COMPARATIVE EFFICACY OF JET NEBULIZER AND METERED DOSE INHALER WITH SPACER DEVICE IN THE TREATMENT OF ACUTE ASTHMA

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***Objective**: To compare the relative efficacy of jet nebulizer and metered dose inhaler (MDI) with spacer for the administration of aerosolized salbutamol in an acute exacerbation of bronchial asthma. **Design**: Randomized prospective study. **Setting:** Emergency Room. **Methods**: In 60 subjects with acute asthma aged between 1 to 12 years, clinical and laboratory assessment of severity at recruitment included heart rate, respiratory rate, pulsus paradoxus, arterial blood gas analysis (all cases) and peak expiratory flow rate (wherever possible). The subjects were randomized into two equal groups to receive aerosolized salbutamol either via nebulizer (Group I) or MDI-spacer (Group II) as per the Consensus Guidelines. The response to therapy was sequentially assessed after 20, 40 and 60 minutes of institution of therapy. **Results:** A significantly ($p < 0.02$) greater number of subjects in Group II presented with severe dyspnea and intercostal muscle retraction (subjective assessment). However, the objectively evaluable outcome parameters were comparable ($p > 0.05$) in both groups at presentation. All the outcome measures showed a significant ($p < 0.05$) improvement with time in both the groups. The recovery parameters were comparable ($p > 0.05$) at different time periods in the two groups. **Conclusion:** MDI-spacer is as effective as a nebulizer for the aerosolized administration of salbutamol in an acute exacerbation of asthma in children. However, for developing countries, distinct advantages (economic and power requirement) argue strongly for utilization of MDI-spacer in preference to nebulizer.*

Key words: *Acute bronchial asthma, Jet nebulizer, Metered dose inhaler, Spacer.*

BRONCHIAL asthma is an important cause of morbidity in childhood. In recent years, the prevalence(l) of this condition and the associated morbidity and mortality(2) have increased. On the basis of available scientific evidence, international guidelines(3-8) have been developed for the optimal management of childhood asthma. Consensus protocols(3) outline and provide a schedule of treatment in acute severe asthma. The main goal of treatment is to rapidly reverse the airflow obstruction. Administration of aerosolized beta-2 agonists is favored for this purpose, The advantages of aerosol therapy include direct drug delivery at the target organ at much lower doses with fewer side effects. Repeated doses or even continuous therapy can also be safely administered.

Nebulization of beta-2 agonists into a wet aerosol has been the conventional method employed for inhalational use, particularly in the institutional set up. Nebulizers are considered to be the optimum method of aerosol delivery in an acute attack of bronchial asthma because

they produce particles of desired size at a slow speed thus requiring no coordination. However, nebulizers are cumbersome, expensive and require power supply. Sometimes infants may not tolerate this relatively noisy equipment for long treatment periods. Further, improper cleaning may result in nosocomial infections. In a developing country like India, uninterrupted power supply and cost concerns, both reparative and maintenance related, preclude the widespread use of nebulizers. Consensus protocols(3-5,7,8) have suggested that an effective alternative is to give beta-2 adrenergic agonists by multiple actuations of a metered dose inhaler (MDI) into a large spacer device. MDI's are compact and portable and this aerosolization mechanism is less expensive than a nebulizer.

Even though Consensus Guidelines(3-5,7,8) recommend the MDI spacer as an alternative mode of therapy, there are few well controlled studies in children(9-16) comparing the relative efficacy of these two methods of aerosolized administration of beta-2 agonists. Unfortunately, even the available data suffer from several limitations: (i) Subjects younger than 3 years were not evaluated; *(ii)* Sample sizes were relatively lower; *(iii)* Severity assessment has not been based on criteria laid down by the Guidelines. Arterial blood gases were not evaluated at the beginning and end of the study; *(iv)* The dose ratios for beta-2 agonists delivered by MDI-spacers and by nebulizers have varied widely (from 1:1 to ' 1:10). In none of studies were the Guidelines(3) regarding drug dosages and schedules followed; and *(v)* Intravenous hydrocortisone prior to the study was sometimes administered which further confounded the issue. The present study was, therefore designed to compare the relative efficacy of jet nebulizer and MDI-spacer in the treatment of an acute exacerbation of bronchial asthma controlling for the aforementioned limitations.

Subjects and Methods

The investigation was conducted in the Pediatric Emergency Room during the period 1994-95. Children between the ages of 1 to 12 years seeking treatment for an acute exacerbation of bronchial asthma were eligible for enrollment in the study. Subjects had experienced more than 2 attacks of wheezing in the past. Bronchial asthma for the purpose of the study was defined as per earlier recommendations(17): "Recurrent episodes of wheezing which occur in response to allergens, exercise or exertion as well as with symptoms suggestive of respiratory infection. On auscultation there should be a high pitched wheeze over most parts of the lung." An acute attack was defined as any episode for which the patients or parents needed to take emergency consultation. Exclusion criteria included: *(i)* Pulmonary tuberculosis, emphysema and other known heart, liver, kidney or lung diseases to limit the evaluation to uncomplicated cases of bronchial asthma; *(ii)* Skeletal disorders involving spine or intercostal muscles or diaphragm involvement; and *(iii)* Age below 1 year to exclude subjects with bronchiolitis (peak incidence 6 months) with relapses. The study was approved by the Institutional Review Committee. An informed verbal consent was obtained from the parents prior to recruitment.

A detailed clinical evaluation (history and examination) was recorded on a pretested proforma and the severity (mild, moderate or severe) of the acute episode of bronchial asthma assessed by Guidelines criteria(3). Investigations performed prior to institution of therapy included peak expiratory flow rate (PEFR) by peak flow meter (Wright's Flow Meter) in subjects able to undergo the evaluation and arterial blood sampling for pO_2, pCO_2 and pH esti-

mation (Eischweiler 2000 blood gas analyzer). The subjects were then randomized (computer generated random numbers) into two treatment groups. Group I comprised children who received aerosolized medications by jet nebulizer. Group II received aerosolized medications by MDI with spacer attachment (with or without attached face mask). A commercial spacer (M/s Cipla) with a volume of 750 ml and one way valve was utilized. Face mask attachment was required in younger subjects (<3 years age) and in children who were too sick to inhale directly from the spacer. For this purpose, the face mask of an Ambu Bag was attached to the commercial spacer (same as above). Inhalation was given in . the lying down position with the spacer inverted to make the valve functional.

Humidified oxygen was given to all patients at a flow rate of 3-4 L/min. Group I received salbutamol nebulizer solution in a dose of 0.15 mg/kg diluted in 2.5 ml of normal saline. Three such doses were given at an interval of 20 minutes. Salbutamol MDI with a spacer device (with or without a face mask) was used in Group II to provide a dose of 2 puffs (100 μg salbutamol per puff) every 5-10 minutes till the end of 60 minutes from the start of therapy.

Children were sequentially examined at 20, 40 and 60 minutes by a single observer (VB) to assess the response to inhaled salbutamol. For obvious reasons, blinding was not possible for this purpose. Response was categorized as good, partial or poor as per the Guidelines recommendations(3). Criteria for assessment included dyspnea (subjective assessment), heart rate, respiratory rate, pulsus paradoxus, auscultatory findings, accessory muscle usage, arterial blood gas analysis (ABG) and PEFR (only in patients above 3 years of age who were able to perform the test). ABG and PEFR were repeated only at end of 60 minutes. Cases with incomplete or poor response at 60 minutes were given further treatment according to the Consensus protocols(3) whereas those with a good response were discharged with advise. The decision for admitting or discharging a patient at this stage was taken by the Senior Resident on duty who was not aware of the randomization group.

For the purpose of sample size calculation, response to nebulizer was considered to be the "gold standard". A sample size of 30 subjects in each group was calculated (unmatched case control comparison) to be sufficient to detect a difference of 30% in the response rate with 95% confidence and 80% power. Relevant statistical analyses performed included Chi square test, Chi square for linear trend, Student 't' test, paired 't' test and analysis of covariance for repeated measures.

Results

A total of 60 subjects (30 in each group) fulfilling the study criteria were evaluated. The two groups were comparable ($p>0.05$) for majority of the characteristics at admission *(Table I*). The sequential changes in the outcome measures evaluated are summarized in *Table II.* As per the Guideline Criteria(3) majority of patients in both groups had either moderate or severe exacerbation at presentation. A significantly ($p<0.02$) greater number of subjects in Group II (MDI with spacer) presented with severe dyspnea and severe intercostal muscle retraction (subjectively assessed parameters). However, the objectively evaluable outcome parameters were comparable ($p>0.05$) in both groups at presentation. All the outcome measures showed a significant 1 ($p<0.05$) improvement with time in both the groups indicating the efficacy of the e treatment modalities employed. After institution of therapy, all the recovery parameters including ABG were comparable

TABLE I-*Comparison of Various Baseline Characteristics.*

Parameters	Group I	Group II
Number	30	30
Males (No.)	13	15
Age (mo)	51.2 (27.1)	44.1 (25.8)
Major presenting symptoms (%)		
Breathelessness	100	100
Wheezing	90	87
Cough	100	100
Nocturnal symptoms	60	63
Fever	40	33
Duration of presenting symptoms (days)		
Breathlessness	2.6 (1.7)	2.1 (1.3)
Wheezing	1.7 (1..4)	1.5 (1.2)
Cough	5.0 (3.4)	4.2 (2.6)
Age of onset (mo)	20.1 (14.5)	18.0 (12.6)
Duration of disease (mo)	29.9 (19.0)	26.0 (22.7)
Frequency of attacks (past 6 mo)	5.9 (3.8)	6.7 (3.8)
Age at diagnosis (mo)	25.6 (3.9)	22.9 (14.5)
No. of hospitalizations (past 6 mo)	1.1 (1.3)	0.9 (1.4)
Time since last attack (days)	32.0 (26.8)	32.0 (26.3)
Weight (Kg)	13.16 (4.6)	11.68 (4.25)
Height (cm)	95.5 (13.7)	91.2 (13.9)

Values are depicted as means (SD) unless otherwise stated.
None of the differences between the two groups were statistically significant ($p>0.05$).

($p>0.05$) at different time periods in the two groups. Only 16 subjects (Group 1-7 and Group II-9) could perform the PEFR at the baseline. The PEFR value was below 40% of the predicted normal for weight, height and sex for all these cases. At 60 minutes, all had PEFR between 40 to 70% the predicted normal except for one child in Group II in whom the PEFR was above 70% of predicted normal.

Table III outlines the sequential categorization of response in the two groups as per outlines by the Guidelines criteria(3). It is obvious that the two modes of aerosolized delivery were equally effective ($p>0.05$). At 60 minutes, the total number of patients showing good response was 47 (24 in Group I and 23 in Group II). No obvious side effects were documented in any patient in both the groups. On the basis of purely subjective impressions of the observer and parents relatives, it was felt that the MDI-spacer was better tolerated than nebulizer, particularly in younger case (time to use, noise and patient resistance).

Discussion

The present study which addressed several lacunae of earlier attempts in this direction(9-16), demonstrated that for aerosolized administration of salbutamol in an acute exacerbation of bronchial asthma, MDI with spacer is as effective as the jet

TABLE II—*Sequential Comparison of Outcome Measures Evaluated.*

Parameter	0 min		20 min		40 min		60 min	
	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II
Grading of dyspnea								
Absent	0(0)	0(0)	0(0)	0(0)	2(7)	2(7)	14(47)	10(33)
Mild	2(7)	0(0)	9(30)	5(17)	17(57)	15(50)	12(40)	13(44)
Moderate	16(53)	9(30)	15(50)	18(60)	9(30)	12(40)	3(10)	6(20)
Severe	12 (40)*	21 (70)	6 (20)	7 (23)	2 (7)	1 (3)	1 (3)	1 (3)
Ability to speak+								
Incomplete sentences	13(44)	8(38)	19(65)	17(81)	24(83)	19(90)	26(90)	20(95)
Phrases	8 (28)	11 (52)	8 (28)	2 (10)	5 (17)	2 (10)	3 (10)	1 (5)
Single words	8(28)	2(10)	2(7)	2(9)	0(0)	0(0)	0(0)	0(0)
Heart rate (per min)	157.6 (8.5)	158.4 (7.2)	153.1 (8.6)	153.2 (8.1)	150.6 (9.6)	148.3 (8.7)	150.2 (11.6)	145.6 (9.4)
Respiratory rate (per min)	59.6 (8.0)	61.2 (6.1)	53.7 (8.2)	55.7 (6.7)	49.1 (7.3)	49.8 (6.8)	38.7 (7.4)	37.7 (6.7)
Accesory intercostal muscle retractions								
No/mild	0(0)	0(0)	4(13)	2(7)	15(50)	12(40)	24(80)	24(80)
Moderate	18(60)	9(30)	20(67)	20(66)	13(43)	17(57)	5(17)	5(17)
Severe	12 (40)*	21 (70)	6 (20)	8 (27)	2 (7)	1 (3)	1 (3)	1 (3)
Pulsus paradoxus (mmHg)	16.3 (3.4)	16.9 2.8	13.5 (3.4)	14.3 (2.9)	11.5 (3.7)	12.1 (3.2)	8.9 (3.7)	9.4 (3.7)
Arterial blood gas analysis								
pH	7.402 (0.066)	7.417 (0.068)			7.430 (0.049)			7.425 (0.049)
pCO_2(mmHg)	28.3 (7.4)	29.8 (8.4)			26.0 (5.0)			26.3 (5.2)
pO2(mmHg)	60.7 (9.7)	57.0 (7.5)			90.2 (24.5)			90.1 (26.1)
O_2 saturation (%)	91.09 (3.19)	89.83 (3.41)			96.29 (2.61)			95.48 (4.39)

Values are depicted as means (SD) or numbers (%).
+ Refers to only those subjects in which this parameter could be evaluated.
Except for* ($p<0.02$), none of the differences between the two groups were significant.

nebulizer. Despite a greater number of children with severe asthma in the MDI-spacer group (subjective assessment), the response at the end of 1 hour of treatment following the Consensus protocols(3) was virtually identical. The utility of MDI-spacer for

TABLE III—*Sequential Categorization of Response.*

Response	Group I	Group II	Total
20 minutes			
Good	2 (7)	2 (7)	4 (7)
Incomplete	20 (67)	18 (60)	38 (63)
Poor	8 (26)	10 (33)	18 (30)
40 minutes			
Good	14 (47)	12 (40)	26 (43)
Incomplete	13 (43)	16 (53)	29 (48)
Poor	3 (10)	2 (7)	5 (9)
60 minutes			
Good	24 (80)	23 (77)	47 (78)
Incomplete[4]	4 (13)	5 (16)	9 (15)
Poor	2 (7)	2 (7)	4 (7)

Values depict numbers (%)
None of the differences between the two groups were significant ($p > 0.05$).

aeroslized administration of beta-2 agonists in acute asthma in children has been reported earlier(9-16). However, the current study, carried out in strict adherence to recommended guidelines(3), documented the efficacy of MDI-spacer (with face mask attachment) in children below 3 years of age also.

Nebulizers are considered to be the method of choice for aerosolized delivery of beta-2 agonists because they require no coordination and produce particles of desired size at a slow speed. However, this methodology has several disadvantages, particularly in the context of developing countries. The device is cumbersome, expensive and requires a source of power supply. MDI-spacers are relatively cheap, compact and easily portable. A significant reduction in hospital costs has been demonstrated even in a developed nation following the substitution of MDI-spacer for nebulizer(18). The estimated annual potential cost savings were $ 83,000 by the hospital and $ 300,000 for the charges to the patients.

Data from two different studies(19,20) suggests that a greater proportion (21% versus 12%) of the inhaled drug reaches the lungs with the MDI spacer in comparison to nebulizer. However, in the current controlled study, this did not translate into a relatively greater clinical efficacy for the MDI-spacer. Nebulizers may have a greater probability of nosocomial infection, if not cleaned properly. MDI-spacers utilize pressurized aerosol at a positive pressure with respect to the atmosphere resulting in a decreased probability of such infection.

The findings of the current study, if confirmed in other settings and larger sample sizes, have tremendous implications for widespread application for management of acute asthma in developing countries like India. The paucity of financial resources, power supply and reparative services for imported equipment, precludes the widespread use of nebulizers for delivery of aerosolized beta-2 agonists in this setting, particularly in peripheral areas. Consequently, systemic beta-2 agonists continue to be administered with a greater possibility of toxicity.

It is concluded that MDI-spacer is as effective as a nebulizer for the aerosolized administration of salbutamol in an acute exacerbation of asthma in children. However, for developing countries, distinct advantages (economic and power requirement) argue strongly for utilization of MDI-spacer in preference to nebulizer.

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