Original Article

Randomized Controlled Trial of Ipratropium Bromide and Salbutamol Versus Salbutamol Alone in Children with Acute Exacerbation of Asthma

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ABSTRACT

Objective. To evaluate effect of addition of ipratropium to salbutamol delivered by metered dose inhaler and spacer in the beginning of treatment of mild to moderate exacerbation of asthma.

Methods. Children between 5 to 15 years of age with mild to moderate exacerbation of asthma were randomized to receive either a combination of ipratropium bromide and salbutamol or salbutamol alone administered by metered dose inhaler and spacer. The effects on clinical asthma score and spirometric parameters were compared.

Results. A total of 60 children were randomized in the study. The baseline characteristics of two groups were comparable. Children getting combination of salbutamol and ipratropium showed significantly greater improvement in percent-predicted PEFR and FEF25-75% than children receiving salbutamol alone.

Conclusion. There was beneficial effect of addition of ipratropium to salbutamol administered by MDI with spacer at the beginning of therapy for mild to moderate acute exacerbation of asthma in children. **[Indian J Pediatr 2006; 73 (11) : 979-983]**
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Key words : *Acute asthma; Ipratropium; Metered dose inhaler; Holding chamber*

The treatment of acute asthma consists of beta agonists and systemic steroids. Majority of patients responds to this treatment and can be managed as outpatients. It has been observed that addition of anticholinergic drugs to salbutamol improves FEV_1 and reduces hospital admission.[1-6] Use of anticholinergic drug is based on premise that cholinergic pathways play an important role in the pathogenesis of asthma exacerbation due to upper respiratory infection, (URI[9]) which is responsible for 50%-60% of acute exacerbation of asthma in children.[7-8]

Ipratropium bromide alone does not lead to much improvement but its use with salbutamol demonstrates significant improvement in FEV_1 and decreased hospitalization rate in children with acute exacerbation of asthma.[1-6] There are no studies to evaluate the effect of administration of these two drugs right at beginning of management of acute exacerbations.

In all the studies salbutamol and ipratropium were administered by nebulizer. There is paucity of data about efficacy of ipratropium and salbutamol being administered using metered dose inhaler (MDI) and spacer in mild to moderate exacerbation of asthma in children. A systematic review comparing MDI with spacer and wet nebulizer delivery of beta agonists in severe acute exacerbation of asthma showed that these two systems are equivalent in adults but MDI with spacer is better in children.[9]

Therefore, the present study was planned to determine the effect of addition of ipratropium to salbutamol at beginning of treatment administered by MDI and spacer in mild to moderate acute exacerbation of asthma in children.

MATERIALS AND METHODS

This double blind randomized placebo-controlled study was conducted at Pediatric Chest Clinic of a tertiary care hospital in north India from November 2001 to May 2003. Children between 5 to 15 years of age of either sex with mild to moderate acute exacerbation of asthma,[10] who

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were able to perform spirometry, were included in the study. Children with severe acute exacerbation; coexisting cardiac or renal disease; known intolerance to salbutamol or ipratropium bromide; glaucoma, urinary retention and children who had used oral bronchodilator in last 12 hours or inhaled bronchodilator within last 6 hours were excluded from the study. Patients could be enrolled twice in study if events were more than one month apart.

After an informed consent from guardians, 60 children with mild to moderate acute exacerbation of asthma were enrolled in study. After enrolment, the demographic profile of patients and details of the illness and treatment were recorded.

Thereafter, base-line parameters like heart rate, respiratory rate, wheeze score (0-3)[11], accessory muscle score (0- 3)[11], modified clinical asthma score (0- 10)[12], and oxygen saturation using a pulse oximeter were recorded. All patients underwent base-line spirometry using COSMED PONY spirometer. In all patients FEV_1, FEV_1%, FVC, FVC%, FEV_1/FVC, FEF_{25-75}, FEF_{25-75}% were recoded. In addition, PEFR was recorded with Wright's peak flow meter. These tests were performed three times and the best of the three results was recorded. Percentage of PEFR was calculated from standard chart.[13] Following recording of these parameters, patients were given drugs according to randomization.

Randomization

Block randomization was done by computer-generated blocks of 6 each. For blinding, similar looking MDIs were labeled A, B, C, D, E, F; 3 of which contained ipratropium and 3 contained placebos. As per random numbers patients were given drugs from these MDIs. A person not involved in the study evaluation did the labeling. The analysis was performed by investigator (RMP), unaware of the labeling of the two groups as drug or control.

Intervention

All patients were administered 4 actuations of salbutamol through similar looking MDI and spacer. Then 4 actuations of either drug (ipratropium) or placebo were given through MDI and spacer as determined by block randomization (A, B, C, D, E, or F) .

Each actuation of salbutamol MDI delivered 100 µg drug and each actuation of ipratropium delivered 20 µg drug. Following each actuation into the spacer, patient was asked to take 5 tidal breaths. After 30 minutes of administration of drugs, heart rate, respiratory rate, oxygen saturation, wheeze score, accessory muscle score, clinical asthma score were reassessed. FEV_1, FEV_1%, FVC, FVC%, FEV_1/FVC, FEF_{25-75}, FEF_{25-75}%, were measured using spirometry. PEFR was reassessed using Wright's peak flow meter.

Thereafter all patients were managed as per standard protocol based on consensus guidelines.[14]

The departmental review board approved the protocol for the study.

Sample size

A sample size of 27 was required to detect difference of 15% in PEFR with power of 95%. It was decided to enroll 60 patients; 30 in each group.

Assessment of blinding

To check the efficacy of blinding, 10 resident doctors were asked to identify the labeled MDIs as to which contained drug and placebo. Only one resident could identify the MDIs (Placebo or Ipratropium) correctly. 90% cases failed to identify.

Statistical Analysis

Data were recorded on a pre-designed performa and managed on an EXCEL spreadsheet. Comparative analysis of baseline parameters of two groups and within the groups before and after treatment and percentage of improvement between these two groups and comparison of two groups after treatment were done using different statistical tests like Student's t-test, Wilcoxon rank-sum and Chi-square test.

Quantitative variable were assessed for normality. Variable following normal distribution were summarized by mean and standard deviation and student 't' test was used to compare mean values between the two groups. Variables following non-normal distribution were summarized by median and range. Wilcoxon rank sum test was used to compare medians in the treatment groups.

Categorical variables were summarized by frequency (%) and Pearson chi-square test was used to compare proportions between the two treatment groups.

STATA 8.0 statistical software used to perform the data analysis. In this study, p value <0.05 was considered as statistically significant.

RESULTS

A total of 60 children with mild to moderate exacerbation of asthma were randomized to receive either salbutamol with ipratropium (Group 1) or salbutamol with placebo (Group 2).

Baseline characteristics like age, sex, diagnosis, current steroid, dose of steroid receiving, any long acting beta agonists, history of URTI, history of exposure, duration of illness, were comparable between the two groups. P values were insignificant except in age (table 1). Treatment received by patients for asthma was comparable in two groups. Twenty-three patients in group-1 and 26 patients in group-2 were receiving inhaled corticosteroids.

Baseline value of variables like heart rate, respiratory rate, wheeze score, accessory muscle score, oxygen saturation, FEV_1, FVC, $FEF_{25-75,}$ FEV_1/FVC, and PEFR were compared and shown in table 2. There was no

TABLE 1. Baseline Profile of Patients Enrolled in Study

	Group 1 (salbutamol with ipratropium)	Group 2 (salbutamol with placebo)	P value
Age (month)	106 ± 25.81	118 ± 25.22	0.04
Sex			
Boys	19	17	0.59
Girls	11	13	
Severity of asthma			
(a) Episodic asthma	0	1	0.76
(b) Mild asthma	9	10	
(c) Moderate asthma	20	18	
(d) Severe asthma	1	1	
Current steroid			
(a) No steroid	7	4	0.3
(b) Budesonide	20	25	
(c) Fluticasone	3	1	
Inhaled Steroid dose (mean ±SD) ug	634.78 ± 194.48	584.61 ± 225.72	0.36
LABA			
(a) Salmeterol	5	4	0.07
(b) Formeterol	0	0	
Duration of illness (yrs)	4.73 ± 3.26	4.123 ± 3.03	0.48
History of URTI			
Yes	18	11	0.07
No	12	19	

LABA: Long acting beta agnosis

statistically significant difference in two groups except in percent predicted FVC (table 2).

In table 3, spirometric parameters, heart rate, respiratory rate, wheeze score, accessory muscle score, clinical asthma score were compared between study group and control group after treatment. There was

TABLE 2. Baseline Comparison of Physical and Spirometric Indices Between Group 1 and Group 2

	Group 1 (salbutamol with ipratropium)	Group 2 (salbutamol with placebo)	P value
Heart rate / min.	111.67 ± 15.14	106.07 ± 16.05	0.17
Respiratory rate / min.	28.6 ± 5.5	29.3 ± 6.81	0.66
Wheeze score	1.5 ± 0.63	1.73 ± 0.52	0.12
Accessory muscle score	0.33 ± 0.66	0.43 ± 0.82	0.83
SPO_2 (%)	95.57 ± 2.34	95.23 ± 2.14	0.57
FEV_1(L)	0.92 ± 0.46	0.9 ± 0.35	0.91
FEV_1%	72.33 ± 37.05	57.41 ± 21.04	0.06
FVC (L)	1.12 ± 0.73	0.96 ± 0.34	0.28
FVC%	71.57 ± 35.60	53.10 ± 19.46	0.02
FEF_{25-75} (l/s)	1.19 ± 0.87	1.22 ± 0.61	0.31
FEF%	80.08 ± 65.46	84.5 ± 129.83	0.31
FEV'1/FVC	89.19 ± 16.50	92.28 ± 16.36	0.47
PEFR (L / min)	158.33 ± 85.34	155.63 ± 62.93	0.89
PEFR%	64.36 ± 28.39	57.33 ± 19.20	0.27
CAS	1.83 ± 1.12	2.07 ± 1.31	0.59

Values are means ± SD

statistically significant greater improvement in percent predicted FEF_{25-75} and percent predicted PEFR in group 1(salbutamol with ipratropium) when compared with group receiving salbutamol alone. There was also greater improvement in percent predicted FEV_1 in Group 1 but it did not reach statistical significance (P=0.05). In other parameters there was no statistically significant difference between two groups after treatment (table 3).

TABLE 3. Comparison of Group 1 and Group 2 After Treatment

	Group 1 (salbutamol with ipratropium)	Group 2 (salbutamol with placebo)	P value
Heart rate / min	119.43 ± 17.09	115.3 ± 18.70	0.38
Respiratory rate / min	27.9 ± 4.67	28.97 ± 5.84	0.44
Wheeze score	1.07 ± 0.83	1.2 ± 0.71	0.51
Accessory muscle score	0.17 ± 0.46	0.43 ± 0.82	0.24
SPO2 (%)	96.97 ± 2.08	96.4 ± 1.69	0.25
FEV_1 (L)	1.07 ± 0.49	1.12 ± 0.40	0.69
FEV_1%	94.07 ± 52.23	72.21 ± 29.56	0.05
FVC (L)	1.43 ± 1.31	1.27 ± 0.72	0.56
FVC%	95.57 ± 63.14	71.61 ± 43.53	0.10
FEF_{25-75}(L / s)	2.19 ± 3.21	1.57 ± 0.85	0.81
FEF_{25-75}%	121.04 ± 90.69	72.22 ± 33.31	0.01
FEV_1 / FVC	92.03 ± 20.37	94.57 ± 9.51	0.54
PEFR (L / min.)	203.3 ± 85.82	188.33 ± 64.38	0.45
PEFR%	82.32 ± 25.93	69.53 ± 19.87	0.04
CAS	1.27 ± 1.20	1.43 ± 1.28	0.57

Values are mean ± S.D.

On comparison of percentage improvement in various spirometric variables in group 1 and group 2, there was no statistically significant difference between the two groups, though there was trend towards greater improvement in group 1 in percent predicted FEV_1, percent predicted FVC, $FEF_{25-75,}$ percent predicted $FEF_{25,75}$, PEFR and percent predicted PEFR.

DISCUSSION

Results of this double blind placebo controlled randomized trial suggest that addition of ipratropium to salbutamol delivered by MDI and spacer in children between age group of 5- 15 years with mild to moderate acute exacerbation of asthma causes statistically significant greater improvement in percent predicted FEF_{25-75} and percent predicted PEFR (p=0.01 and 0.03 respectively) than with salbutamol alone. There was a trend towards greater improvement in clinical asthma scores (CAS) and percent predicted FEV_1, percent predicted FVC, FEF_{25-75}, PEFR with the combination but these did not reach statistical significance.

In the present study, ipratropium and salbutamol was delivered through MDI and spacer in the beginning of treatment. There are no studies that used a combination of salbutamol and ipratropium administered by metered

dose inhaler in the beginning of treatment of mild and moderate acute exacerbations of asthma.

Beck *et al*[15] conducted studies in children adding single dose of ipratropium to salbutamol; the medications were delivered using a nebulizer. The authors observed significant improvement in FEV_1 at 60 minute in ipratropium group 20.6% *vs* 3.5% ($p<0.05$) but at 40 minute there was no statistically significant improvement. The other study amongst children done by Storr and Lenney[16] did not report any advantage of using the combination.

There are some studies that have evaluated the effect of multiple doses of ipratropium. Goggin *et al*[17] and Rayner *et al*[18] did not report any benefit with the use of ipratropium. On the other hand, Schuh *et al*,[4] Quireshi *et al*,[5] and Zorc *et al*[19] observed better response in the combination group.

Plotnick *et al* conducted a systematic review to clarify the issue of efficacy of addition of anticholinergics in treatment of acute exacerbations of asthma.[20] They observed that there was no reduction in hospitalization with use of a single dose of ipratropium. However, addition of multiple doses of the drug reduced the hospital admissions by 30% and also improved the lung function.[20]

The use of anti-cholinergic drugs in acute exacerbations of asthma is based on the role of autonomic nervous system pathways in acute exacerbations.[21]

Our results do suggest some benefit of addition of ipratropium at the beginning of the treatment. No child needed hospitalization; however, this may be due to the fact that only children with non-severe exacerbations were studied. Further studies will be required to evaluate this mode of delivery of the combination at the outset to children with severe acute exacerbation of asthma.

Our study had some limitations. We used lower doses of ipratropium (80 μg) compared with at least 250 μg in other studies, where the medication was nebulised. A larger dose may lead to greater benefit and this may be considered when a study, to evaluate the effects in children with severe exacerbations, is planned. We performed the spirometry evaluation at 30 minutes after the administration of the drugs. This may be too short a time for complete effect of ipratropium. However, this was done as the treatment guidelines for mild / moderate exacerbation of asthma in children recommends first assessment at 30 minutes. As ipratropium has delay in onset of action, performance of the spirometry at a later time may have shown different results. There was difference in the baseline characteristics for age and percentage predicted FVC in two groups. This difference was attributed to chance, as the study was a randomized trial. The difference in age might affect the feasibility of performing spirometry if one group has more children below 7 years of age. In the present study, no child was excluded because of poor performance of spirometry. Total number of children below 7 years of age was 4 (2 in each group). Therefore, it is unlikely to affect the results of spirometry. Though there was a difference in baseline FVC between the two groups, there was no statistically significant difference in the percentage improvement in FVC, when the 2 groups were compared.

We conclude that addition of ipratropium to salbutamol administered by metered dose inhaler leads to some improvement in spirometric parameters in children with mild or moderate acute exacerbations of asthma. It will be worthwhile to study the effect of this combination, administered by MDI on children with severe acute exacerbations.

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