Objective: To compare the improvement in peak expiratory flow rate (PEFR) of patients presenting to the emergency department with acute severe asthma by using the following two regimens of broncho-dilator therapy. A) Salbutamol nebulization. b) Salbutamol plus Ipratropium bromide nebulization. c) To compare the hospital admission rates in the above mentioned two treatment groups. **Design:** A comparative study. **Place and Duration of Study:** Military Hospital Rawalpindi, Feb 2002 to Dec 2002. **Material and Methods:** Sixty adult asthmatic patients with peak expiratory flow rate (PEFR) less than 200 liters per minute were randomly assigned to nebulization treatment with salbutamol (5.0 mg initial dose followed by 2 more doses at 30 and 60 minutes) or the same salbutamol regimen plus ipratropium bromide (0.5 mg). The primary end point was change in PEFR. The PEFR was measured at 30 minutes, 60 minutes and 90 minutes after the onset of study protocol. The proportion of admission in the two groups was examined as secondary end point. **Results:** The increase in PEFR over time was significantly greater in combined ipratropium plus salbutamol group (p = 0.01) also the proportion of admitted patients was less in combined salbutamol plus ipratropium bromide group 4/30 vs 11/30, p = 0.036. **Conclusion:** The data suggested that combined ipratropium bromide plus salbutamol nebulization was superior to salbutamol nebulization alone and it should be used in the initial management of patients who present with acute severe asthma.

**Key words:** Acute Asthma, PEFR, Salbutamol, Ipratropium Bromide.

**INTRODUCTION**
Asthma is defined as a chronic inflammatory disorder of the airways characterized by reversible airflow obstruction causing cough, wheeze, chest heaviness and shortness of breath. Environmental factors play an important role in the causation of bronchial asthma. There is evidence that the prevalence and severity of asthma are rising. The number of deaths from asthma are also increasing contrary to the trend for other common treatable conditions. Any patients with acute asthma should be treated with nebulized salbutamol as first line treatment in addition to systemic anti-inflammatory therapy and oxygen inhalation. Systemic corticosteroids are effective primary treatment for patients with moderate to severe exacerbation or for patients who fail to respond promptly and completely to inhaled beta adrenergic agonist therapy. Since the early 1970s, there has been a renewed interest in the use of anticholinergic medications given the increase in prevalence, morbidity and mortality of asthma in the past...
decades and the need to develop alternatives to therapy with beta agonist agents\textsuperscript{6}. The use of both classes of broncho-dilator either simultaneously or in sequence has produced positive results\textsuperscript{7,10}. The use of ipratropium bromide seems indicated in the initial emergency department treatment of children and adults with severe acute asthma. The studies reported an important reduction in hospital admission rates. Regarding lung functions, significant differences favoring the combination treatment also were observed\textsuperscript{10}.

In the present study, we sought to determine whether combined ipratropium and salbutamol nebulization treatment had better clinical outcomes compared with salbutamol treatment alone in adult asthmatics with markedly airflow. The pattern of salbutamol administration involved repeated use of nebulized doses, in keeping with common ED practice. The primary question addressed was whether combined ipratropium and salbutamol nebulization resulted in greater airflow improvement. A secondary question was whether combined treatment was associated with a lower proportion of hospital admission.

PATIENTS AND METHODS
Sixty adult patients known to have asthma were considered for recruitment from the emergency department if they met the following criteria.

Inclusion Criteria
1. Age 18-45 years.
2. Capable of performing peak expiratory flow measurements.
3. Peak expiratory flow rate less than 200 L/min.

Exclusion Criteria
The following were excluded:
1. Patients with a history of glaucoma or prostatism.
2. Pregnant females.
3. Patients who received anti-cholinergics in the previous 24 hours.

Asthma was defined as:
1. Having a history of asthma diagnosed by a physician.
2. Having had a broncho-dilator prescribed by a physician.
3. Having had episodes of wheezing that improved with beta agonist inhalers.

METHODOLOGY
Patients who agreed to participate in the study had measurements of peak expiratory performed in the sitting position without nose clips. A mini Wright Peak Flow meter (by Clement Clarke International Ltd. London) was used for peak flow measurements. Recruited patients were randomly assigned to treatment with either salbutamol or salbutamol plus ipratropium bromide. Randomization was performed on the basis of a random assignment list generated using the random table. Each treatment designation was placed in a closed envelop the uninvolved E.D. staff used to administer treatment according to the treatment designation to which the patient would do and the staff would not communicate the details of the treatment to the study physician who happened to be the resident physician on duty in the E.D. A randomized double blind study design was thus employed on a convenience sample of patients selected as described above.

For those receiving salbutamol alone. 5.0 mg of salbutamol was administered using nebulizer Borea \textsubscript{F\textsubscript{400}} initially for 10 minutes and then at 30 and 60 minutes after the start of study protocol using the same 5.0 salbutamol dose. For those receiving combination therapy, 0.5 mg ipratropium bromide using atrovent nebule was added to the first dose of salbutamol 5.0 mg administered by nebulizer Borea \textsubscript{F\textsubscript{400}}, followed by two more doses of 5.0 mg only at 30 and 60 minutes. The duration of nebulization for each dose was 10 minutes.
An improvement of 90 liters per minute in PEF was deemed by the study physician as clinically significant. Heart rate, presence of agitation, tremors or accessory respiration muscles retractions, respiratory rate, any symptomatic complaints and PEF were recorded at baseline and then at 30, 60 and 90 minutes after the start of study protocol. Medical histories were obtained from the patients including past and current asthma treatment and complications. The admission criteria was designed and consisted of the presence, after treatment, of any of the following:-

1. Respiratory rate in excess of 24/min.
2. Use of accessory muscles of respiration.
3. Arterial PCO₂ greater than 44 mmHg.
4. Arterial Po₂ on (room air) less then 75 mmHg.
5. Associated diseases such as pneumonia or a febrile illness with a temperature greater than 102°F.

The final disposition of the patient was also noted (admission, discharge or leaving against medical advice). The percent predicted PEF was calculated from the normative data charts for predicted PEF based on age height and sex of the patient and using the formula.

$$\text{Percent Predicted PEF} = \frac{\text{Measured PEF} \times 100}{\text{Predicted PEF}}$$

The primary end points of peak expiratory flow rate and percent predicted PEF were analyzed. The proportion of admissions in the two groups were examined as a secondary end point. The data was recorded on SPSS version 10. Descriptive statistics were used to calculate mean PEF in relation to time in both the groups. Independent samples “t” test was used to test the significance of difference between means:

**RESULTS**

60 patients were recruited for this study and were divided in to two groups of 30 patients each. The group which received only salbutamol was termed the control group while the other group which received salbutamol plus ipratropium bromide was designated as treatment group.

Both the groups received treatment according to the study protocol.

There was a significant different peak flow response overtime (Fig 1) between the two groups p = 0.01. Despite a lower initial mean PEF, later peak flows showed higher values for the ipratropium plus salbutamol group compared with salbutamol only group (Table I).

<table>
<thead>
<tr>
<th>Table I. Descriptive Statistics</th>
</tr>
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<tbody>
<tr>
<td>Treatment Group</td>
</tr>
<tr>
<td>Baseline mean PEF</td>
</tr>
<tr>
<td>Mean PEF at 30 Min</td>
</tr>
<tr>
<td>Mean PEF at 60 Min</td>
</tr>
<tr>
<td>Mean PEF at 90 Min</td>
</tr>
<tr>
<td>Mean % predicted PEF at baseline</td>
</tr>
<tr>
<td>Mean % predicted PEF at 30 min</td>
</tr>
<tr>
<td>Mean % predicted PEF at 60 min</td>
</tr>
<tr>
<td>Mean % predicted PEF at 90 min</td>
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</tbody>
</table>

Significance improvement in PEF of more than 90 liters/min was achieved by 66.7% of the patients in the salbutamol only group while 33.3% did not show
significant improvement (Fig 2). In the salbutamol plus ipratropium group 93.3% of the patients achieved significant level of improvement in PEFR while only 6.7% could not achieve it.

36.7% admitted as compared to 63.3% who were discharged from the E.D. In the salbutamol plus ipratropium group only 13.3% were admitted while 86.7% were discharge from E.D. after treatment, \( p = 0.036 \).

When the percent predicted PEFR was used as the dependent variable, a similar level of significance was observed in favor of ipratropium plus salbutamol group \( "p < 0.001" \) (Fig 3).

The proportion of patients admitted was significantly greater in the salbutamol only group (Fig 4 & Table II).

**Table-II. Hospital Admission \( (p = 0.036) \)**

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Treatment Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted</td>
<td>11</td>
<td>04</td>
<td>15</td>
</tr>
<tr>
<td>% within group</td>
<td>36.7%</td>
<td>13.3%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Discharge d from ER</td>
<td>19</td>
<td>26</td>
<td>45</td>
</tr>
<tr>
<td>% within group</td>
<td>63.3%</td>
<td>86.7%</td>
<td>75.0%</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>% within group</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This study demonstrates that initial treatment with ipratropium bromide and salbutamol results in more broncho-dilator than salbutamol alone in asthmatic patients with PEFR less than 200 liters/min. In addition, the important clinical outcome of hospitalization requirement was significantly lower in the ipratropium...
plus salbutamol group. An examination of Table I demonstrates that the increase in airflow in this study, as measured by the mean PEFR and mean percent predicted PEFR showed a greater absolute difference in proportionate improvement over baseline when ipratropium plus salbutamol group is compared with the salbutamol only group.

Patients in the salbutamol plus ipratropium group had more severe initial peak flow impairment but showed more improvement in PEFR as compared to the patients in salbutamol alone group. Similar observations were made by Schuh et al11 and O’Driscoll et al12, who noted (in children and adults respectively) that patients with more severe airflow obstruction had a greater benefit from the combination therapy with ipratropium and beta agonists. Kamei et al13 also showed a significant improvement in pulmonary function using combination of beta agonists and oxitropium bromide but hospital admission rate did not show statistically difference. The clinical outcome of the ipratropium plus salbutamol group in my study was significantly better in terms of the proportion of admissions. Similar observations were made by Rodrigo et al14 and Nakano et al 15, both of them recorded a lower hospital admission rate for the group receiving combination of anti-cholinergics and beta agonists.

CONCLUSION
The use of ipratropium bromide seems indicated in the initial E.D. treatment of patients with severe acute asthma. It resulted in a significant improvement in airflow obstruction and led to lower hospital admission rates. Patients with more severe airflow obstruction had a greater improvement in PFER. The use of ipratropium bromide in patients with severe acute asthma led to lesser hospital admission rates thus contributing towards savings in health services resources.

REFERENCES
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