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Efficacy of inhaled salbutamol therapy via nebulizer versus metered dose inhaler & spacer in children with acute exacerbation of asthma.

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Abstract

Global initiative against asthma (GINA) guidelines advocates Metered dose inhaler with spacer (MDIs) as the preferred mode for salbutamol aerosol therapy during acute asthmatic exacerbations as compared to use of Nebulizers. However, in practice, Nebulizers continue to be the preferred device for this purpose perhaps due to apprehensions about adequate drug delivery specially in young children and in those with significant respiratory distress.

Objectives: To compare the efficacy of aerosolized salbutamol delivery via MDIs versus Nebulizer for the treatment of acute asthmatic exacerbations in children.

Methods: In a prospective interventional study, 120 children with acute asthmatic exacerbations were randomized in two treatment groups- One group received Salbutamol via a jet nebulizer (0.15mg/kg/dose), while another group received it via MDIs (10 puffs below 5 years age, 20 puffs in older children). Inhalations were given at 0, 20 and 40 minutes after enrollment and each case was assessed at 20, 40 and 60 minutes, before next inhalation, for age-appropriate response parameters.

Results: Cumulative response rate at the end of 60 minutes was comparable in two treatment groups using MDIs and Nebulizer i.e., 88.3% and 80% respectively. However, the response was significantly faster in MDIs group i.e., higher at the end of 40 minutes i.e., 65% versus 43.3% in Nebulizer group (p value 0.027). Mean response time was also significantly lower in MDIs

group versus nebulizer group (p value 0.02). This Inter-group difference in 40-minute response rate and mean response time was significant only in older children above five years of age and not in younger ones.

Conclusions: MDIs is at least as effective as nebulizer for salbutamol aerosol therapy in acute asthma with added advantage of faster response, specially in older children.

Keywords: Asthma, Efficacy, Exacerbation, Metered Dose Inhaler, Nebulization, Salbutamol.

Introduction

Acute asthmatic exacerbation is a leading cause of emergency hospital visits in children, burdening not only the family but also the health care services. Early and appropriate treatment of these exacerbations at home or emergency rooms is necessary not only to avoid unnecessary morbidity and hospitalizations but also to improve the quality of life.

Management of acute asthmatic attacks revolves around aerosolized Salbutamol therapy, conventionally delivered via jet Nebulizers. Low-cost nebulizers are frequently used, even at home, for this purpose. However, nebulizers are bulky and noisy equipment's, which need regular electric power supply. Sometimes, these nebulizers can also be the source of infections due to sharing of tubes or chambers etc.

Several studies have shown that Metered dose inhaler with or without spacers (MDIs) are at least as effective as Nebulizers for aerosolized salbutamol therapy (1-6). Global initiative against asthma (GINA) guidelines, advocates MDIs as the preferred mode for salbutamol delivery during acute asthmatic exacerbations (7-8). However, nebulizers continue to be the most commonly used device in actual practice perhaps due to apprehensions regarding adequacy of the drug delivery atthe siteofaction, especially in young children and in those with significant respiratory distress.

Presentstudy aimstocomparetheefficacy ofsalbutamol aerosol therapyviaMDIsversus Nebulizer for the treatmentofacuteasthmatic exacerbations in children.

Patients and Methods

This prospective randomized controlled open-label trial was carried out in the emergency pediatric ward of a large teaching hospital over 18 months period, after permission from institutional ethics committee.

Total 120 children of 3 -12 years of age, presenting in the pediatric emergency ward with clinical diagnosis of asthma and consenting to participate were enrolled in this study. Children below 3 years were not included due to diagnostic difficulties and higher probability of wheezing due to non-asthma causes. Cases with imminent respiratory failure were also excluded as they were directly transferred to intensive care unit.

All enrolled cases were subjected to detailed clinical and necessary laboratory evaluation for severity assessment of the attack as per age-appropriate GINA guidelines 2018 (7-8) and randomized in two study treatment groups, using block randomization of 10 cases per block to ensure nearly equal numbers in each group.

Sample size was calculated using an online calculator (9) considering at least 20% difference in the response between two study groups as significant with a power of 80% and alpha error of 0.05. Accordingly, a sample size of 51 in each group was found to be adequate, which was further inflated to 60 to account for logistic problems and exclusions.

Two study groups were treated with salbutamol aerosol therapy with different delivery systems as follows:

- Nebulizer group was given three doses of salbutamol nebulization (0.15mg/kg/dose diluted in 3 ml of normal

saline) at 0, 20 and 40 minutes, using a Hudson's chamber with/without face mask, connected to the oxygen source at 6 L/min. Each nebulization lasted for 4-5 minutes.

- MDIs groupreceived salbutamol via a metered dose inhaler and non-valve spacer device thrice at 0, 20 and 40 minutes, with/without face mask. Total numbers of puffs (100 mcg/ puff) used per dose varied with age - 10 puffs for cases below five years age and 20 puffs for older children. Number of puffs was calculated to deliver about 0.06 - 0.1 mg/kg/dose, which may be considered as equivalent to the dose delivered via nebulization, considering 20-30% drug delivery to lower airways by MDIs versus 10% by nebulizer[10]. After delivery of all puffs, the child was allowed to inhale through the device for 4-5 min. Prior to the use, spacer was primed with 6-8 doses of salbutamol to eliminate the effect of electrostatic charge, if any.

Each case was re-assessed at 20 minutes and 40 minutes (just before the delivery of next dose) and then at 60 minutes (final assessment), for all the parameters included in age-appropriate severity assessment of acute exacerbation based on GINA guideline 2018 (7-8). After the final assessment, the patient was managed further as per unit protocol. All patients, even those responded satisfactorily were kept in hospital for observation for next 24 hours, as per hospital policy.

Primary outcome parameter used in this study was "Cumulative response rate" at the end of each assessment point i.e., 20, 40 and 60 minutes, defined as the percentage of cases with desired therapeutic response on all age-appropriate severity parameters in two study groups. Cases who did not achieve desired therapeutic response at the end of 60 minutes were considered as Treatment failures and transferred to intensive care for further management. Secondary outcome parameters were - a) Mean response time among the responders in each treatment group and b) Solicited side-effects or difficulties observed during the therapy.

Base-line data in two study groups regarding patient's demographic characteristics, severity of the disease, and severity of present exacerbation was compared using two-tailed Fisher exact test for categorical variables and unpaired student 't' test for continuous variables. Inter-group differences in the response rates at different time periods were tested by two-tailed Fisher Exact test, while inter-group difference in the mean response time was analyzed using unpired student t test.

Results

Forty-eight out of 120 study cases were under five years of age for whom different severity parameters were used than for older children as per GINA guidelines. Over half of all study cases had well-controlled disease prior to the present exacerbation (55.5%) and 50.8% were on preventer medications.

Table 1 depicts that there was no significant difference in the demographic profile, Pre-exacerbation control status, preventer treatment profile and severity of the present exacerbation between two study groups. Among all cases, 56.7% had severe exacerbation on the basis of age-appropriate severity parameters. Under-five cases had relatively higher proportion of severe exacerbations (81.3%) as compared to older cases (40.3%).

As shown in table 2, Cumulative response rate at the end of 60 minutes was marginally higher among cases treated with MDIs as compared to those treated with Nebulizers (88.3% vs. 80.0%) though the difference was not statistically significant. However, cumulative response rate was significantly higher at the end of 40 minutes in MDIs group than in the Nebulizer group i.e.

65.0% vs. 43.3% respectively (p 0.027).

Table 4 shows no significant difference in cumulative response rates between two groups in children below five years of age at any of the assessment time-points. In contrast, table 5 suggests significantly faster response in MDIs-treated group among older children, as obvious from the 40 min response rate of 65.7% in this group vs. 29.7% in Nebulizer group, with difference being statistically significant at p value 0.004.

Table 6 reveals that mean response time among the responder cases was significantly lower in MDIs group i.e. 41.89 ± 13.16 minutes as compared to Nebulizer group i.e. 47.92 ± 12.20 minutes. However, this difference was observed only in children above 5 years (44.24±12.00 minutes vs. 52.41± 09.88 minutes; p 0.0052) and not in younger cases (38.00 ± 14.36 minutes vs. 41.05 ± 12.43 minutes; p value 0.483).

Tachycardia, vomiting and tremors were commonest side effects noted following aerosol therapy, though there was no significant difference in side effects according to the mode of delivery.

Discussion

Present study re-affirms that salbutamol inhalation, irrespective of the mode of delivery, is an effective intervention to control acute asthmatic exacerbation, with over 80% response rate at the end of one hour.

Study also suggests that both the modes of aerosolized salbutamol delivery - Nebulizer or MDIs, are equally effective in terms of the response rate at the end of 60 minutes. However, the response is relatively faster in MDIs group, as obvious from the significantly lower response time among responders and significantly higher cumulative response rate at 40 minutes.

While many studies in the past have shown comparable efficacy of salbutamol delivery by MDIs vs. Nebulizer in terms of overall response rate (1-6), very few have compared the rapidity of response between these modes.

A Cochrane review by Cates CJ et al (2013) revealed significantly shorter duration of emergency department stay in children who received salbutamol via MDIs (70 minutes) as compared to those by a nebulizer (103 minutes) (with 95% CI -43 to -24 minutes, moderate quality evidence). (11)

Mathew et al(2008) in a systemic review of 39 studies including 2 systemic reviews for children <18 years, concluded that bronchodilator delivery through MDI with spacer is comparable, but not superior to nebulizer in terms of clinical response and adverse events in the Indian context. Results cannot be directly applied to children less than two years and those with life-threatening acute exacerbations. (1)

Faster response with the use of MDI+S has been explained as a result of the fractionally higher drug delivery at the lower airways (20-30%) via MDIs as compared to about 10% by nebulizers. (10)However, some studies have found this difference even while using the equivalent doses calculated by factoring this difference. (12)

Sub-group analysis in present study indicates that relatively faster response in MDI+S group was largely due to the differences in older children beyond five years of age. Lack of similar observation in younger cases was perhaps due to the difficulties in holding the face-mask on an apprehensive young kid for MDIs use, which can lead to some wastage of the drug. (13) More cooperative older children can use MDIs directly and studies have shown that therapeutic response to spacer is better when used directly rather than with face- mask. (14)

Nebulizer therapy has been reported to have greater side effects due to increase in salbutamol absorption and

higher plasma levels, though no such difference was observed in this study. (12).

To conclude, present study indicates that MDIs is as effective as nebulizer in treating acute asthmatic attacks with added advantage of faster response, especially in older children. Being simple, portable and non-electricity dependent device, Further, MDIs appears to a better option, for home use or at rural health centers with erratic power supply.

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Table 1: Comparative case characteristics of two study groups

Case Characteristics	Group A(Nebulization)	Group B(MDIs)	Statistical Difference(p value)
Age*			
≤60 months	23 (38.3%)	25 (41.7%)	0.852
>60 months	37 (61.7%)	35 (58.3%)	0.852
Gender			
Male	34 (56.7%)	31 (51.7%)	0.714
female	26 (43.3%)	29 (48.3%)	0.714
Age of onset			
36 months	26 (43.3%)	15 (25.0%)	0.053
37-59 months	27 (45.0%)	36 (60.0%)	0.143
≥60 Months	07 (11.7%)	09 (15.0%)	0.789
Severity of disease			
Controlled	34 (56.7%)	32 (53.3%)	0.854
Partially controlled	22 (36.6%)	27 (45.0%)	0.457
Uncontrolled	04 (06.7%)	01 (01.7%)	0.366
Preventor Medication			
Yes	32 (53.3%)	29 (48.3%)	0.715
No	28 (46.7%)	31 (51.7%)	0.715
Severity of acute attack			
Mild	23 (38.3%)	29 (48.3%)	0.465
Severe	37 (61.7%)	31 (51.7%)	0.465

Table 2: Cumulative Number of cases achieving desired response at different assessment points

Assessment point	Group A (Nebulization)	Group B (MDIs)	Statistical difference (p value)
Baseline	00 (00.0%)	00 (00.0%)	-
20 minutes	03 (05.0%)	09 (15.0%)	0.125
40 minutes	26 (43.3%)	39 (65.0%)	0.027
60 minutes	48 (80.0%)	53 (88.3%)	0.317
No response	12 (20.0%)	07 (11.7%)	0.317

Table 3: Cumulative Number of cases below 5 years of age achieving desired response at different assessment points

Assessment point	Group A (Nebulization)	Group B (MDIs)	Statistical difference (p value)
Baseline	00 (00.0%)	00 (00.0%)	-
20 minutes	03 (13.0%)	06 (24.0%)	0.465
40 minutes	15 (65.2%)	16 (64.0%)	1.000
60 minutes	19 (82.6%)	20 (80.0%)	1.000
No response	04 (17.4%)	05 (20.0%)	1.000

Table 4: Cumulative Number of cases above 5 years of age achieving desired response at different assessment points

Assessment point	Group A (Nebulization)	Group B (MDIs)	Statistical difference (p value)
Baseline	00 (00.0%)	00 (00.0%)	-
20 minutes	00 (00.0%)	03 (08.6%)	0.109
40 minutes	11 (29.7%)	23 (65.7%)	0.004
60 minutes	29 (78.4%)	33 (94.3%)	0.086
No response	08 (21.6%)	02 (05.7%)	0.086

Table 5: Mean response time in two study groups

Cases	Group A (Nebulization)	Group B (MDIs)	Statistical difference (p value)
Total cases	47.92 ± 12.20	41.89 ± 13.16	0.019
Cases < 5 years age	41.05 ± 12.43	38.00 ± 14.36	0.483
Cases >5 years age	52.41±09.88	44.24±12.00	0.0052