

# Nebulized Salbutamol Vs Salbutamol and Ipratropium Combination in Asthma

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**Abstract. Objective :** To see the additional benefit of combined frequent nebulization with salbutamol and ipratropium bromide in acute attack of asthma with moderate severity. **Methods :** Fifty asthmatic children in the age range of 6-14 years were divided into two equal groups. Group I children were nebulized with three doses of Salbutamol alone (0.03 ml/kg/dose) and Group II children were given combined nebulization of Salbutamol (dose as in group I) and Ipratropium bromide (250 µgm/dose for three doses) at 20 minutes interval. Children were observed at 15, 30, 60, 120, 180 and 240 minutes interval. **Results :** A significant improvement in % of PEFr starting at 30 minutes and lasting the entire study period of 4 hours was noted in both the groups. However on analysis of variance the results were better in group II. **Conclusion :** Frequent combined nebulization with Salbutamol and Ipratropium bromide is beneficial in acute asthma of moderate severity. [Indian J Pediatr 2004; 71 (2) : 121-124] E-mail : dr\_anitassharma@sifymail.com

**Key words :** Bronchial asthma; Acute exacerbation; Nebulized Salbutamol; Ipratropium bromide; Salbutamol combination

Frequent administration of nebulized  $\beta_2$  agonist at the onset of an acute asthmatic attack has been reported to be more effective.<sup>1,2</sup> However, even with this aggressive approach some residual obstruction is left which is unresponsive to  $\beta_2$  agonist.<sup>3-6</sup> Various drug combinations have been tried to improve this.<sup>3,5</sup> Significant and consistent improvement has been reported only when  $\beta_2$  agonists were combined with anticholinergic agents.<sup>7</sup> Thereby indicating that a significant residual cholinergic mediated bronchomotor tone was persisting even after maximal treatment with  $\beta_2$  agonists.

Combined use of  $\beta_2$  agonist and anticholinergic drug (ipratropium bromide) has been reported to have independent but additive mode of action. Thus this combination is reported to attain longer and greater bronchodilatation early in an acute attack of asthma.<sup>8-11</sup>

Although ipratropium bromide, has been used as an agonist to  $\beta_2$  agonist therapy for a long period in adults<sup>12-16</sup>, its role in the management of Pediatric asthma is still an area of uncertainty.

The recent international guidelines on the management of asthma have also varied recommendations on the use of ipratropium bromide.<sup>2,16-18</sup> The National Heart, Lung and Blood Institute<sup>2</sup> recommends the repeated combined nebulization with Salbutamol and ipratropium in an acute attack of severe exacerbation. However, Warner and Naspitz<sup>16</sup> have suggested it to be used in moderate asthma and have not mentioned its use in patients with severe asthma. British guidelines<sup>17</sup> have mentioned it to be used in severe attack only, if life threatening features are

present. In contrast Canadian Guidelines<sup>18</sup> do not advocate its use in acute asthma.

In view of different recommendation the present study was undertaken.

## MATERIALS AND METHODS

For this study fifty children between the age range of 6-14 years, who reported to emergency department in acute exacerbation of bronchial asthma were enrolled after a written consent. The project was cleared by Board of Studies from ethical point of view. Diagnosis of bronchial asthma was suggested by periodicity of symptoms, nocturnal attacks, seasonal variations and symptoms produced by allergen exposure or exertion and were supported by atopy in the patient or the family. An acute attack was defined as an episode of increasing cough, inability to speak in sentence and drink, wheezing and chest recession.<sup>19</sup>

### Exclusion Criteria

Children with life threatening or severe attack characterized by cyanosis, silent chest or poor air entry, marked dyspnoea so that child was unable to speak even 3-4 words, PEFr < 30% for that height, those who had received bronchodilator six hours prior to admission, and with a history of previous admission to intensive care unit were excluded from the study.

Baseline parameters recorded were - respiratory rate (RR), heart rate (HR), chest wall recession, systolic blood pressure, diastolic blood pressure, pulse pressure, temperature, chest auscultation, working of accessory

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muscles of respiration, nasal flaring, ability to drink and speak in sentence or 5-8 words, auscultation findings, height, weight, age and PEFR by Wright's mini peak flow meter (the best of three consecutive values taken and then expressed as percentage of predicted for that height).<sup>20</sup>

Total and differential leukocyte count, eosinophil count, urine examination, X-ray chest PA view examination and stool for ova were done in all the children.

This was a prospective randomized study and children were divided into two groups of twenty five children each. The study was not blind so as not to interfere with emergency treatment of patients.

Group I (n=25)-Each child was nebulized with salbutamol sulfate 0.03 ml/kg/dose (150 µg/kg/dose) of 0.5% respiratory solution to a maximum of 1 ml (5.0 mg) per dose. It was diluted 1:1 in 0.9% isotonic saline to a volume of 3 ml and nebulized via a tight fitting face mask using compressed air nebulizer over a period of 10 minutes. The same dose was repeated twice at the interval of 20 minutes each time.<sup>2</sup>

Group II (n=25)-Each child was nebulized with combination of 250 µgm/dose (1 ml of 0.025% solution) of ipratropium bromide and salbutamol sulfate (as in group I) thrice at 20 minutes interval.<sup>2</sup>

In both the groups oxygen was administered via nasal prongs at a flow rate of 3L/minutes.<sup>21</sup> Children were evaluated at 15, 30, 60, 120, 180 and 240 minutes intervals and were kept under observation for 4 hours.

The primary outcome was noted by the improvement in percentage of predicted PEFR. The percentage of predicted value of PEFR was calculated<sup>20</sup> as: Percentage

$$\text{Predicted value of PEFR} = \frac{\text{Observed PEFR}}{\text{Predicted PEFR}} \times 100$$

A good response was indicated by a sustained increase of at least 20% in the PEFR compared to pre treatment value at all the intervals of four hours of observation.<sup>20,22</sup> Secondary outcome was noted by improvement in RR, PR, wheeze score,<sup>22</sup> dyspnoea score,<sup>22</sup> use of accessory muscles scores,<sup>22</sup> auscultation findings and ability to drink and speak in sentence. A poor response was indicated by the converse of above. A failure of particular protocol was noted if no relief in symptoms occurred after a maximum dose of that drug or if a relapse occurred during initial 4 hours of observation period.<sup>22</sup>

## RESULTS

Both the groups were comparable for baseline parameter (Table 1). Thirty three patients (44%) were not taking any treatment, 14 (18.7%) were on treatment from qualified doctors but had no treatment slips, 76 (8%) were on cough syrups (without bronchodilators) and 22 (29.3%) had stopped their bronchodilator drugs abruptly.

TABLE 1. Baseline Parameters of the Two Groups

Parameter	Group I	Group II
Age (years)	10.3 ± 0.5	10.6 ± 0.5
Family history (%)	28	28
Inability to speak in sentence (%)	92	96
Inability to drink fluid (%)	76	84
PEFR (%)	35.4 ± 0.9	34.5 ± 0.9
HR(per minute)	135.3 ± 3.9	133.5 ± 3.8
RR (per minute)	32.2 ± 1.4	33.4 ± 1.2
Systolic blood pressure (mm Hg)	127.6 ± 2.9	132.7 ± 2.9
Diastolic blood pressure (mm Hg)	84 ± 2.7	86 ± 2.5
Accessory muscle score	2.5 ± 0.1	2.6 ± 0.1
Dyspnoea score	2.5 ± 0.1	2.6 ± 0.1
Wheeze score	2.4 ± 0.1	2.5 ± 0.1

Within each group, a significant improvement in PEFR percentage was noted at all the study intervals after nebulization. In both the groups results were more marked at 30 minutes and sustained throughout the entire study period of 4 hours.

But with analysis of variance test the percentage improvement in PEFR was significantly better in group II as compared to group I at all the study intervals (Table 2).

Similarly, although wheeze score, dyspnoea score, accessory muscle use score showed a intragroup decrease, but with analysis of variance analysis the results were more marked in group II and remained so throughout the four hours study period.

Adverse effects noted were tremors (8 in group I; 4 in group II), vomiting (3 in group I, 1 in group II, cough (nil in group I, 6 in group II) and transient eye irritation (2 in group II only). All the side effects were self limiting and subsided on their own within three hours.

Four patients (in group I) and three in (group II) failed to respond and were put on alternate treatment (steroids and aminophylline). They were labelled as failures but were not excluded from final analysis. Four patients in group I and one patient in group II required hospitalization. They had relapsed after 4 hours of study period.

## DISCUSSION

In the present study, combined nebulization with Salbutamol and Ipratropium Bromide resulted in significantly more reduction in mean dyspnoea score, wheeze score and accessory muscle score ( $p < 0.05$ ), along with a significant improvement in PEFR, as compared to nebulized salbutamol only.

While some other studies,<sup>23-27</sup> have also reported that the combination of the two drugs when used together or in sequence has additive and long lasting action, others have reported no benefit.<sup>28,29</sup>

Scheh *et al*,<sup>23</sup> in their studies noted that the combination of the two drugs, was safer, effective and resulted in decreased hospitalization than salbutamol alone. Yet another study<sup>30</sup> noticed a two time increase in FEV<sub>1</sub> from

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**TABLE 2. Changes in Parameters After Treatment**

Time after starting treatment (minutes)		PEFR change	% p value	Wheeze score	p value	Dyspnoea score	p value	Accessory muscle score	p value
15	I	15.84 ± 0.78	<0.05	1.84 ± 0.13	>0.05	2.0 ± 0.13	>0.05	2.08 ± 0.13	>0.05
	II	18.16 ± 0.97		1.68 ± 0.15		1.8 ± 0.13		1.72 ± 0.14	
30	I	23.08 ± 0.56	<0.001	1.52 ± 0.15	<0.05	1.64 ± 0.17	<0.05	1.72 ± 0.1	<0.001
	II	27.96 ± 0.59		1.08 ± 0.13		1.20 ± 0.12		1.12 ± 2.4	
60	I	30.08 ± 0.63	<0.001	0.80 ± 0.15	>0.05	1.24 ± 0.15	<0.05	0.92 ± 0.15	<0.01
	II	34.52 ± 0.98		0.52 ± 0.14		0.84 ± 0.11		0.36 ± 0.09	
120	I	29.68 ± 0.65	<0.001	0.44 ± 0.10	<0.05	0.60 ± 0.11	<0.05	0.36 ± 0.09	>0.05
	II	34.92 ± 0.90		0.16 ± 0.07		0.24 ± 0.09		0.16 ± 0.07	
180	I	30.00 ± 0.62	<0.001	0.34 ± 0.10	<0.01	0.52 ± 0.10	<0.05	0.48 ± 0.10	<0.05
	II	35.24 ± 0.78		0.16 ± 0.07		0.16 ± 0.07		0.20 ± 0.08	
240	I	28.8 ± 0.64	<0.001	0.52 ± 0.1	<0.05	0.60 ± 0.24	<0.05	0.52 ± 0.10	<0.05
	II	35.56 ± 0.68		0.2 ± 0.08		0.20 ± 0.08		0.20 ± 0.08	

baseline with the use of combination of Salbutamol and Ipratropium. The combined use of these two drugs has been reported to have independent and additive action and reported to attain greater peak and sustained bronchodilatation.<sup>12,24,26,27</sup> This can be accounted for by their different mechanism of action,<sup>30</sup> times of peak effect and duration of action.<sup>27</sup> While ipratropium blocks pulmonary muscarinic receptors mainly in the large central airways,<sup>31-34</sup> salbutamol blocks  $\beta_2$  adrenoceptors in both central and peripheral airways.<sup>7,35</sup> Moreover the bronchodilator effect of nebulized salbutamol peaks within 10 minutes,<sup>25</sup> that of ipratropium has been shown to take 30-120 minutes.<sup>7,12,36</sup> However, the duration of action of ipratropium is longer as compared to salbutamol.<sup>36</sup> Thus the addition of anticholinergic to sympathomimetic agents increases the degree and duration of bronchodilatation but avoids the likelihood of additive side effects.<sup>37</sup>

A few other studies,<sup>30,38</sup> have used  $\beta_2$  agonist and ipratropium in sequence. They noticed that inhaled ipratropium produced a significant additional increase in FEV<sub>1</sub> after the maximal effect from salbutamol has been attained. But no beneficial effect was noted if ipratropium was used prior to salbutamol. Thereby suggesting the presence of a significant cholinergic component to bronchospasm in many asthmatic children which might have been responsible for some of the residual airways obstruction after treatment with Salbutamol alone.

A few other studies,<sup>39,40</sup> have reported that combined use of the two drugs was as effective as sequential usage.

But they, did not notice any extra benefit of adding ipratropium.

### CONCLUSION

Combined nebulization with Salbutamol and Ipratropium bromide (three times at 20 minutes intervals) was found to be safe, effective and having additive action. Since, goal of treatment in an acute attack of asthma is not only to abort the attack quickly but also to have a sustained action also. Therefore, the combined nebulization can be used safely in children. However larger studies are required if guidelines and clinical practice are to become evidence based.

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