Comparison of salbutamol efficacy in children- *via the metered-dose inhaler (MDI) with Volumatic® spacer and via the dry powder inhaler, Easyhaler®, with the nebulizer* - in mild to moderate asthma exacerbation: a multicenter, randomized study

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Summary

Background: **β_2 agonist administered via a nebulizer is the standard treatment for acute asthma exacerbation. There are some limitations for the use of nebulization. We conducted a study to determine the efficacy of salbutamol administered via the pMDI with Volumatic® spacer and the Easyhaler®(DPI) compared to nebulization in mild to moderate asthma exacerbations in children.**

Methods: **A multicenter, randomized, controlled study was conducted in children between 5 and 18 years of age who presented at an emergency or outpatient department. They were randomized to receive either 6 puffs of salbutamol via the pMDI with Volumatic® spacer, or via the Easyhaler®, or 0.15 mg/kg of salbutamol nebulized via oxygen (or compressed air). The primary outcome was the clinical response which was assessed using the modified Wood's asthma score. The secondary outcomes were: hospitalization, asthma re-visit within 3 days, systemic corticosteroid use and adverse events. The clinical score, oxygen saturation, PR, RR, BP and adverse events were recorded at time 0 (before treatment) and 20, 40 and 60 minutes after drug administration.**

Results: **There were no statistically significant differences in the clinical response between the three groups at the 1st, 2nd or 3rd dose or for the SpO_2 or the respiratory rate while the children in the Easyhaler® group had significantly less tachycardia after the 2nd dose. No significant adverse events were noted among the three groups.**

Conclusions: **Salbutamol administered via pMDI with Volumatic® spacer or DPI (Easyhaler®) are as effective as salbutamol given via a nebulizer in providing effective relief of mild to moderate severity acute asthma exacerbation in children between 5 and 18 years of age. *(Asian Pac J Allergy Immunol 2011;29:25-33)***

Key words: *salbutamol, pMDI, DPI, Easyhaler, nebulizer*

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Introduction

Asthma is a worldwide high burden disease.[1] In Thailand, the prevalence of childhood asthma has increased three-fold in less than a decade, from 4.3% in 1987[2] to 13.5% in 1994[3] and 14.1% in 2001.[4] Despite the introduction of many international treatment guidelines since 1995, asthma exacerbation is still a major problem at the emergency room of many hospitals.[5] Inhaled rapid-acting β_2 agonist is the mainstay of treatment for acute exacerbation in all age groups.[1]

In general, β_2 agonist administered via a nebulizer is the standard treatment for acute

Table 1. Modified Wood's asthma score [14]

Clinical	Score 0	Score 1	Score 2
Cyanosis	No	In room air	In FiO_2 0.4
Inspiratory breath sounds	Normal	Unequal	Decreased or absent
Accessory muscle used	No	Moderate (subcostal retraction)	Maximal (suprasternal + subcostal retraction and/or flaring ala nasi)
Wheezing	No	Moderate (expiratory wheezing)	Marked (inspiratory + expiratory wheezing)
Cerebral function	Normal	Depressed or agitated	Coma

exacerbation especially in young children.[1,6-7] There are, however, some limitations for the use of nebulization, e.g. its inconvenience, slow implementation, high cost and uncontrolled particle sizes.[8] The pressurized metered-dose inhaler (pMDI) which is small, portable and can be used very quickly, has advantages when compared with nebulization.[9-10] Rapid-acting β_2 agonist delivered via MDI is, therefore, recommended as the most cost effective treatment for mild to moderate exacerbations in a community setting.[1]

Dry powder inhalers (DPI)—*another type of aerosol delivery device*—have been reported as an alternative for acute asthma. DPIs are easier to use than MDIs because they are breath-actuated and do not contain propellants; however, currently they are not recommended as the standard treatment.[1] The reluctance to use these effort-dependent, breath-actuated devices in an acute setting may be due, in part, to the belief that either inspiratory flow is sufficiently compromised during an acute exacerbation, or children may not be able to perform the inspiratory manoeuver correctly. These limitations, it is assumed, will limit the amount of medication being effectively delivered into the small airway.

Easyhaler®, a novel multiple dose powder inhaler, has been developed to be handled identically to the pMDI.[11] Koskela et al. have shown that a reasonably low inspiratory flow rate through Easyhaler® produces an equivalent improvement in lung function as a correctly used pressurized metered dose inhaler (pMDI) with a spacer.[12] The study had a limited number of patients and the study group was made up of children over 7 years of age and adults.

Neither pMDI nor DPI is widely accepted for use for acute asthma exacerbation in the emergency room in Thailand. A study on the efficiency of the 3 delivery devices in the treatment of acute asthma exacerbation was published but it had a small number of patients [13]. We, therefore, conducted a study to determine the efficacy of the pMDI with Volumatic® spacer and the Easyhaler®(DPI) compared to nebulization for delivering salbutamol for the treatment of mild to moderate acute asthma exacerbations in Thai children.

Methods

Study Design

A multicenter, randomized, controlled study—*involving 7 centers in various parts of Thailand*—was conducted to compare the efficacy and safety of salbutamol administered via (a) pMDI connected to a Volumatic® spacer, (b) an Easyhaler®, and (c) a nebulizer for the treatment of mild to moderate acute asthma exacerbations in children. The patients were assessed for: (a) the first hour for their response to treatment (b) adverse events and (c) asthma re-visits during the 3-day treatment period.

Study population

Included in this study were asthmatic children between 5 and 18 years of age who came with acute exacerbation to the outpatient department (OPD) or the emergency room (ER) between October, 2004 and December 2006. All of the cases were mild to moderate in severity during the acute episode (i.e., $\leq$ 7 on the modified Wood's asthma score).[14] Informed consent was obtained from patient's parent or guardian prior to enrollment.

The criteria for exclusion were the presence of other conditions, such as: heart, liver, kidney and chronic pulmonary diseases, brittle asthma, and severe exacerbation requiring intensive care or mechanical ventilation. We also excluded patients who (a) were allergic to salbutamol or had some other contraindication to its use, (b) had repeated exacerbation of asthma within 7 days after entry into the study, or (c) were not able to use the DPI.

Study medications

The experimental groups comprised patients who received 6 puffs of salbutamol (600 µg)

Table 2. Demographics and baseline characteristics of the study groups and asthma severity before enrollment

	MDI with Volumatic® N = 68	Route Easyhaler® N = 71	Nebulizer N = 77
Sex, male, n (%)	37 (54.4)	49 (69.0)	53 (68.8)
Age (years), mean ± SD	9.36 ± 2.68	9.25 ± 2.58	9.02 ± 2.57
Weight (kg), mean ± SD	31.32 ± 11.39	32.79 ± 11.87	29.96 ± 11.51
Height (cm), mean ± SD	133.05 ± 15.23	133.53 ± 15.29	131.13 ± 15.78
Duration of asthma from 1st diagnosed (month)			
Mean ± SD	55.85 ± 38.43	61.42 ± 39.00	59.79 ± 40.92
Current treatment, n/N* (%)			
No ICS	44/67 (65.7)	43/71 (60.6)	52/76 (68.4)
ICS	12/67 (17.9)	9/71 (12.7)	15/76 (19.7)
ICS + other controllers	11/67 (16.4)	19/71 (26.8)	9/76 (11.8)
Severity of asthma, n/N* (%)			
Intermittent	40/68 (58.8)	40/71 (56.3)	47/76 (61.8)
Mild persistent	13/68 (19.1)	12/71 (16.9)	14/76 (18.4)
Moderate persistent	14/68 (20.6)	19/71 (26.8)	14/76 (18.4)
Severe persistent	1/68 (1.5)	0	1/76 (1.3)
Exacerbation within 12 months, n/N* (%)	55/66 (83.3)	56/68 (81.2)	62/74 (83.8)
No. of exacerbation/year			
Median (P25 - P75)	2.5 (1.0 - 5.5)	2.0 (1.0 – 5.0)	3 (2.0 - 5.1)
Hospitalization during 12 months, n/N* (%)	12/66 (18.2)	13/70 (18.6)	12/75 (16.0)
Short-acting beta2-agonist used, n/N* (%)	37/62 (59.7)	40/68 (58.8)	39/70 (55.7)
Modified Wood's Clinical Score			
Mean ± SD	3.91 ± 1.22	3.40 ± 1.36	3.57 ± 1.14

* Some missing data

with Volumatic® spacer (Volumatic®, Glaxo administered either via the pMDI (Ventolin® Evohaler® 100 µg/dose, GlaxoSmithKline, U.K.) Wellcome, U.K.), 2 puffs repeated 3 times or via the DPI (Buventol® Easyhaler® 100 µg/dose, Orion Corporation, Finland), 1 puff repeated 6 times, and the control group who received 0.15 mg/kg of salbutamol (0.5% Ventolin® Respiratory® Solution, GlaxoSmithKline, U.K.), maximum to 5 mg, added to normal saline solution to 3 mL, nebulized via oxygen flow 6-8 LPM or compressed air.

Outcome Measurements

The primary outcome was the clinical response to inhaled salbutamol, assessed by the modified Wood's asthma score (Table 1).[14] The number and percentage of successfully treated patients after the 1st, 2nd and 3rd doses of salbutamol administration, in 20-minute intervals, defined as those with a clinical score reduction ≥ 50% from baseline, or clinical scores ≤ 3.

The secondary outcomes were: (a) hospitalization (b) asthma re-visit within 3 days after enrollment (c) systemic corticosteroid use and (d) adverse events in terms of palpitation, tremor, headache and hypertension. Hypertension was defined as an average systolic blood pressure and/or diastolic blood pressure ≥ 95th percentile for sex, age and height on three or more occasions using the Blood Pressure Table from the National Health and Nutrition Examination Survey (NHANES).[15]

Methodology

The patients who came to the outpatient department (OPD) or the emergency room (ER) and met the eligible criteria were randomized into 3 groups to receive the study medications according to the approved protocol. Data including the modified Wood's asthma score, demographic characteristics, asthma history, vital signs (viz., pulse rate, respiratory rate and blood pressure) and oxygen saturation were recorded at baseline. Each patient was given an initial dose of salbutamol which was repeated at 20-minute intervals until the study endpoint was achieved, to a maximum of 3 treatments.

Table 3. Study end points

	MDI with Volumatic® N = 68	Route Easyhaler® N = 71	Nebulizer N = 77	P-value
No. of successfully treated patients, n (%)				
1st dose	32 (47.1)	36 (50.7)	46 (59.7)	0.688
2nd dose	14 (20.6)	10 (14.1)	12 (15.6)	
3rd dose	3 (4.4)	5 (7.0)	3 (3.9)	
No. of failure	19 (27.9)	20 (28.2)	16 (20.8)	
(95% CI)	(23.2 – 32.7)	(23.5 – 32.9)	(17.1 – 24.5)	
SpO_2, (%), mean ± SD				
Time : 0 min.	96.4 ± 1.9	96.5 ± 2.1	95.9 ± 2.6	0.201
Time : 20 min	96.9 ± 1.8	96.9 ± 1.9	97.0 ± 1.8	0.938
Time : 40 min	96.7 ± 1.9	96.6 ± 1.5	97.0 ± 1.5	0.556
Time : 60 min	96.8 ± 1.8	97.0 ± 1.4	96.7 ± 1.4	0.587
RR (breaths / min.), mean ± SD				
Time : 0 min.	29.9 ± 8.1	28.7 ± 7.2	30.2 ± 9.0	0.509
Time : 20 min	26.3 ± 6.2	24.9 ± 5.4	27.0 ± 7.8	0.141
Time : 40 min	26.4 ± 5.8	24.6 ± 5.5	27.8 ± 8.5	0.091
Time : 60 min	25.7 ± 5.9	24.7 ± 5.4	26.6 ± 7.5	0.328
PR (/ min.), mean ± SD				
Time : 0 min	110.0 ± 19.6	102.8 ± 18.6	106.9 ± 20.9	0.104
Time : 20 min	114.4 ± 22.6	107.3 ± 17.0	113.9 ± 22.9	0.083
Time : 40 min	118.3 ± 20.9[a]	108.0 ± 16.6	120.4 ± 25.5[a]	0.017*
Time : 60 min	115.5 ± 20.1[a]	107.5 ± 18.0	117.4 ± 21.8[a]	0.042*
Hospitalization, n (%)	1 (1.5)	1 (1.4)	2 (2.6)	0.832
Systemic corticosteroids used after treatment, n (%)	53 (77.9)	46 (64.8)	55 (71.4)	0.230
Re-visit within 3 days, n (%)	8 (11.8)	7 (9.9)	3 (3.9)	0.197

[a] Significant different from Easyhaler®

Each patient was sequentially assessed by the same investigator for (a) the response of the studied medication (i.e., the modified Wood's asthma score), (b) oxygen saturation, and (c) vital signs at 20, 40 and 60 minutes after each treatment. Adverse events in terms of palpitation, tremor, headache and hypertension were recorded.

After 60 min of treatment, the patients were considered hospitalized if the clinical score was ≥ 5 or was considered to be indicated by the attending pediatricians. The patients with a good response were discharged and treated according to orders of the same doctors. The patients were followed up and re-assessed for 3 days by visits or telephone.

Statistical analysis

This study was designed with 80% power with a null hypothesis that there was no difference between treatment with pMDI with Volumatic® spacer, DPI (Easyhaler®) and nebulized salbutamol with respect to the percentage of successfully-treated patients after salbutamol administration as primary outcome. A *p*-value of <0.05 was considerd to be the level of significance. The power calculation was based on the assumption that the upper limit of difference across the groups was not greater than 15% and that the success rate in nebulized salbutamol group was expected to be between 80% and 90%. To achieve 80% or 90% of the success rate, 112 and 63 participants per group, respectively, were required.[16] According to the limitation of funding, this study recruited at least 63 participants per arm to determine the clinical equivalent of the three inhalation methods with the success rate in the nebulizer group of 90%.

Descriptive statistics were used to present the endpoint outcome measurements. Normality of distribution and homogeneity of variance were determined using the Kolmogorov-Smirnov test and Levene's F-test for continuous variables. Analysis of Variance (ANOVA) and multiple comparisons by Bonferroni adjustment were used to detect the differences in the mean values between the groups. The Chi-square test or

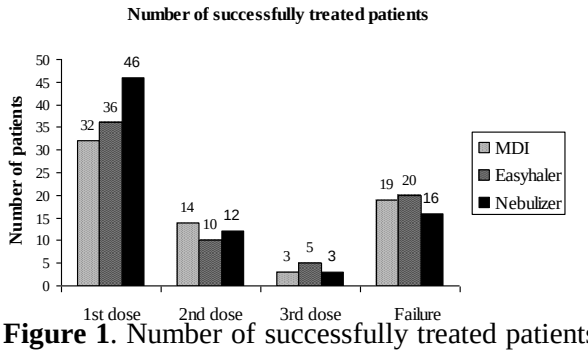

Figure 1. Number of successfully treated patients with study medications

Fisher's exact test were used for categorical variables. For all analyses a 2-sided probability value below 0.05 was considered to indicate statistical significance.

The study was conducted in accordance with good clinical practice (GCP), and was approved by each institution's ethics committee. All of the patients and their parents received oral and written information about the study, and gave written informed consent prior to participation.

Results

During the study period, 216 children from 7 centers who met the eligible criteria were enrolled with the consent of the parents. Salbutamol was administered either via pMDI with a Volumatic® spacer, an Easyhaler® , or a nebulizer in 68, 71 and 77 children, respectively. The between-group demographic characteristics, clinical conditions, severity of illness, and current treatments were comparable. (Table 2)

There were no significant differences between the three groups (pMDI with Volumatic®, Easyhaler® , and nebulizer) vis-à-vis the percentage of successfully-treated children at 1st, 2nd and 3rd dose of salbutamol. (Table 3, Figure 1) Although the success rate of the study groups in this study showed only 72% - 80%, the test of non-inferiority demonstrated statistical significance ($p < 0.001$), based on the difference of upper limit of success rates between pMDI with Volumatic®, Easyhaler® and nebulizer not greater than 10 % or 15%.

The mean oxygen saturations from baseline (time 0) among groups were slightly increased in all 3 groups after the first dose. (Table 4, Figure 2) The mean respiratory rates were decreased in all groups after the 1st dose (Table 4, Figure 3), although the mean pulse rates for all 3 groups were increased after the 1st dose, and the treatment caused significantly less tachycardia when administered via the Easyhaler®. (Table 4, Figure 4)

Only 4 children (1 in the pMDI group, 1 in the Easyhaler group, and 2 in the nebulizer group) were hospitalized after rescue medication. The median duration of asthma symptoms was only 1-2 days. Systemic corticosteroids, mostly oral prednisolone, were administered after the 3rd dose of salbutamol in 77.9%, 64.8% and 71.4% in the MDI, the Easyhaler, and the nebulizer group, respectively. Eighteen children re-visited the emergency room within 3 days due to persistence of asthmatic symptoms. Most of the study

Table 4. Mean change of oxygen saturation, respiratory rates and pulse rates from baseline for the three groups

	Route			P-value
	MDI with Volumatic®	Easyhaler®	Nebulizer	
SpO_2 (%)				
Time : 0 to 20 min.	0.47 ± 1.67	0.45 ± 1.39	0.82 ± 1.74	0.511
Time : 0 to 40 min.	0.45 ± 1.80	0.45 ± 1.81	0.90 ± 1.69	0.426
Time : 0 to 60 min.	0.68 ± 2.07	0.82 ± 2.01	0.75 ± 1.94	0.960
RR (breaths / min.)				
Time : 0 to 20 min.	-2.11 ± 5.35	-4.00 ± 4.55	-3.02 ± 3.64	0.203
Time : 0 to 40 min.	-3.35 ± 5.23	-4.60 ± 4.60	-4.41 ± 4.70	0.486
Time : 0 to 60 min.	-4.84 ± 5.73	-5.42 ± 4.71	-5.64 ± 538	0.793
PR (beats / min.)				
Time : 0 to 20 min.	5.34 ± 12.87	1.29 ± 12.63	5.70 ± 13.80	0.266
Time : 0 to 40 min.	6.47 ± 14.14	1.68 ± 10.96	9.28 ± 15.02 [a]	0.047*
Time : 0 to 60 min.	4.32 ± 13.06	0.61 ± 13.64	7.45 ± 14.43	0.093

[a] Statistical significance different between Easyhaler® and Nebulizer

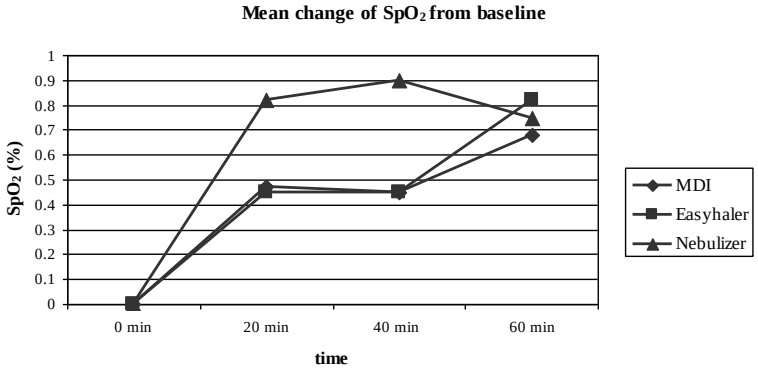

Figure 2 Mean change of oxygen saturation among the three groups one hour after treatment

endpoint measurements were not statistically different between the three groups. (Table 3)

The mean blood pressures were not significantly different between the three groups after treatment; however, hypertension at 60 min after treatment was found in 18.8% of children in the nebulizer group, which was higher than in the pMDI and DPI groups, 4.3% and 12.5% respectively. Only seven children complained of tremor and palpitation after treatment. None of the children complained of headache after treatment. None of the adverse events were statistically different between the three groups. (Table 5)

Discussion

This study has demonstrated the comparable efficacy of salbutamol administered via (a) pMDI with Volumatic® spacer, (b) DPI (Easyhaler®), and (c) nebulizer, for the treatment of mild to moderate exacerbations of acute asthma in children. The incidence of adverse effects (including tremor, palpitation) were acceptable and not different between the three groups, except that tachycardia at 40 and 60 min were found significantly more often in the nebulizer groups as compared to DPI group. Our findings are in agreement with previous reports that indicated pMDI was as effective as a nebulizer[17] or DPI[18].

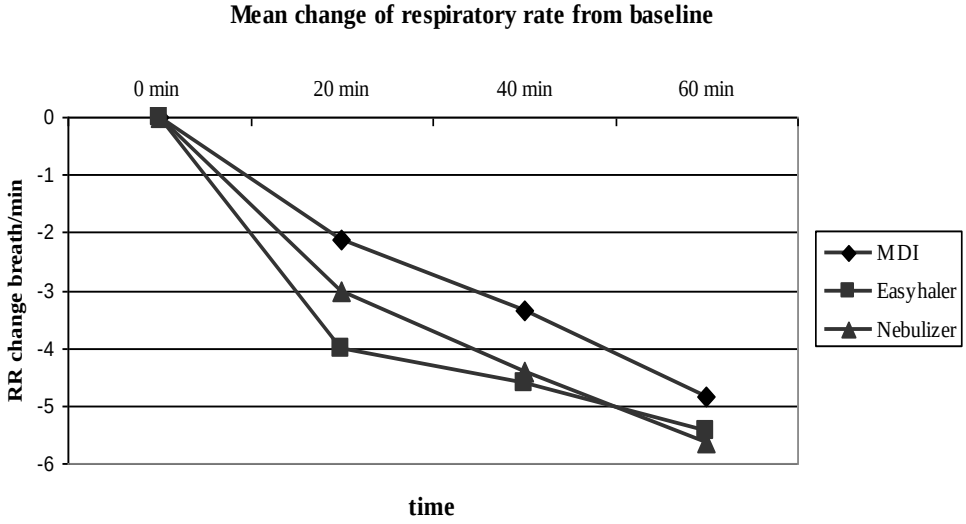

Figure 3. Mean change of respiratory rate for the three groups one hour after treatment

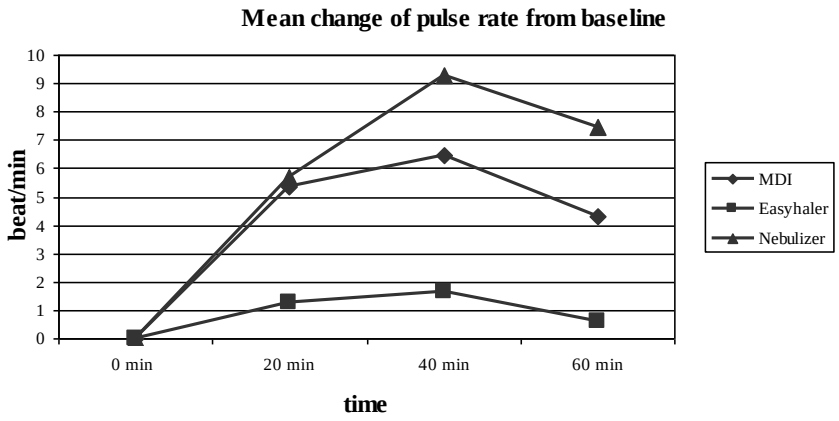

Figure 4. Mean change of pulse rate for the three groups one hour after treatment

Although most of the previous studies were conducted to compare the efficacy between only 2 different devices, i.e., pMDI versus nebulizer or pMDI versus DPI, the current study was conducted to compare three delivery devices.

The increasing types and numbers of inhaler devices make choosing the most appropriate device, especially for children, challenging. The degree of lung penetration for different devices should be taken into account when considering their efficacy in the treatment of acute asthma exacerbation. Many studies *performed in children* have demonstrated the comparable efficacy of rapid-acting β_2 agonist delivered via pMDI and a nebulizer[19-22]; pMDI and DPI.[18] A recent meta-analysis *regarding the aerosol delivery device for acute asthma exacerbation* concluded that rapid-acting β_2 agonist delivered by pMDI with spacer showed it to be at least equivalent to a nebulizer in both children and adults.[10] Moreover, a systematic review in young children showed that pMDI is more efficacious than a nebulizer for decreasing the hospital admission rate from the emergency department and improving the symptom score.[17] It was also noted that small children usually cry when a face-mask is put on resulting in lower lung penetration.[23]

Although many studies have provided evidence supporting the numerous advantages of pMDI with spacer—*and the GINA guideline also recommends this delivery device for the treatment of acute exacerbation*[1]—nebulization is still the preferable route of β_2 agonist administration in the ER of many hospitals. One of the explanations given is that nebulization needs less cooperation of the pediatric patient and it seems to foster confidence in parents (and physicians) because it generates a visible mist for several minutes, ensuring that the patient is getting medication. Indeed, the efficacy of pMDI depends on the proper inhalation technique and the amount of drug delivered to the lungs: it takes between 4 and 10 puffs of a pMDI to equal a single nebulizer treatment.[24-26]

A metered-dose inhaler is the most difficult device to use effectively, especially in children, and teaching them how to use pMDI correctly may be a real obstacle in a busy ER. DPIs are breath-attenuated, easier to teach and no spacer is required. Adequate inspiratory flow is the limiting factor which makes physicians reluctant to use this delivery device in acute asthma patients. Our study showed that Easyhaler®, a multidose DPI, produces improvement in the clinical score which is not different from either a pMDI or nebulizer. Our results—*as with a previous study*[18]—confirm that DPI may be an alternative device for the first-line treatment of acute asthma exacerbation in children. This study randomly enrolled 9 and 4 children aged below 6 years old into the pMDI with Volumatic® spacer, and DPI (Easyhaler®) groups, respectively. We did not have any problem in teaching these children to use either device (pMDI or DPI).

The equivalent dose of salbutamol delivered via pMDI-spacer or DPI to nebulizer has yet to be agreed upon. There is a high variation in the ratio of salbutamol given via nebulizer to pMDI-spacer reported in the literature, 1:1 to 1:12.5.[13, 27] The current study compared 600 μg of salbutamol via pMDI with Volumatic® spacer and DPI via Easyhaler® to the dose of 0.15 mg/kg via

Table 5. Adverse events of study medications

	MDI with Volumatic® N = 46*	Route Easyhaler® N = 48*	Nebulizer N = 48*	P-value
BP (mm Hg), mean ± SD				
Systolic				
Time : 0 min	105.5 ± 14.0	106.6 ± 11.8	103.4 ± 11.7	0.446
Time : 60 min	103.7 ± 9.1	107.2 ± 12.5	106.4 ± 12.2	0.313
Diastolic				
Time : 0 min	66.1 ± 11.3	68.1 ± 8.3	64.5 ± 9.9	0.205
Time : 60 min	64.1 ± 9.4	69.0 ± 10.4	65.6 ± 11.4	0.072
Hypertension, n/N* (%)	2/46 (4.3)	6/48 (12.5)	9/48 (18.8)	0.098
Tremor, n/N* (%)	2/43 (4.7)	1/45 (2.2)	4/52 (7.7)	0.498
Palpitation, n/N* (%)	2/44 (4.5)	0	5/52 (9.6)	0.088

* Some missing data

no significant difference of FEV_1 between groups of children who received salbutamol delivered at different MDI doses (200, 600 and 1000 µg) as compared to 0.15 mg/kg via nebulizers.[20,28] Our findings support the previous reports that salbutamol given via pMDI and DPI, at a dose of not more than 600 µg/dose is adequate to relieve exacerbation symptoms.

One center in this study found that the change of oxygen saturation was significantly increased at 20 min from baseline in the nebulizer group, when compared to the other 2 groups.[29] However; our study showed that the SpO_2 increased from baseline in all 3 treatment groups with no statistically significant difference. The oxygen saturation was not significantly increased in the nebulizer group because some centers used air compressors to generate aerosol instead of oxygen flow. The respiratory rates were also decreased from baseline after treatments in the same manner.

Salbutamol delivered via Easyhaler® caused significantly less tachycardia at 40 and 60 min of dosing than the other 2 groups while the children in the nebulizer group had higher incidence of hypertension after 60 min of treatment. These systemic findings might result from a greater salbutamol dose and more systemic absorption of the drug with the nebulizer, as indicated by many previous studies.[13,20,28] The incidence of other adverse effects, including tremor and palpitation, were acceptable and not different between the three groups.

Only 4 children (1.9%) were hospitalized and 18 (8.3%) re-visited to the hospital within 3 days due to asthma symptoms. Most children received systemic corticosteroid together with rescue medications after β_2 agonist inhalation, which is probably the reason for the low-rates of hospitalization.

The current study did not standardize the clinical score assessment among the raters to ensure the reliability of outcomes; neither did we conduct our study as a double-blind, which might have caused some bias in the outcome assessments. Most of clinical score components; however, were objective measures, such as respiratory rate and oxygen saturation.

In conclusion, this study shows that salbutamol administered via pMDI with Volumatic® spacer or DPI (Easyhaler®), as compared to administration by nebulization, provided effective relief of mild to moderate severity acute asthma exacerbation in children between 5 and 18 years of age.

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