A Comparative Study of Efficacy of Salbutamol via Metered Dose Inhaler with Volumatic Spacer and via Dry Powder Inhaler, Easyhaler, to Nebulization in Mild to Moderate Severity Acute Asthma Exacerbation in Childhood

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Background: *Rapid-acting inhaled beta-2 agonist is standard treatment in acute asthmatic patient; it causes smooth muscle dilatation, gives rapid action and has less side effect compared with parenteral and oral form. There are many forms of inhaler including nebulization, MDI and DPI. In Thailand the most common form of salbutamol administration for the treatment of acute exacerbation of asthma is via nebulization.*

Objective: *To compare the clinical effectiveness and side effects of salbutamol via MDI with Volumatic spacer and via DPI (Easyhaler), with nebulization in mild to moderate severity of acute asthma exacerbation in childhood.*

Material and Method: *A prospective, randomized controlled study in children, aged 5-18 years old with mild to moderate severe asthmatic attack, is done at the Emergency Room, QSNICH during October 2004 to February 2006. These children with acute asthma attack are randomly-assigned to 3 groups of different salbutamol administrations: group 1 via nebulization, group 2 via MDI with volumatic spacer and group 3 via DPI (Easyhaler). Salbutamol is administered and clinical responses: asthma score, oxygen saturation, PR, RR, BP and side effects (tremor and palpitation) are recorded at 0, 20, 40 and 60 minutes after the drug administrations. The drug will be repeated every 20 minutes for the total maximum of 3 times. If there is no clinical improvement, they will be admitted to the hospital for further management.*

Results: *There are 54 asthmatic children, 35 male (64.8%) and 19 female (35.2%). Their mean age is 8.4 $\pm$ 2.3 years. There are 18 patients in each group. There is no significant difference in efficacy of salbutamol among the 3 groups as measured by asthma score, O_2 saturation, PR, RR and BP. Tremor are equally observed in all 3 groups (5.5%) while palpitation are observed in 11.1% of group 1 and 2 only. One patient in group 2 and 3 are admitted while no patient in group 1 is.*

Conclusion: *Rapid-acting inhaled beta-2 agonist via MDI with volumatic spacer and DPI (Easyhaler) can be used effectively compared with nebulization form in treating mild to moderate degrees of acute exacerbation of asthma in children with comparable side effects.*

Keywords: *Salbutamol, Nebulization, Metered dose inhaler, Volumatic spacer, Dry powder inhaler, Easyhaler*

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Asthma is one of the most common chronic diseases and its prevalence is increasing worldwide, especially in children[1]. The increase in asthma prevalence in developing countries suggests that environmental factors and pollution may be more important than genetic factors in the development of asthma[2,3]. In Thailand, the prevalence of asthma in children is 14.5% in 2001[4], as compared to 4.3% in 1987[5].

Rapid acting inhaled beta-2-agonists are recommended to use as reliever medication for treatment of acute exacerbation of asthma. There are many

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forms of inhaled beta-2 agonists, such as nebulizer, metered dose inhaler (MDI) and dry powder inhaler (DPI). Nebulized beta-2-agonist has been effectively and widely used in children, especially in young children, but it takes high cost, more time-consuming, less convenience and most patients have to go to the hospital. Studies in adults and children showed that beta-2-agonists administered via MDI with spacer are as effective as nebulizer in acute asthmatic attack[6-14]. MDI-spacer form is more convenient and cheaper than nebulizer.

DPI, another form of beta-2-agonists, is developed to help patients having problems with the correct use of MDI. Despite the increase use of DPI in treatment of acute attack in the ambulatory setting[15-21], there is still reluctance to use especially in children, due to the question that inspiratory flow may not sufficient and inadequate amount of drug is received or they may not be able to use correctly. The uses of MDI-spacer and DPI in acute asthma are not widely used in Thailand. Therefore, the aim of the study is to compare the efficacy and side effects of the 3 different delivery methods in the treatment of acute exacerbation of asthma in children.

Objectives

1. To compare the efficacy of salbutamol delivered via nebulizer, MDI-spacer and DPI in mild to moderate severity acute asthma attack in children, aged 5-18 years

2. To study the side-effects of salbutamol in 3 different forms

Material and Method

This study is one part of the multi-center study (7 centers) in various parts of Thailand. It is a prospective randomized study, done at Queen Sirikit National Institute of Child Health (QSNICH), during October 2004 - February 2006. Acute asthmatic patients who are seen at the Emergency Room, QSNICH will be enrolled if they meet with the following criteria:

Inclusion criteria

1. Aged 5-18 years

2. Mild to moderate severity (assessed by Modified Wood's Clinical Score) score ≤ 7

3. Informed consent by parents/guardians

Exclusion criteria

1. Patients with severe degree of acute attack (score > 7), ET tube needed, or ICU admission

2. Recurrent wheezing within 7 days after 1st enroll

3. Patients with:

- history of using ventilator and ET tube
- underlying diseases: cardiac, renal and liver diseases
- broncho-pulmonary dysplasia or chronic lung diseases
- contraindication or allergy to salbutamol
- brittle asthma

Study groups and medications

These patients are randomly assigned into 3 groups, receiving different salbutamol preparations with different drug delivery methods as follow:

Group 1 – nebulizer, using 0.5% Ventolin respiratory solution 0.03 ml/kg/dose (maximum dose 1 ml) diluted with NSS to 3 ml, delivered via an oxygen-driven, flow 6-8 L/min

Group 2 – MDI spacer, using 6 puffs of Ventolin evohaler (100mg/puff) delivered via Volumatic spacer, 2 puffs at a time for 3 times

Group 3 – DPI (Easyhaler), using 6 puffs of Buventol Easyhaler (100/mg/puff), 1 puff at a time for 6 times

Treatments are repeated at 20-minutes interval until the patients have improved, *i.e.* the clinical scores reduce $\leq$ 50% from baseline or clinical score ≤ 3, or a total of 3 treatments. If they failed 3 treatments, they will be admitted to the hospital for proper management.

Measurements of clinical scores, pulse rate (PR), respiratory rate (RR), and oxygen saturation (by pulse oximeter) are performed at 0, 20, 40 and 60 minutes after the study medication by one doctor throughout the study. Side effects such as tremors and palpitation are recorded by the same doctor who evaluates these patients.

Statistical analysis

Data analysis is done by using SPSS for Window version 11. Chi-square test is used for categorical data and Student t-test is used for continuous variable data. $p < 0.05$ is considered statistically significant.

Results

Fifty-four patients, 35 boys (64.8%) and 19 girls (35.7%) are enrolled and completed the study, 18 in each treatment group. Mean age is 8.4 ± 2.3 years old. Mean weight and height are 27.3 ± 9.0 kgs. and

128.6 ± 14.7 cms. respectively. Mean duration of asthma is 5.4 ± 3.2 years. The demographic data and severity of asthma are shown in Table 1. Baseline clinical score, pulse rate (PR), respiratory rate (RR), BP and oxygen saturation are shown in Table 2 and 3 (at time 0 of each group). After treatment, clinical scores are improved in all 3 groups, without a statistical difference between groups (Table 2-4). There is no statistical difference in number of treatments, O_2 saturation, RR, and PR ($p > 0.05$) at time 0, 20, 40 and 60 min. in all 3 groups (Table 2-4). Eventhough, patients in the nebulizer group has higher PR at 20 and 40 min. but it is not significant.

Comparing the change in clinical scores, oxygen saturation, RR, and PR from baseline among groups, the patients in the nebulizer group has a significantly higher change in oxygen saturation from baseline at 20 min ($p < 0.05$), when compared to MDI-

Table 1. Demographic data of the patients in 3 groups

Parameter		Nebulizer	MDI-spacer	DPI	Total
Sex	boys	15 (83.3%)	9 (50.0%)	11 (61.1%)	35 (64.8%)
	girls	3 (16.7%)	9 (50.0%)	7 (38.9%)	19 (35.2%)
Age (years)	Mean	7.8 ± 2.1	8.8 ± 2.3	8.5 ± 2.6	8.4 ± 2.3
	5-9	14 (77.8%)	7 (38.9%)	12 (66.7%)	33 (61.1%)
	10-13	4 (22.2%)	11 (61.1%)	5 (27.7%)	20 (37.0%)
	14-18	0	0	1 (6.6%)	1 (1.9%)
BW (kgs)		25.8 ± 6.6	29.2 ± 9.9	27.0 ± 10.3	27.3 ± 9.0
Ht (cm)		125.5 ± 12.6	132.1 ± 12.9	128.2 ± 17.9	128.6 ± 14.7
Duration of asthma (years)		5.0 ± 3.5	5.8 ± 2.6	5.3 ± 3.5	5.4 ± 3.2
Severity	Mild intermittent	15 (83.3%)	15 (83.3%)	14 (77.8%)	44 (81.5%)
	Mild persistent	3 (16.7%)	2 (11.1%)	4 (22.2%)	9 (16.7%)
	Moderate persistent	0	1 (5.6%)	0	1 (1.8%)
On inhaled steroids		2 (11.1%)	2 (11.1%)	1 (5.5%)	5 (9.2%)
Asthma attack (no/year)		1.1	0.8	1.2	1.1

Table 2. No. of treatment, asthma score and clinical parameters: compare nebulizer and MDI-spacer

Parameters	Time (min)	Nebulizer (n = 18)	MDI-spacer (n = 18)	p-value
No. of treatment		1.4	1.2	
Asthma score, mean (95%CI)	0	3.6 (3.05-4.15)	4.0 (3.74-4.26)	0.39
	20	1.8 (1.02-2.58)	2.2 (1.65-2.75)	0.44
	40	1.3 (0.84-1.76)	1.7 (1.44-1.96)	0.24
	60	1.0 (0.58-1.42)	1.7 (1.24-2.16)	0.10
O_2 saturation (%), mean (95%CI)	0	96.2 (95.46-96.94)	97.0 (96.35-97.65)	0.14
	20	97.6 (96.77-98.43)	97.0 (95.98-98.02)	0.33
	40	97.2 (96.94-97.46)	97.0 (95.94-98.06)	0.79
	60	97.0 (96.74-97.26)	97.3 (96.56-98.04)	0.44
RR (bpm), mean (95%CI)	0	36.3 (31.89-40.41)	32.5 (29.77-35.23)	0.11
	20	33.6 (29.95-37.25)	29.5 (26.87-32.13)	0.16
	40	31.4 (28.07-34.73)	28.3 (26.22-30.38)	0.12
	60	30.1 (27.87-33.33)	28.1 (25.83-30.37)	0.25
PR (bpm), mean (95%CI)	0	116.1 (106.12-126.08)	107.5 (97.52-117.48)	0.23
	20	119.1 (109.67-128.53)	109.2 (97.92-120.48)	0.18
	40	124.3 (114.22-134.38)	111.0 (101.48-120.52)	0.05
	60	114.2 (101.9-126.5)	108.1 (98.35-117.85)	0.42
BP (mm.Hg), mean (95%CI)	P_s 0	102.7 (97.8-107.6)	108.9 (103.69-114.11)	0.56
	P_d 0	70.6 (66.49-74.71)	74.8 (70.22-79.38)	
	P_s 60	108.0 (102.64-113.36)	106.0 (101.79-110.21)	0.44
	P_d 60	71.7 (67.49-75.91)	71.6 (67.99-75.21)	

Table 3. No. of treatment, asthma score and clinical parameters: compare nebulizer and DPI (Easyhaler)

Parameters	Time (min)	Nebulizer (n = 18)	DPI (Easyhaler) (n = 18)	p-value
No. of treatment		1.4	1.3	
Asthma score, mean (95%CI)	0	3.6 (3.05-4.15)	3.6 (3.14-4.06)	0.88
	20	1.8 (1.02-2.58)	2.2 (1.55-2.85)	0.51
	40	1.3 (0.84-1.76)	1.7 (1.19-2.21)	0.30
	60	1.0 (0.58-1.42)	1.6 (1.14-2.06)	0.07
O_2 saturation (%), mean (95%CI)	0	96.2 (95.46-96.94)	96.5 (95.76-97.24)	0.53
	20	97.6 (96.77-98.43)	96.8 (95.88-97.72)	0.23
	40	97.2 (96.94-97.46)	96.7 (95.78-97.62)	0.43
	60	97.0 (96.74-97.26)	97.0 (96.21-97.79)	1.00
RR (bpm), mean (95%CI))	0	36.3 (31.89-40.41)	33.0 (30.32-35.68)	0.16
	20	33.6 (29.95-37.25)	28.5 (25.68-31.32)	0.07
	40	31.4 (28.07-34.73)	27.8 (25.21-30.39)	0.07
	60	30.1 (27.87-33.33)	26.3 (24.17-28.43)	0.10
PR (bpm), mean (95%CI)	0	116.1 (106.12-126.08)	109.3 (100.24-118.36)	0.33
	20	119.1 (109.67-128.53)	113.5 (103.79-123.21)	0.45
	40	124.3 (114.22-134.38)	112.0 (103.22-120.78)	0.07
	60	114.2 (101.9-126.5)	111.2 (102.56-119.84)	0.69
BP (mm.Hg), mean (95%CI)	P_s 0	102.7 (97.8-107.6)	102.0 (97.24-106.76)	0.33
	P_d 0	70.6 (66.49-74.71)	70.0 (65.79-74.21)	
	P_s 60	108.0 (102.64-113.36)	102.2 (97.02-107.38)	0.44
	P_d 60	71.7 (67.49-75.91)	68.3 (64.97-71.63)	

Table 4. No. of treatment, asthma score and clinical parameters: compare MDI-spacer and DPI (Easyhaler)

Parameters	Time (min)	MDI-spacer (n = 18)	DPI (Easyhaler) (n = 18)	p-value
No. of treatment		1.2	1.3	
Asthma score, mean (95%CI)	0	4 (3.74-4.26)	3.6 (3.14-4.06)	0.32
	20	2.2 (1.65-2.75)	2.2 (1.55-2.85)	0.91
	40	1.7 (1.44-1.96)	1.7 (1.19-2.21)	0.88
	60	1.7 (1.24-2.16)	1.6 (1.14-2.06)	0.74
O_2 saturation (%), mean (95%CI)	0	97.0 (96.35-97.65)	96.5 (95.76-97.24)	0.40
	20	97.0 (95.98-98.02)	96.8 (95.88-97.72)	0.80
	40	97.0 (95.94-98.06)	96.7 (95.78-97.62)	0.60
	60	97.3 (96.56-98.04)	97.0 (96.21-97.79)	0.44
RR (bpm), mean (95%CI)	0	32.5 (29.77-35.23)	33.0 (30.32-35.68)	0.85
	20	29.5 (26.87-32.13)	28.5 (25.68-31.32)	0.65
	40	28.3 (26.22-30.38)	27.8 (25.21-30.39)	0.82
	60	28.1 (25.83-30.37)	26.3 (24.17-28.43)	0.31
PR (bpm), mean (95%CI)	0	107.5 (97.52-117.48)	109.3 (100.24-118.36)	0.81
	20	109.2 (97.92-120.48)	113.5 (103.79-123.21)	0.56
	40	111.0 (101.48-120.52)	112.0 (103.22-120.78)	0.88
	60	108.1 (98.35-117.85)	111.2 (102.56-119.84)	0.67
BP (mm.Hg), mean (95%CI)	P_s 0	108.9 (103.69-114.11)	102.0 (97.24-106.76)	0.12
	P_d 0	74.8 (70.22-79.38)	70.0 (65.79-74.21)	
	P_s 60	106.0 (101.79-110.21)	102.2 (97.02-107.38)	0.13
	P_d 60	71.6 (67.99-75.21)	68.3 (64.97-71.63)	

spacer and DPI group, but there is no statistical difference at 40 and 60 min (Fig. 1). Others are not significant ($p > 0.05$) (Fig. 2-4).

Side effects and admission (Table 5)

Tremor was found in all 3 groups (each has 1 patient). Concerning palpitation, there is 2 patients in

Table 5. Side effects and admission

Side effects	Nebulizer	MDI with spacer	DPI	Total
Tremor (%)	1 (5.5%)	1 (5.5%)	1 (5.5%)	3 (5.5%)
Palpitation (%)	2 (11.1%)	2 (11.1%)	0	4 (7.4%)
Admission (%)	0	1 (5.5%)	1 (5.5%)	2 (3.7%)

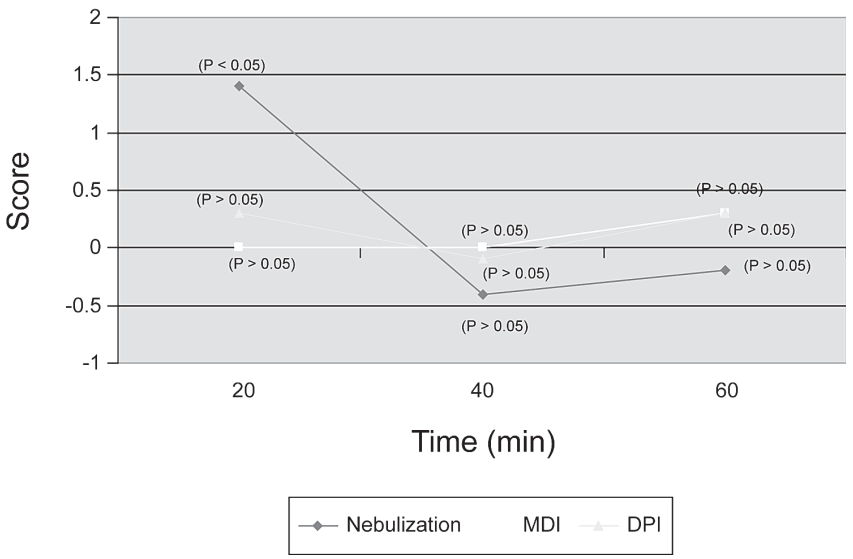

Fig. 1 Change of oxygen saturation from baseline among groups

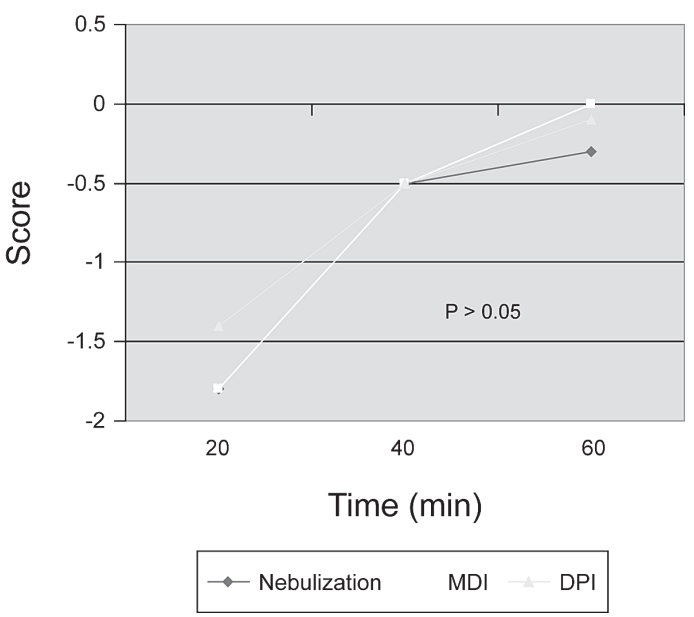

Fig. 2 Change of asthma score from baseline among groups

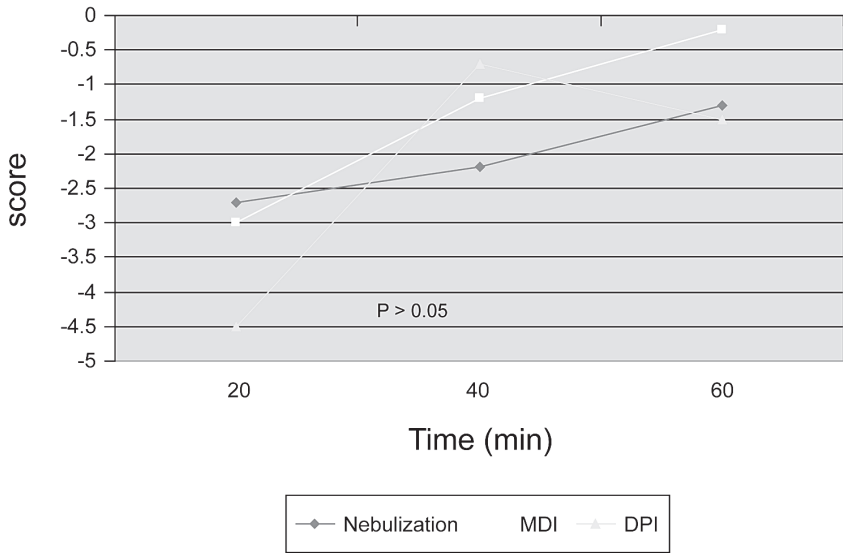

Fig. 3 Change of respiratory rate from baseline among groups

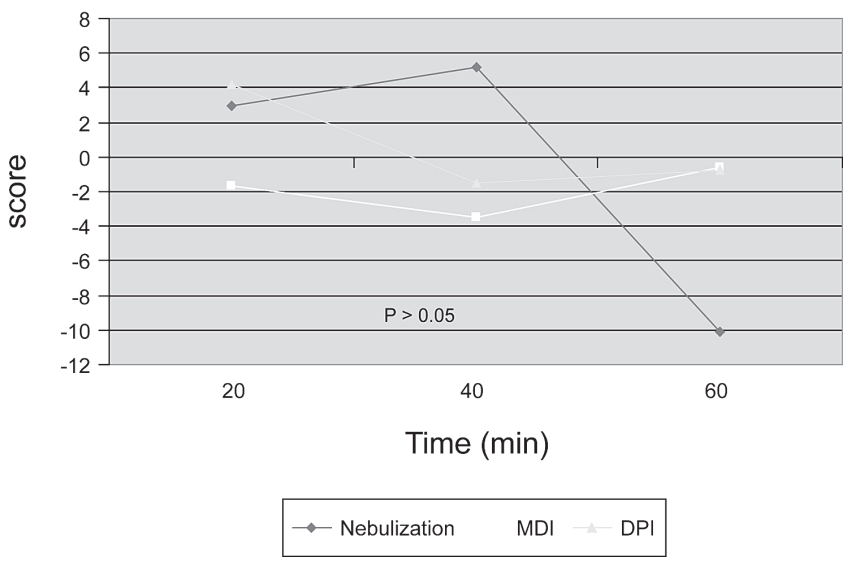

Fig. 4 Change of pulse rate from baseline among groups

the nebulizer group, 2 in MDI-spacer and 0 in DPI group. Two patients are admitted to the hospital; 1 in the MDI and 1 in DPI group.

Discussion

Rapid-acting beta-2-agonists are recommended for the treatment of acute asthma attack. There are many studies proved the efficacy of rapid-acting beta-2 agonists delivered via nebulization, MDI-spacer and DPI. Most of the studies are conducted both in adults and children, but studies among children have been limited. Haahtela, et al[15], studied in 20 asthmatic patients, aged 23-66 years, using salbutamol MDI 800 mg and DPI form (Easyhaler). They found that there were no significant differences in changes among FEV_1, FVC and PEF. The same result, studied in children, was

found by Juntunen-Backman, et al[16], when comparing MDI-spacer and Easyhaler.

This study shows the comparable efficacy of salbutamol aerosol therapy (evaluated by using clinical scores, number of treatment, oxygen saturation, RR and PR) via nebulizer, MDI-spacer and DPI in the treatment of mild to moderate severity asthma attack.

The equivalent dose of MDI-spacer, DPI to nebulizer salbutamol has yet to be agreed on. Doses of salbutamol administered via MDI-spacer and DPI varied among studies. There is a high variation in the ratio of salbutamol doses given via nebulizer to those given via MDI-spacer. The wide range reported in the literature (1:1 to 1:12.5)[22-28] is a reflection of different study designs and delivery systems. This study uses 600 mg of salbutamol both in MDI-spacer and DPI groups. For nebulized salbutamol, the dose of 0.15 mg/kg is used, the same in most studies. The average dose of salbutamol is 5.67 mg for nebulizer, and 0.75 mg for MDI-spacer and DPI. The ratio of MDI-spacer/DPI: nebulizer is 1:7.56.

The change of O_2 saturation from baseline at 20 min. in the nebulizer group is significantly increased, compared to the other 2 groups ($p < 0.05$). It is due to the effect of oxygen used to drive pressure for nebulization, but at 40 and 60 min., the change of oxygen saturation is not different in all 3 groups.

Comparing side-effects and admission, they are also not different among the 3 groups. Therefore, the use of salbutamol via MDI-spacer and DPI in asthma attack seems to be less expensive, less amount of drugs and more convenient when compared with nebulization. However, use of MDI-spacer and DPI for aerosol therapy may have some limitation in some children that they cannot do it correctly or have less inspiratory effort to inhale the dry powder form. Therefore, when physicians select the aerosol therapy, the following should be carefully considered: devices/drugs availability, clinical setting, age, ability to use the devices correctly, cost, convenience and patients' preferences in order to achieve maximum efficacy of treatment for each individual patient.

Conclusion

The efficacy of salbutamol delivered via nebulizer, MDI-spacer and DPI is not different. Concerning less cost, easier application and less systemic side effects, MDI-spacer and DPI should be considered in the treatment for acute exacerbation of asthma in children with mild to moderate severity.

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การเปรียบเทียบประสิทธิผลการใช้ยาขยายหลอดลม salbutamol แบบ metered dose inhaler ร่วมกับ volumatic spacer และแบบ dry powder inhaler, easyhaler กับการสูดยาแบบฝอยละออง ในผู้ป่วยเด็กโรคหืดที่มีอาการหอบเฉียบพลันความรุนแรงระดับน้อยถึงปานกลาง

มุกดา หวังวีรวงศ์

ภูมิหลัง: ปัจจุบัน rapid-acting inhaled beta-2 agonist เป็นยามาตรฐานในการรักษาโรคหืดหอบในระยะ เฉียบพลัน โดยออกฤทธิ์ทำให้กล้ามเนื้อเรียบของหลอดลมคลายตัว ให้ผลรวดเร็ว มีผลข้างเคียงน้อยกว่าชนิดฉีด และชนิดรับประทาน การบริหารยามีหลายวิธี เช่น nebulizer, MDI with spacer, dry powder (easyhaler) ในประเทศไทยนิยมใช้วิธี nebulizer ในการรักษาอาการหอบเฉียบพลันในผู้ป่วยเด็ก

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบประสิทธิผลและผลข้างเคียงของการใช้ยา salbutamol ผ่านทาง MDI with volumatic spacer และ easyhaler กับวิธี nebulizer ในการรักษาอาการจับหืดเฉียบพลัน ระดับความรุนแรงน้อยถึงปานกลางในเด็ก

วัสดุและวิธีการ: การศึกษาเชิงทดลองทางคลินิกแบบไปข้างหน้า ในผู้ป่วยโรคหืดอายุตั้งแต่ 5-18 ปี ที่มีอาการหอบเฉียบพลันความรุนแรงระดับน้อยถึงปานกลางที่มารับการรักษาที่แผนกฉุกเฉินของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ระหว่างเดือนตุลาคม พ.ศ. 2547 ถึง กุมภาพันธ์ พ.ศ. 2549 แบ่งผู้ป่วยเป็น 3 กลุ่มตามวิธีการบริหารยาดังต่อไปนี้ กลุ่มที่ 1 nebulizer กลุ่มที่ 2 MDI with volumatic spacer กลุ่มที่ 3 DPI (easyhaler) หลังได้รับยาจะประเมินค่า asthma score, oxygen saturation, PR, RR, BP และผลข้างเคียงของยาที่ 0, 20, 40 และ 60 นาที การให้ยา salbutamol จะให้ทุก 20 นาที โดยจะให้มากที่สุด 3 ครั้ง ถ้าผู้ป่วยอาการไม่ดีขึ้น จะรับไว้รักษาใน โรงพยาบาลต่อไป

ผลการศึกษา: ผู้ป่วยเด็กโรคหืดที่มีอาการหอบเฉียบพลันรุนแรงระดับน้อยถึงปานกลางจำนวน 54 ราย ที่มาพบแพทย์ที่แผนกฉุกเฉินของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี เพศชาย 35 ราย (64.8%) เพศหญิง 19 ราย (35.2%) อายุเฉลี่ย 8.4 $\pm$ 2.3 ปี แบ่งเป็น 3 กลุ่ม ๆ ละ 18 ราย พบว่าประสิทธิผลการให้ยาขยายหลอดลมทั้ง 3 แบบไม่แตกต่างกัน ทั้งค่า asthma score, oxygen saturation, PR, RR, BP สำหรับผลข้างเคียงของยา พบอาการมือสั่นร้อยละ 5.5 เท่ากันทั้ง 3 กลุ่ม ส่วนอาการใจสั่นพบร้อยละ 11.1 เฉพาะในกลุ่มที่ 1 และ 2 เท่านั้น ผู้ป่วยที่ต้องรับไว้ในโรงพยาบาล 2 ราย เป็นผู้ป่วย 1 ราย ในกลุ่ม 2 และ 1 ราย ในกลุ่ม 3 ไม่มีผู้ป่วยในกลุ่ม 1 ที่ต้องรับไว้ในโรงพยาบาล

สรุป: การให้ยา salbutamol โดยบริหารผ่านทาง MDI with volumatic spacer และ dry powder (easyhaler) ในการรักษาภาวะจับหืดเฉียบพลันในผู้ป่วยเด็กโรคหืดความรุนแรงระดับน้อยถึงปานกลาง มีประสิทธิผลและผลข้างเคียงไม่แตกต่างกับการสูดยาแบบฝอยละออง