Comparison of Salbutamol Delivered via Jet Nebulizer With a Metered Dose Inhaler (MDI) Plus a Spacer for Asthma Exacerbation of Children: A Randomized Clinical Trial

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Received: 18 Feb. 2019; Accepted: 28 Jul. 2019

Abstract- Asthma is the most common chronic illness in children and is a major reason for pediatric emergency department visits. Beta-2 agonists are considered the most effective drugs for immediate relief in the symptoms. This study aimed to compare the effectiveness of salbutamol delivered via jet nebulizer with a metered-dose inhaler (MDI) plus a spacer for asthma exacerbation in the pediatric emergency departments. The study was a randomized control, parallel-group design in children with age ranging from 6 months to 14 years, presenting in the emergency department with an acute asthma attack. A total of 116 patients were recruited for the study. Sixty-two patients were enrolled in the MDI/spacer group, and 54 patients were in the nebulizer group. Patients were assessed at baseline (0 min) and 15, 30, 45 and 60 min after commencement of the nebulizer and MDI/spacer. The response of each group to treatment was compared. The parents were counseled for their child enrolment in the study, which was approved by the Human Ethics Committee of Shahid Beheshti University of Medical Sciences. Ethic code was IR.SBMU.SM.REC.1394.19. The patients in both treatment groups demonstrated statistically noticeable improvement in clinical scores at all study assessment periods. Results revealed that salbutamol via MDI/spacer was as effective as salbutamol nebulization during the treatment of asthma exacerbations. Salbutamol MDI/spacer is equally efficacious when compared to nebulization. Therefore, because Salbutamol MDI/spacer is more user-friendly and affordable, it is preferable to be used in emergency departments.

Acta Med Iran 2019;57(11):672-677.

Keywords: Asthma; Metered-dose inhalers; Nebulizer; Salbutamol; Wheezing

Introduction

Asthma in children is the major cause of hospitalization and school absence (1,2). The prevalence of asthma is on the rise in children, despite all the preventative measures taken to control this condition (3). The obstruction of respiratory airways during an asthma attack leads to the poor functioning of the lungs, which can be life-threatening. Inhaled Beta 2 agonists dilate the airways very quickly and thus relieves the respiratory symptoms. Salbutamol administered by metered-dose inhaler (MDI) and the nebulizer is an effective remedy for acute asthma attacks (4). The most obvious advantage of using nebulizer is the fact that it does not require the coordination between the patient's breathing and the delivery of aerosol (5,6). Accordingly, in children with respiratory distress nebulizers are suitable means of drug administration (7). Nebulizers deliver only 10 % of the medication dose to the lungs (6) while inhaled medication by MDI plus spacer help the lungs to absorb around 21% of the given dose (8). As a result, prescribing a higher dose of the drug via nebulizer is required for effective treatment. Using nebulizers necessitates some other equipment, which is costly. Besides, it is time-consuming for the hospital personnel, requires a power supply, and may act as a potent source of nosocomial infection. Whereas using salbutamol via MDI with a spacer is cheaper, more accessible, and does not require any other equipment except MDI.

However, while there are good reasons for the use of the MDI with a spacer, inhalation via nebulizer is still being used in pediatric emergency departments (ED).

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However, in our country, no study has been conducted till date to compare these two methods of drug delivery in a pediatric asthma attack in order to offer a more effective remedy with fewer expenses on families and society. The current study aimed to assess patients' response to the medication as well as the impact of these two treatment approaches on acute asthma attacks in patients.

Materials and Methods

The present study was a randomized clinical trial conducted from 2016 to 2017. A total of 116 children who visited Mofid children's hospital emergency department (ED) for the acute asthmatic attack were enrolled in the study. Sampling was done convenience and then allocated randomly using Excel RANDBETWEEN function to control (nebulizer) and intervention (MDI) groups. The parents were counseled for their child enrollment in the study. Sealed opaque envelopes were used for randomization after taking informed patient consent. The study was approved by the Human Ethics Committee of Shahid Beheshti University of Medical Sciences. Blinding was not possible because of the nature of the intervention, but it was ensured that both groups received the same monitoring.

Inclusion criteria

Age 6 months -14 years, wheezing present on auscultation, and a score> 4 on the respiratory distress assessment scale (RDAS) (9,10).

Exclusion criteria

Severe respiratory distress requiring admission in a pediatric intensive care unit, and a patient diagnosed with bronchopulmonary dysplasia, cystic fibrosis or congenital cardiopulmonary disorders.

A minimum sample size of 53 was estimated for each group, considering the 95% confidence and 90% power based on literature review using the following formula:

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 (s_1^2 + s_2^2)^2}{(\mu_1 - \mu_2)^2} = \frac{(2.57 + 1.28)^2 (1.2^2 + 1.2^2)}{(2.1 - 1.2)^2} \cong 53$$

It should be noted that the sample size was expanded to 116, including 62 patients received MDI and 54 nebulizers (Figure 1).

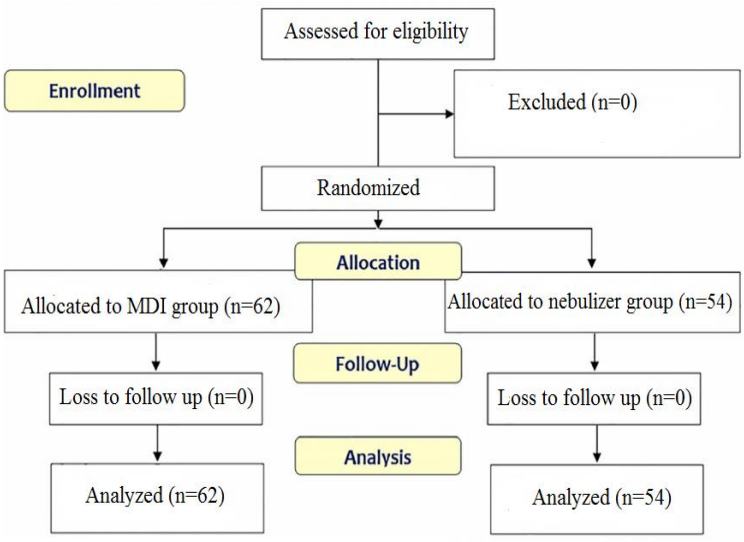

Figure 1. Follow-up diagram of patients (According to the consort statement)

Study design

The initial clinical assessment was done by one of the investigators, and all eligible patients were randomly assigned to receive salbutamol either through a nebulizer or an MDI with a spacer. The patients allocated to the MDI- spacer group, received between 2 and 10 puffs of salbutamol MDI (depending on weight) (11), at 15-min intervals via a valve aerosol-holding chamber device with the aero-chamber masks sealed to their faces and held there for 30 seconds up to five times. The patients who were assigned to nebulizer inhalation therapy received 0.15 mg per kg of salbutamol (maximum dose of 2.5 mg), up to 5 times every 15 minutes. Clinical scores were determined according to oxygen saturation (pulse

oximetry), respiratory rate, auscultation and chest wall retraction (Table1) (9). Scores were calculated along with clinical assessment at baseline (0 min) and in the 15th, 30th, 45th and 60th minutes after initiation of treatment, respectively. This scoring system assigns a number from 0-3 for each parameter, and the final score varies from 0 -12. A higher score means an increase in the severity of the asthma attack. The information was recorded in a questionnaire, and the response to the treatment was determined based on the improvement in their clinical scores. Confidentiality was kept while recording the necessary patient clinical information. Both groups were prescribed the necessary amount of supplementary oxygen. In this study, the level of oxygen saturation was monitored by the SAZGAR GOSTAR vital signs monitor. Omron ultrasonic NE-17 ultra A-I-R nebulizer was used in the study.

Primary outcome

The score of the Respiratory Distress Assessment Scale in children with asthma using salbutamol through the MDI.

Statistical analysis

The data were analyzed using SPSS 22 software (SPSS Inc., Chicago, IL). The Kolmogorov Smirnov was done, indicating the normal distribution of the data. The student's t-test, chi-square test, and independent samples test were used to compare characteristics of the two groups. Wilcoxon Signed Ranks Test was applied for evaluating clinical score trends. In order to compare the clinical scores in two groups Man-Whitney Test was used.

Results

The present study was composed of 116 patients (74 males and 42 females) with an asthma attack. Sixty-four children were treated with salbutamol MDI-spacer and 54 with salbutamol nebulizer at random. There was no significant statistical difference in the baseline characteristics of the two intervention groups (Table 2).

In all patients, the duration between symptom initiation and hospital presentation was analyzed (crosstab and chi-square tests) (Table 2). There was no statistical difference between the two groups regarding the emergency department time visit from the onset of symptoms (P=0.31) (Table 2). Patients' oxygen saturation was categorized according to RDAS, and the scores were analyzed (Wilcoxon Signed Ranks Test). There was an improvement in oxygen saturation scores in both groups over time when compared to the scores at the time of initiation of therapy. There was no significant difference between the two intervention groups when patient oxygen saturation scores were compared (Table 3).

The results of asthma clinical scores according to the parameters assigned in table 1 were summarized as table 4. There was no significant statistical difference between the two groups in asthma attack severity according to baseline (0 min) asthma clinical scores (Table 4). The patients in both treatment groups demonstrated improvement in the clinical score at all study assessment periods (Table 4). Among the patients 71 individuals needed additional treatment; 36 patients in the MDI-spacer group and 35 in the nebulizer group received additional treatment, but this did not lead to any significant statistical difference (P=0.58).

Table 1. Respiratory Distress Assessment Scale

Variable		Points			
		0	**1**	**2**	**3**
Respiratory rate (per min)		< 30	31-45	46-60	>60
Wheezing *	**Expiration**	No	Yes	Yes	Yes
	Inspiration	No	No	Yes	Yes
	Without stethoscope	No	No	No	Yes
Retractions	**Supraclavicular**	No	Mild	Moderate	Marked
	Intercostal	No	Mild	Moderate	Marked
	Subcostal	No	Mild	Moderate	Marked
	Pulse oximetry (%sat.)	≥93	89-92	85-88	<85

*If not wheezing because of hypoventilation: score 3.

Table 2. Clinical characteristics of the two groups

		MDI+spacer (n=62)	Nebulizer (n=54)	*P*
Age (months)*		52.47±33.01	39.12±37.87	0.06
Weight (kilogram)*		18.85±9.06	15.57±10.01	0.06
Gender		Male:40, Female: 22	Male: 34, Female: 20	1
Symptom duration		--	--	0.31
<24hr		14(22.6%)	7(13%)	--
24-48 hr		13(21%)	16(29.6%)	--
>48 hr		35(56.5%)	31(57.4%)	--
Allergic conditions(n)	**Atopic dermatitis**	-	3(5.6%)	--
	Allergic rhinitis	1(1.6%)	-	--
	Food allergies	5(8.1%)	3(5.6%)	--
Parental/allergic conditions	**Atopic dermatitis**	3(4.8%)	-	--
	Allergic rhinitis	5(8.1%)	11(20.4%)	--
	Food allergies	3(4.8%)	2(5.7%)	--
	Asthma	9(14.5%)	10(18.5%)	--
	Medication (Prior to ER visit) Bronchodilator	24(%38.7)	16(29.6%)	0.40
	Inhaled corticosteroids	15(24.2%)	10(18.5%)	0.60

* values are expressed as mean ± SD, ER: Emerency Room

Table 3. The analysis of the oxygen saturation scores (mean ± SD)

Time assessment	MDI + spacer score	Nebulizer score	*P*
0	1.92±0.70	2.17±0.66	0.058
15 min	1.63±0.70	1.74±0.73	0.39
30 min	1.42±0.56	1.39±0.56	0.72
45 min	1.27±0.51	1.28±0.49	0.86
60 min	1.81±0.42	1.17±0.42	0.85

Table 4. Clinical asthma score (mean±SD)

Stratum	Time assessment	MDI+space	Nebulizer	*P*
	0	7.98±2.17	7.95±2.03	0.96
	15 min	7.09±2.27	6.91±2.13	0.70
≤ 20	30 min	6.57±2.10	6.00±1.91	0.18
	45 min	6.20±2.13	5.68±1.91	0.22
	60 min	5.64±2.02	5.16±1.59	0.22
	0	7.94±1.98	7.70±2.62	0.78
	15 min	6.61±1.94	7.40±2.45	0.35
> 20	30 min	5.94±1.47	6.50±2.46	0.45
	45min	5.39±1.33	5.00±2.15	0.53
	60 min	5.00±1.18	5.50±2.22	0.44
	0	7.95±2.13	7.91±2.13	0.89
	15 min	6.94±2.20	7.00±2.18	0.88
All	30 min	6.37±1.97	6.09±2.01	0.34
	45 min	5.94±1.99	0.69±1.99	0.34
	60 min	5.42±1.86	5.19±1.74	0.33

Discussion

Asthma is one of the most common causes of visiting the hospital which accounts for up to 8% of all pediatric ED visits (12). Inhaled selective beta 2 agonists are the essential treatment for children with acute asthma exacerbations, which can be delivered via MDI with spacer or nebulizer devices (13).

In the present study, 66 (57%) of children were brought to ED after 48 hours since the first respiratory symptoms initiated, and 65.5% of the patients did not receive any bronchodilator prior to ED visit. The findings above indicate the fact that either the patients or their caregivers were not adequately trained and educated to start therapy in case of asthma exacerbations at home or the asthma attack was the first presentation of their disease. We should not ignore the effect of education in any aspect of asthma treatment especi lly in pediatrics (14).

The current study revealed that both treatment

approaches were effective in the treatment of acute asthma attacks. In both groups, the patients' asthma clinical score experienced a sharp decline in the 15th minute compared to the baseline, and which continued till the last. Therefore, both approaches are equally effective in alleviating acute asthma attacks. Although there were some controversy overdoses administered via MDI with a spacer and a nebulizer, this can be explained according to previous studies of drug deposition in the lung. Twenty-one percent of salbutamol via MDI spacer reaches patients' lungs, whereas only half this amount (10%) reaches lungs when the nebulizer is used for a drug administered (6,8). Consequently, salbutamol MDI/spacer dose to nebulized dose ratio of 1: 3 is relatively equal.

Benito-Fernandez J *et al*., conducted a similar study in 2004 in which the MDI group was collected through a prospective cohort study, and the nebulizer group data were obtained from a retrospective study. They demonstrated that administration of salbutamol by MDI with a spacer is an efficient replacement for a nebulizer for the treatment of asthma attacks in the pediatric ED (15). In our study, both groups were studied prospectively, thus making results more reliable. In another study that was done by Closa *et al.,* terbutaline was given to young children by MDI with spacer and nebulizer. Accordingly, both methods were equally effective means of delivering beta-2 agonists to infants and small children with acute wheezing (9). As oppose to mentioned studies and our study as well, Robertson CF *et al*., showed that administration of salbutamol via MDI spacer was less effective than a jet nebulizer in relieving asthma attacks in children. In addition, improvement in the clinical score was more noticeable for patients above 25 kg who were treated with nebulizer than that of the MDI spacer group (16). This difference could be because of different study populations when compared to our study. Based on our findings, the children's response to both treatment approaches were nearly the same without any significant statistical difference, and patients' weight did not affect their response to the treatment. Previous studies (16,17) in which spirometry was employed to compare the impact of both treatment modes could not evaluate children below five years and those with severe asthma attacks due to lack of cooperation. However, in the present study, the clinical score system was used in order to compare two groups, so that we could assess children with a severe asthma attack and even infants as well. When both the treatment approaches are compared, the results show that salbutamol spray is cheaper in comparison with a nebulizer (18). Based on the study which was conducted on children aged 2 to 24 months there were lower admission rates in the MDI spacer group children with a more severe asthma attack (19). On the other hand, salbutamol MDI is portable and easily usable on a trip or at home. Neither electricity nor any power supply is required to use salbutamol MDI. Nebulizer device is expensive and, therefore, a financial burden for both patients and hospitals. Using nebulizer is time-consuming for hospital personnel. Unlike MDI devices, the same nebulizer machine is used for all patients. Consequently, there is a high risk of infection associated with the use of nebulizer (20,21).

The strength of our study include having prospective and randomized controlled trial design with large sample size. The limitation of our study included the use of employed electrostatic spacers. The use of such devices causes the chamber to absorb some of the aerosol particles, leading to lower dose delivery of the medication (20). Consequently, if we had not electrostatic devices, more drug deposition would have been in lungs leading to increased salbutamol MDI impact. The impact of these two treatment modes depends on how they are administered by hospital personnel. It is possible that some of the medication goes to waste if children get agitated, so it would be a good idea to use oxyhood instead of the mask when prescribing nebulizer for infants.

We employed the electrostatic spacers in our study. The use of such devices causes the chamber to absorb some of the aerosol particles, which leads to lower delivery of the medication (22). Consequently, if we used not electrostatic devices, more drug deposition would be in the lungs as well as increased salbutamol MDI impact.

The small sample size of our study is a potential limitation. There is still need for further studies to access additional information about the salbutamol MDI impact.

Comparing the advantages and disadvantages of both treatment modes, we conclude that salbutamol MDI with a spacer is more user-friendly and more affordable both for patients and hospitals. Besides, there is a lower risk of infection as well as fewer side effects. Considering the fact that both treatment modes have a similar impact on acute asthma attacks in children, it is preferable to use salbutamol by MDI/spacer. Additionally, there is parents' ignorance, especially when asthma shows signs of deterioration, leading to delayed initiation of treatment. Therefore, parents and patients must be educated on how to detect and manage asthma exacerbation. To increase the accuracy of results, we recommend conducting a more extensive study in the future.

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