$ 3.52.¹⁴

In another study involving adults with acute asthma, Raimondi *et al.* noted that U\$ 11.25 was spent, per patient, on nine nebulizations, U\$ 21.44 on a metered-dose inhaler with spacer (36 jets), and U\$ 18.72 on a dry-powder inhaler (36 capsules).¹⁵

In Brazil, Vilarinho *et al.* used a nebulizer and metered-dose inhaler with a homemade spacer and found that the cost of treatment with the spray represented 22% of the cost with the nebulizer, but both groups needed oxygen inhalation, which was supplied only to the children who used the nebulizer, thus significantly increasing the costs with the nebulizer.⁵

The mean direct cost of the treatment per child was calculated by a formula especially developed for this study, with an inversely proportional result to the number of patients who used a given device, and directly proportional to the price of the device. For the sample of this study, nebulizers and commercially available spacers were considerably more expensive, but these costs were calculated only considering the drug and the devices, not indicating the real costs of these treatment options at this health unit. A more comprehensive calculation should be made including drugs, devices, handling time, administration of the drug, expenditures with electric power, costs with labor force, and

length of stay at the outpatient clinic. This way, we can have a more accurate idea of the costs of different treatments available for children with acute asthma attacks in our setting, which will help us find other alternatives with similar efficiency and lower costs.

Our conclusion is that the metered-dose inhaler with commercially available spacer is as efficient as the nebulizer, homemade spacer, and dry-powder inhaler in treating acute attacks of mild to moderate asthma in school-aged children and adolescents, and produces fewer adverse events, but has a high cost. Nebulizers should be considered as a second-line device for the management of acute asthma attacks. The metered-dose inhaler with homemade spacer is an efficient and inexpensive alternative, but it should be used with caution, because it causes more tachycardia and tremors than commercially available spacers.

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