ORIGINAL ARTICLE LOWER AIRWAYS

Comparison of the bronchodilating effects of albuterol delivered by valved vs. non-valved spacers in pediatric asthma

Carlos E. Rodriguez-Martinez[1,2,3], Mónica P. Sossa-Briceño[4] & Jose A. Castro-Rodriguez[5]

[1]Department of Pediatrics, School of Medicine, Universidad Nacional de Colombia, Bogota, Colombia; [2]Department of Pediatric Pulmonology and Pediatric Critical Care Medicine, School of Medicine, Universidad El Bosque, Bogota, Colombia; [3]Research Unit, Military Hospital of Colombia, Bogota, Colombia; [4]Department of Internal Medicine, Clínica Reina Sofía, Bogota, Colombia; [5]Departments of Pediatrics and Family Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

To cite this article: Rodriguez-Martinez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Comparison of the bronchodilating effects of albuterol delivered by valved versus non-valved spacers in pediatric asthma. *Pediatr Allergy Immunol* 2012: **23**: 629–635.

Keywords
asthma; pediatrics; therapeutics; inhalation spacers

Correspondence
Carlos E. Rodriguez-Martinez, MD, MSc, Department of Pediatrics, School of Medicine, Universidad Nacional de Colombia, Avenida Calle 127 No. 20-78, Bogota, Colombia
Tel.: + 57 1 2595500
Fax: + 57-1 2595520
E-mail: carerodriguezmar@unal.edu.co

Accepted for publication 22 August 2012

DOI:10.1111/pai.12008

Abstract

Introduction: Inhaled therapy using a metered-dose inhaler (MDI) with attached valved holding chamber has been increasingly recognized as the optimal method for delivering bronchodilators for asthma treatment. However, mainly due to the high cost of these valved holding chambers in many developing countries, the use of non-valved spacers is frequent, despite the scarce evidence that supports their efficacy. The aim of this study was to compare the bronchodilator response to albuterol administered by MDI with and without a valved spacer.

Methods: In a randomized, two-period, two-sequence crossover clinical trial, we analyzed 31 stable asthmatic children (6–18 yrs of age) on two consecutive days, who were randomly assigned to receive 100 μg of albuterol MDI through either a locally produced valved spacer or a non-valved spacer. The next day, a crossover treatment was employed through the use of the other spacer. Spirometry was recorded before and after each albuterol administration.

Results: As we were not able to identify any sequence or carryover effect, we tested for treatment effects in both periods. No significant differences in the absolute change in FEV_1 (0.20 ± 0.17 vs. 0.18 ± 0.16, $p = 0.63$), FVC (0.07 ± 0.13 vs. 0.07 ± 0.16, $p = 0.88$), or MMEF (0.49 ± 0.31 vs. 0.43 ± 0.39, $p = 0.53$) after bronchodilator administration were found between the use of valved and non-valved spacers.

Conclusions: In stable asthmatic children, albuterol administered through MDI using a non-valved spacer produces a bronchodilator response similar to that of a spacer with a valve that requires an inhalatory opening pressure (with flows between 2 and 32 l/min) that even toddlers with bronchial obstruction can easily generate.

In Colombia, symptom prevalence for asthma, allergic rhinitis (AR), and atopic eczema (AE) are substantial. In a cross-sectional, population-based study realized in six cities during the academic year 2009–10, the current prevalence of asthma symptoms was 12% (95% CI, 10.5–13.7), the current prevalence of AR symptoms was 32% (95% CI, 29.5–33.9), and of AE symptoms was 14% (95% CI, 12.5–15.3) (1). Inhaled therapy using a metered-dose inhaler (MDI) with attached valved holding chamber has been increasingly recognized as the optimal method for delivering bronchodilators for asthma treatment (2), even for acute asthma exacerbations in young children (3). However, the high cost and the unavailability of commercially produced valved holding chambers have limited their widespread use in low- and middle-income countries (4). As alternatives for reducing costs, home-made spacers (5–7) and more recently, commercially produced non-valved spacers attached to an MDI have been widely used in these countries for delivering bronchodilators for asthma treatment, despite the scarce evidence that supports their efficacy.

Valved holding chambers have several theoretical advantages over non-valved spacers: improvement of coordination with the inspiratory flow, reduction of the size of the aerosol particles, avoidance of leaking of the aerosol from the spacer, prevention of the ingress of moisture into the spacer,

prevention of dilution of the aerosol in the spacer, and elimination of the cold-Freon effect (8, 9). On the other hand, advantages of non-valved spacers have been reported compared to valved holding chambers: an increase of lung deposition of the aerosol, especially in patients whose inspiratory effort can overcome the resistance of the valves only with difficulty, such as young children and patients with airway obstructions, and the ability to minimize the amount of dead space in the spacer (5). However, the clinical implications of these theoretical advantages for each of the two types of spacers have not been established conclusively.

The aim of this study was to compare the bronchodilator response of an albuterol MDI with attached valved spacer compared to the bronchodilator response of an albuterol MDI with attached non-valved spacer in a sample of stable asthmatic children.

Methods

In a randomized, two-period, two-sequence crossover trial, we examined a consecutive sample of 31 pediatric patients between 6 and 18 yrs of age with stable asthma from the outpatient clinic for lung diseases at the Clinica Infantil Colsubsidio, Bogota, Colombia (Figure 1). Patients were eligible if they were older than 5, had typical symptoms of asthma, including cough, wheezing, chest tightness, and shortness of breath, and had evidence of an increase of 12% or more in forced expiratory volume in the first second (FEV_1) following administration of 200–400 μg of albuterol (2). Patients were excluded if they did not have the ability to perform technically acceptable and reproducible forced expiratory maneuvers or if they had had an asthmatic exacerbation during the preceding 4 wks. All parents or guardians provided informed consent prior to enrollment in the study. The study was approved by the local ethics board.

The study was conducted during two periods on two consecutive days. The first day, one puff (100 μg) of albuterol MDI (Ventilan®, 100 μg/dose; GlaxoSmithKline, Colombia, South America) was administered to patients with a non-valved spacer or with a valved spacer, after which, after a washout period of 24 h, we interchanged the two groups, patients receiving on the second study day the same dose of albuterol with the other spacer. The groups and treatment periods were randomized, using a random number table.

The non-valved spacer used was 500 ml of non-transparent plastic, with attached face mask (Inhalocámara para niños RBS®, Raúl Baena Sendoya & CIA. Ltda., Bogota, Colombia; Fig. 2a). The valved spacer was 500 ml of transparent plastic, with face mask, with a one-way inspiratory valve (Inhalocámara®, Chalver Laboratorios, Bogota, Colombia; Fig. 2b). Before use, the spacers were washed with a pH neutral detergent and allowed to dry in the open air, in order to reduce their electrostatic charge.

Because the valved spacer used is not one of the traditionally used valved holding chambers, we conducted a rigorous evaluation of pressure and flow characteristics of the valve, because of the effects these characteristics may have on the study results. We measured the pressure required for opening

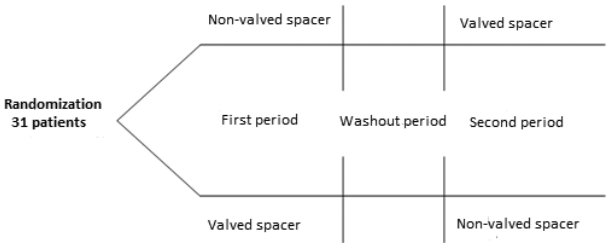

Figure 1 Crossover trial with two treatment arms separated by a 24-h washout period.

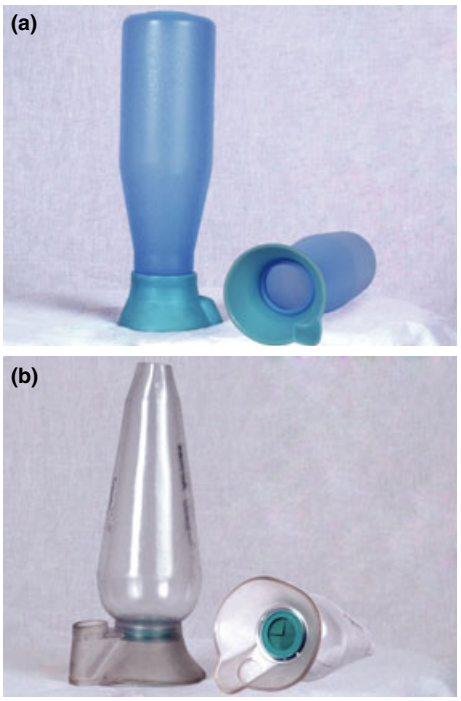

Figure 2 (a) Non-valved spacer; (b) valved spacer.

the valve of the spacer at different flows after calibration. To perform the measurements, we used a Sechrist® ventilator model IV-200, producing a continuous flow that allowed us to measure the pressure drop, using two piezometers and a differential pressure transducer (WIKA MANOMETER® AG CH-6285 HITZKIRCH, Switzerland), which indicates the opening of the valve. To perform these measurements, the mask of the spacer was removed, and a flow restrictor with a 3.5 mm outlet was attached to simulate the conditions of the patient. Pressure measurements were performed in triplicate, with flows between 2 and 32 l/min delivered both in increasing and decreasing order, with an average ambient temperature of 24.7°C, an average relative humidity of 66%, and an atmospheric pressure of 640 mmHg, using medical-type air (no water, oil, or contaminants), and additional measurements were performed with 100% oxygen instead of air.

The first day of the study, demographic data of the patients were recorded. Prior to the performance of the spirometry,

patients did not receive albuterol or bromide ipratropium during the previous 6 h, theophylline during the previous 12 h, or salmeterol or formoterol during the 24 h prior to the performance of the test. None of the patients were receiving leukotriene antagonists. Inhaled steroids and antihistamines were not suspended before the performance of the spirometry.

Through the performance of spirometry, FEV_1, forced vital capacity (FVC), maximum mid-expiratory flow ($FEF_{25–75\%}$ or MMEF), and the ratio of FEV_1 and FVC, or FEV_1/FVC index were measured and recorded. Spirometries were performed by the same technician and with the same spirometer (Jaeger MasterScope PC®; Jaeger, Hoechberg, Germany), and at the same time (8 AM) on the two study days, after daily calibration of the equipment. The tests were performed while patients were standing, using a nose clip without allowing flexing of the neck, and fulfilling the criteria for acceptability and reproducibility of the American Thoracic Society and the European Respiratory Society (10). All patients had previous experience with the testing of lung function. Each of the patients performed a minimum of three and a maximum of eight forced expiratory maneuvers, which were carried out until the two largest FEV_1 and FVC values did not differ by more than 150 ml each.

After the baseline spirometry, patients were randomized to receiving one puff (100 μg) of albuterol MDI (Ventilan®, 100 μg/dose; GlaxoSmithKline, Colombia, South America) with a valved spacer or with a non-valved spacer. For the administration of albuterol, patients were told to breathe at tidal volume with mouth open and without attempting to synchronize the discharge of MDI with their inhalation. Special care was taken to achieve a good seal between the mask and the face (11). After performing baseline spirometry and administering albuterol, patients were told to sit for 15 min in a room free of exposure to cigarette smoke, after which the measurement of post-bronchodilator spirometry was carried out, in the same manner as baseline spirometry had been performed. The technician who performed pre-and post-bronchodilator spirometry was unaware of the type of spacer that had been used to administer the albuterol.

Sample size

Using the method proposed by Wellek and Blettner (12) for calculating the sample size for crossover trials and based on repeated spirometric measurements carried out during the previous 3 months in our asthma clinic, through which a standard deviation (s.d.) of 11% for FEV_1 was determined, we calculated a minimum sample size of 27 patients to detect a difference of 12% in FEV_1 between the two groups, with a statistical significance of 0.05 and a power of 80%.

Statistical analysis

Continuous variables are presented as mean ± s.d. Categorical variables are presented as percentages. The differences between measurements of the main spirometric indices before and after administration of albuterol with each type of spacer were compared using the paired t-test or the Wilcoxon signed-rank test, as appropriate.

The period effect occurs when the underlying condition or disease, or the responsiveness to treatment, changes between different study periods. The carryover effect occurs when a difference is seen in the response to treatment between periods of study because the treatment effect of one period continues upon measuring the outcomes of the next period. The evaluation of the response to albuterol administered with the two types of spacers (treatment effect) was calculated after excluding the possibility of a period effect or interactions of treatment per period (carryover effect) (13). These period and carryover effects were analyzed according to the methodology proposed by Hills and Armitage (14). However, due to the fact that the statistical test to detect a carryover effect is of low power, the criterion of the investigators was also taken into account for determining whether the washout period was sufficient to exclude the presence of this effect. To evaluate the presence of the treatment effect, we calculated the mean difference of each of the major spirometric indices between the two treatment periods, using the student's t-test for independent samples or the Mann–Whitney *U*-test, as appropriate. The agreement of measurements of the main spirometric indices between the two spacers was analyzed through the construction of the Bland–Altman plot (15). All other statistical tests were two-tailed and were taken to a significance level of 0.05. Statistical analysis was performed using the statistical package STATA 10.0 (Stata Corporation, College Station, TX, USA).

Results

A total of 32 patients met the inclusion criteria, but the measurements of one of them were not included in the analysis because his spirometric maneuvers did not meet the criteria of acceptability (10). Therefore, spirometric measurements were analyzed for 31 patients, of whom, 15 (48.4%) were assigned to receive albuterol with the non-valved spacer on the first day of the study and with the valved spacer on the second day (group 1), and the remaining 16 (51.6%) were assigned to receive albuterol with spacers in the reverse order (group 2). In the measurements made with the non-valved spacer, the average basal predicted FEV1, CVF, and MMEF were 103.3 ± 18.9, 117.1 ± 15.2, and 64.4 ± 24.1%, respectively, and the average post-bronchodilator predicted FEV1, CVF, and MMEF were 115.1 ± 17.2, 120.1 ± 14.1, and 85.9 ± 24.4%, respectively. In the measurements made with the valved spacer, the average basal predicted FEV1, CVF, and MMEF were 104.6 ± 20.1, 116.4 ± 16.8, and 66.6 ± 22.6%, respectively, and the average post-bronchodilator predicted FEV1, CVF, and MMEF were 114.1 ± 17.6, 119.7 ± 14.4, and 84.8 ± 25.9%, respectively. The demographic data and the absolute values of baseline measurements of spirometric indices are presented in Table 1.

Analysis of the period and carryover effects

We found no evidence of difference between the two periods for FEV_1 (1.84 ± 0.56 vs. 1.84 ± 0.58, p = 0.98, respectively), for FVC (2.48 ± 0.75 vs. 2.47 ± 0.76, p = 0.89, respectively) or for the MMEF (1.43 ± 0.66 vs. 1.49 ± 0.65, p = 0.85, respectively). There was also no evidence of carryover effect

Table 1 Demographic characteristics and baseline spirometric values of the patients included in the study

	Total sample	Group 1 Non-valved/valved spacer (n = 15)	Group 2 Valved/non-valved spacer (n = 16)
Age [years; mean (s.d.)]	9.7 (3.0)	9.8 (3.1)	9.6 (3.0)
Gender, M/F	19/12	9/6	10/6
Weight [kg; mean (s.d.)]	35.9 (13.7)	33.2 (10.5)	38.4 (16.1)
Height [cm; mean (s.d.)]	135.1 (14.6)	133.7 (10.5)	136.5 (15.9)
FEV_1 [l; mean (s.d.)], first period	1.84 (0.56)	1.62 (0.44)	2.0 (0.63)
FEV_1 [l; mean (s.d.)], second period	1.84 (0.58)	1.62 (0.46)	2.0 (0.61)
FVC [l; mean (s.d.)], first period	2.48 (0.75)	2.28 (0.62)	2.67 (0.83)
FVC [l; mean (s.d.)], second period	2.47 (0.76)	2.24 (0.64)	2.68 (0.83)
MMEF [l/s; mean (s.d.)], first period	1.43 (0.66)	1.17 (0.48)	1.69 (0.71)
MMEF [l/s; mean (s.d.)], second period	1.49 (0.65)	1.26 (0.5)	1.71 (0.7)
FEV_1/FVC [mean (s.d.)], first period	74.3 (8.3)	71.2 (8.2)	77.2 (7.7)
FEV_1/FVC [mean (s.d.)], second period	74.9 (9.4)	72.8 (10.0)	77.0 (8.6)

FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow.

for FEV_1 ($p = 0.60$), for FVC ($p = 0.52$), or for the MMEF ($p = 0.70$). Additionally, it was considered that the washout period used in the study (24 h) was sufficient to establish that the carryover effect was not present.

Analysis of the treatment effect

Because no period or carryover effect was present, we used the measurements obtained in the two study periods to determine the treatment effect.

The change that occurred in FEV_1 after albuterol administration was not significantly different when using the non-valved spacer as compared to the valved spacer (0.21 ± 0.16 vs. 0.18 ± 0.18 lt, $p = 0.60$, respectively). Similarly, the difference in this change was not statistically significant for the measurements of FVC (0.07 ± 0.12 vs. 0.08 ± 0.15 lt, $p = 0.70$, respectively) or for MMEF measurements (0.49 ± 0.31 vs. 0.42 ± 0.38 lt, $p = 0.42$, respectively). The proportion of patients who had a significant post-bronchodilator response (a cutoff point $\geq$ 12%) (16) with the use of the non-valved spacer was identical to that of those who had a significant post-bronchodilator response with the use of the valved spacer (13/31 vs. 13/31, $p = 1.0$).

The Bland–Altman plots show the agreement of the main post-bronchodilator spirometric indices between the two spacers. Fig. 3 shows that the mean difference in the measured FEV_1 between the two spacers was −0.02 l, and their corresponding 95% limit of agreement was −0.38 to 0.34 l. One outlier was seen. Fig. 4 shows a mean difference in the measured FVC of −0.01 l with a limit of agreement that varies from −0.40 to 0.37 l. Here, three outliers were found. Fig. 5 shows a mean difference in the measured MMEF of −0.04 l/s with a limit of agreement from −0.64 to 0.56 l/s. One outlier was seen. The points in each of the three plots show random distribution.

Valve features of the valved spacer

The pressures required to open the valve of the valved spacer for different flows ranged from 2 to 32 l/min and were measured in triplicate. The average values of the valve opening pressure of the spacer ranged from 0.005 to 0.33 kPa among these flow rates. The measurements did not vary significantly when using air or 100% oxygen to generate the flow (data not shown).

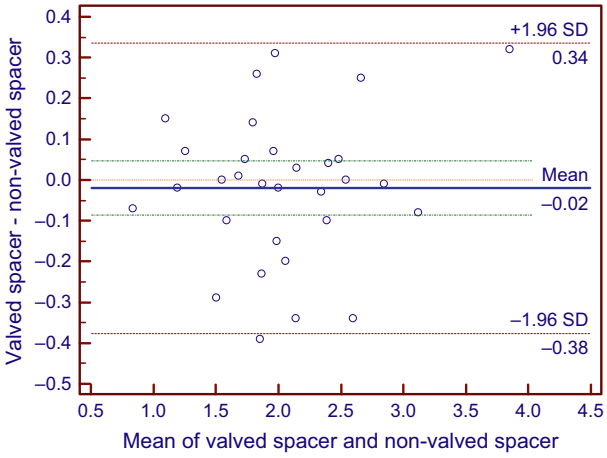

Figure 3 Bland and Altman plot displaying the difference in FEV_1 measurements plotted against the mean FEV_1 measurements. Horizontal lines are drawn at the mean difference and at the mean difference ± 1.96 s.d. of the differences (dashed line).

Discussion

In the present crossover trial, we found that the MDI albuterol at low doses produced a similar degree of bronchodilation in stable asthmatic children when administered with a non-valved spacer to that when administered with a spacer with a valve that requires an inhalatory opening pressure (with flows between 2 and 32 l/min) that even toddlers with bronchial obstruction can easily generate. Bland–Altman plots also showed good agreement of the main post-bronchodilator spirometric indices between the two spacers.

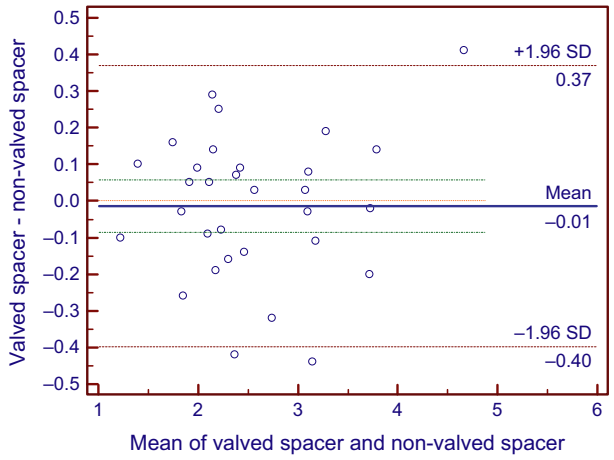

Figure 4 Bland and Altman plot displaying the difference in FVC measurements plotted against the mean FVC measurements. Horizontal lines are drawn at the mean difference and at the mean difference ± 1.96 s.d. of the differences (dashed line).

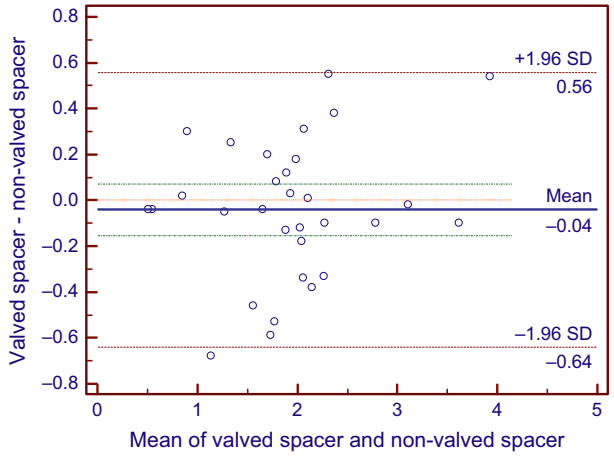

Figure 5 Bland and Altman plot displaying the difference in MMEF measurements plotted against the mean MMEF measurements. Horizontal lines are drawn at the mean difference and at the mean difference ± 1.96 s.d. of the differences (dashed line).

Our findings are consistent with those reported by Zar et al., who in a randomized controlled trial compared the response to bronchodilator treatment given via a conventional valved holding chamber (Aerochamber®) or a non-valved spacer consisting of a low-cost plastic bottle in young children with acute lower airway obstruction. They found no significant differences in outcomes such as rate of hospitalization, change in clinical score, oxygen saturation, number of bronchodilator treatments, and use of oral corticosteroids (17). Likewise, Dahiya et al., compared the efficacy of five types of spacers (a 750 ml spacer with valve, a 165 ml spacer with valve, a 250 ml spacer without valve, a 1000 ml indigenously made spacer without valve, and a 500 ml indigenously made spacer without valve) in 150 children 5–14 yrs of age with persistent asthma, using 200 μg of albuterol. They reported that changes in peak expiratory flow (PEF) and percentage improvement were comparable among all five groups and that changes in FEV_1 and percentage improvement were also comparable, irrespective of severity of baseline airway obstruction (18). Also, a recent Cochrane meta-analysis that compares the efficacy of bronchodilator therapy given via commercially produced spacers (valved holding chambers) with home-made spacers (non-valved spacers) in children with acute exacerbation of bronchospasms or asthma did not identify a difference in any outcome between the two type of devices (19).

Moreover, those findings are supported by Kissoon et al., who determined the quality of fine particle fraction (<4.7 μ) and ultrafine particle fraction (<3.3 μ) of three bottles (from 280 to 500 ml) commonly used as spacers and compared their performance to a commercially available valved holding chamber, and found that all of the sample bottle spacers emitted a higher amount of fine and ultrafine particles than the valved holding chamber and MDI alone, concluding that the sizes of particles obtained from the bottle spacers are those that have a high probability of reaching the lower airways (20). Likewise, Wilkes et al., compared the performance of four spacers (toilet paper roll, Ellipse, Optihaler, Myst Assist) and five holding chambers (Aerochamber®, Optichamber®, Aerosol Cloud Enhancer®, Medispacer®, and Inspirease®) *in vitro* and found that compared with the MDI alone, all of the accessory devices reduced aerosol mass median aerodynamic diameter (MMAD) and increased lung–throat ratio. They reported that the fine particle dose of albuterol was 40% higher with the Ellipse, it was equivalent with the toilet paper roll, Aerochamber®, Optichamber®, and Medispacer®, and it was 33–56% lower with the Optihaler®, Myst Assist®, Aerosol Enhacer®, and Inspirease® (21).

However, Kofman et al., in a randomized clinical trial of parallel design conducted in 34 asthmatic children without recent exacerbations, compared the bronchodilator response to albuterol 100 μg administered with a valved holding chamber (Aerochamber®) to that with a non-valved spacer similar to that used in our study. They found a significantly greater degree of bronchodilation when albuterol was administered with the valved holding chamber than when administered with a non-valved spacer (22). Possible explanations for the conflicting results between the latter study and ours are differences in the inhalation technique used (patients were instructed to carry out three slow deep breaths through the mouth with a post-inspiratory pause of at least 8 s after each one in the Kofman et al. study vs. being instructed to tidal breathe through the mouth after administration of albuterol without attempting to synchronize the discharge of the inhaler with inhalation in our study); the characteristics of the valved spacers [Aerochamber® used by Kofman et al., has its own strict quality control vs. a new locally produced valved holding chamber in our study, but which has been proven to have a valve with inhalatory opening pressure that even toddlers with bronchial obstruction can easily generate (23, 24)]; and the type of design used in each study (crossover vs. parallel), because the crossover design, upon eliminating variation between

subjects, makes it more efficient than parallel studies with similar sample sizes (25). These parallel studies (especially if they have a small sample size, as does the study by Kofman et al.) may have other factors than the studied intervention that can cause differences between compared groups (26, 27).

The greater variability of the MMEF compared to FEV_1 and FVC that we found in our study is in agreement with the literature, which has shown that MMEF has considerably more variability than the FVC and FEV1, and therefore, it has been recommended that MMEF only should be considered after determining the presence and clinical severity of impairment and should not be used to diagnose disease in individual patients (10).

Of note is the fact that less than half of the patients included in the study had an increase of 12% or more in FEV_1 after administration of the albuterol. This finding could be due to the use of 100 mcg of albuterol in our study instead of 200–400 μg, which is the most frequently used dose for assessing response to bronchodilator administration. Additionally, it has been reported that a cutoff point of 12% in bronchodilator response has shown only a modest sensitivity in confirming the diagnosis of bronchial asthma (28).

In addition to these inhalotherapy aspects, certain other important asthma aspects must be taken into account when treating asthmatic children to obtain adequate symptoms control, especially in low- and middle-income countries. Avoiding nursery schools and smoking in pregnancy, breast-feeding babies > 3 months, and improving mothers' education, have been described as interventions that could potentially lower the prevalence of wheezing during the first years of life in these countries (29). Moreover, strong parental beliefs regarding the need for medication, higher concern about potential side effects of medication (30), and depressive symptoms and anxiety in parents of asthmatic children have been associated with uncontrolled asthma and a greater prevalence and severity of wheezing early in life (31, 32).

Potential limitations of this study are the following: First limitation is the type of valved spacer used (a locally produced one). However, the main objective was to compare a non-valved spacer with a valved one commonly used in our population and not to use a traditional branded spacer, whose cost is higher for our population and for massive use in a nationwide public asthma program in Colombia and other similar low- to middle-income countries. On the other hand, the locally produced valved spacer used in the present study was tested with satisfactory response in terms of pressure required to open the valve, which even toddlers with bronchial obstruction can easily generate (2). The second limitation is the low doses of albuterol (100 μg) used in the study. However, low doses of albuterol were used to better determine the differences between the two types of spacers, because the higher the dose administered; the less likely it would be to detect differences between the two types of devices (22). Nevertheless, to determine the type of spacer most appropriate for use in low- to middle-income countries, it is important to perform additional studies with a greater number of subjects, in children under 5 yrs of age, and with various doses of bronchodilators.

In conclusion, this study showed no advantage for using a valved spacer over a non-valved spacer with respect to the response to low doses of albuterol in stable asthmatic children.

Acknowledgments

The authors thank Leon Dario Jimenez Posada Engineer, Mechanical Engineer specializing in biomedical engineering, business manager for Emco SA, and Dr. Maria Claudia Guzman, Pediatric Intensivist in the Intensive Care Unit of Hospital Santa Clara, for their strong cooperation in the assessment the characteristics of the spacer with valve used in the study. Likewise, we thank Mr. Charlie Barrett for his editorial assistance.

Potential conflicts of interest

The authors declare they have no conflict of interest related to the spacers used in this study.

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