Introduction

Acute severe asthma (ASA) in children is the third most common cause of hospital admission and one of the most common causes of Paediatric intensive care unit (ICU) admission.\(^1\) The prevalence of asthma is rising and the number of deaths from asthma has increased.\(^2\) According to the US Centre for Disease Control and Prevention (CDC) Asthma Surveillance Survey, the prevalence of current asthma during 2001-2003 prevalence was estimated at 8.5% in children, and the burden of asthma increased more than 75% from 1980-1999.\(^3,4\) Asthma is also a common respiratory disorder in Pakistan.\(^5\) Up to 4% of children attending the out-patient department (OPD) in one study suffered from bronchial asthma.\(^6\) From 1975 to 1993, the number of deaths nearly doubled in people aged 5-14 years.\(^7\) In the northeastern and midwestern United States, the highest mortality rate has been among persons aged 5-34 years.\(^8\) According to report from CDC and the National Centrefor Health Statistics, 187 children aged 0-17 years died from asthma, or 0.3 deaths per 100,000 children in the year 2002.\(^3\)

ASA is a life-threatening medical emergency characterised by episodes of increasing cough, wheezing, chest recession and inability to speak or drink, resulting in respiratory failure if not managed in time.\(^8\)

Common triggers of ASA are viral infections, allergens (cockroaches, dust mites, pollens and molds), air pollution and tobacco smoke.\(^9,10\)

Standard treatment of ASA is use of inhaled short-acting \(\beta_2\) agonists (salbutamol), systemic corticosteroids and supplemental oxygen.\(^10\) Current guidelines recommend use of a combination of \(\beta_2\) agonists and anti-cholinergics (ipratropium) for ASA.\(^11,12\) Frequent nebulisation with \(\beta_2\) agonist at the onset of an ASA has been reported to be effective, but some cases may require combination of salbutamol along with ipratropium for relief of obstruction. This may result in significantly longer bronchodilation in ASA.\(^13,14\)

Available data shows a response rate of 88.5% with the use of salbutamol alone,whereas response was found to be 100% when salbutamol was used in combination with ipratropium bromide.\(^14\) Thus combination therapy may reduce the ASA burden and emergency room visits.

Though there are local studies on various aspects of asthma, there is no local study published so far comparing the response of nebulised salbutamol alone with combination of ipratropium bromide. The current study was planned to compare the two approaches.
Patients and Methods
The randomised controlled trial (RCT) was conducted at the National Institute of Child Health (NICH), Karachi, from October 1, 2009, to March 31, 2010, and comprised children 2-14 years of age who visited emergency room (ER) with ASA. For ASA evaluation, clinical score by Bentur Modification (BM) 5-10 (moderate) and >10 (serve exacerbation) was used. Bentur modification is based on 4 parameters: heart rate (HR), respiratory rate (RR), wheezing, accessory muscle usage. Each parameter has minimum 0 and maximum 3 score (Appendix).

The sample size was calculated on the basis of frequency of asthma disease being 8.5%. It was calculated at 95% confidence interval (CI) with 4% precision, using EPI software 6.

The study was conducted after obtaining approval from the institutional ethics committee and informed consent from the parents concerned. The patients were randomly allocated to two equal groups: Group A (GA; salbutamol) and Group B (GB; salbutamol plus ipratropium bromide).

GA received 3 doses of salbutamol (0.03 ml/kg/dose) only 15 minutes apart and GB received 3 doses of ipratropium (250 ug/dose) in combination with salbutamol (0.03 ml/kg/dose) with same time interval.

Response to treatment was assessed after 15 minutes of the last dose and a change in severity category (improvement) from baseline to lower category was taken as improvement.

All demographic and clinical data was recorded in a pre-designed proforma. Statistical analysis was done using SPSS 10. Frequencies and percentages were computed for gender, age groups and Bentur categories in both groups. Mean ± standard deviation (SD) were computed for age, HR, RR and Bentur clinical score in the two groups. Efficacy was compared between the groups by chi-square test. P<0.05 was considered significant.

Appendix: Bentur Modification.

<table>
<thead>
<tr>
<th>Score</th>
<th>Heart Rate</th>
<th>Resp: Rate</th>
<th>Wheezing</th>
<th>Accessory Muscle usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;110</td>
<td>&lt;40</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>111-130</td>
<td>40-50</td>
<td>End Expiratory only</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>131-150</td>
<td>51-60</td>
<td>Inspiratory and expiratory (with steth)</td>
<td>Moderate with tracheosternal (tug)</td>
</tr>
<tr>
<td>3</td>
<td>&gt;150</td>
<td>&gt;60</td>
<td>Loud wheezing without stethoscope or silent chest</td>
<td>Severe with nasal flaring</td>
</tr>
</tbody>
</table>

Mild <5
Moderate 5-10
Severe >10.

Results
The 200 patients in the study were divided into two groups of 100(50%) each. Overall, there were 112(56%) males and 88(44%) females (Male: female ratio = 1.27:1). In GA, there were 58(58%) males and 42(42%) females (M:F = 1.4:1), while in GB, there were 54(54%) males and 46(46%) females (M:F = 1.2:1). Overall mean age of children was 9.2±2.9 years (range 2-14 years). The mean age in GA was 9.1±3 years and 9.3±2.8 years in GB. Overall, 123(61.5%) patients were between 7 and 11 years of age.

Regarding baseline severity score, in GA it was 5-10 in 62 (62%) and >10 in 38(38%) cases. In GB, it was 5-10 in 59(59%) and >10 in 41(41%) cases (Table-1).

The mean baseline HR, RR and Bentur clinical score (BCS) in GA were 128.8±14.1, 58.6±5.6 and 8.4±2.3 respectively compared to 128.9±11.8, 58.9±5 and 8.6±3.1 in GB (Table-2).

After treatment, BCS was <10 in 93(93%) children in GB and in 84(84%) in GA (Table-3).

Table-1: Age and gender distribution.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group -A N (%)</th>
<th>Group -B N (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>58 (58)</td>
<td>54 (54)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (42)</td>
<td>46 (46)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-6 years</td>
<td>18 (18)</td>
<td>15 (15)</td>
<td>33 (16.5)</td>
</tr>
<tr>
<td>7-11 years</td>
<td>57 (57)</td>
<td>63 (63)</td>
<td>120 (60)</td>
</tr>
<tr>
<td>&gt;11 years</td>
<td>25 (25)</td>
<td>22 (22)</td>
<td>47 (23.5)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>200 (100)</td>
</tr>
</tbody>
</table>

Table-2: Baseline descriptive statistics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A Mean±SD (Range)</th>
<th>Group B Mean±SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>9.1±3 (2-13)</td>
<td>9.3±2.8 (2-14)</td>
</tr>
<tr>
<td>Heart Rate at the time of admission</td>
<td>128.8±14.1 (111-157)</td>
<td>128.9±11.8 (112-156)</td>
</tr>
<tr>
<td>Respiratory Rate at the time of admission</td>
<td>58.6±5.6 (51-74)</td>
<td>58.9±5 (51-75)</td>
</tr>
<tr>
<td>Bentur clinical score</td>
<td>8.4±2.3 (3-12)</td>
<td>8.6±3.1* (2-12)</td>
</tr>
</tbody>
</table>

SD: Standard Deviation.

Table-3: Comparative bentur clinical scores.

<table>
<thead>
<tr>
<th>Group</th>
<th>n (%)</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P - Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>84 (84 %)</td>
<td>8.4 ± 2.3</td>
<td>4.9 ± 2.1</td>
<td>0.001</td>
</tr>
<tr>
<td>B</td>
<td>93 (93 %)</td>
<td>8.6 ± 3.1</td>
<td>4.4 ± 2.4</td>
<td>0.007</td>
</tr>
</tbody>
</table>

J Pak Med Assoc
Mean BCS became 4.9±2.1 in GA, and 4.4±2.4 in GB (p>0.05).

After treatment, 69(82%) of the 84 children with BCS<10 in GA, had mild exacerbation (<5 score), whereas 15(18%) showed moderate exacerbation (5-10 score). In GB, 72(77.4%) of the 93 children with BCS<10 had mild exacerbation (<5 score) and 21(22.6%) children showed moderate exacerbation (5-10 score).

Discussion
Asthma prevalence, hospitalisation rate and deaths have increased according to epidemiologic studies from the 1970s and 1980s. These result in an increased attention on asthma management, including in children. An expert committee convened by the National Heart, Lung and Blood Institute of the National Institutes of Health, published a guideline for asthma management in children.

Inhaled anti-cholinergic agents such as atropine have long been known to be effective for acute asthma, but until recently their use has been limited because of the systemic side effects. Ipratropium bromide is a synthetic derivate of atropine that was designed to act locally in the lung with minimal systemic absorption. Studies of efficacy and safety of ipratropium bromide has been conducted predominantly in adults. If it is used alone, ipratropium bromide has been shown to reduce bronchospasm with minimal cardiovascular or other systemic effects. When combined with β-agonist, ipratropium bromide improves pulmonary function above that seen with β-agonist alone.

The role of ipratropium in paediatric asthma therapy is limited. Several studies comprising children with severe asthma exacerbation have found improvement in pulmonary function when ipratropium bromide was added to β-agonist. But the benefit of ipratropium bromide with β-agonist combination in children with moderate asthma exacerbation and among young children who were unable to perform pulmonary test was still unknown.

Ipratropium bromide is of low lipid solubility, and thus is poorly absorbed systemically. Toxic effects of this drug are therefore negligible, even at very high doses, because less than 1% of it is found in blood.

In the present study after treatment for maximally 3 doses of drugs 15 minutes apart, 93% children in GB showed improvement in clinical scores while in GA, 84% children showed improvement in clinical score. It means efficacy was relatively high in GB, but the results was not statistically significant (p>0.05).

Global data shows improvement observed in 88.5% of children who received only salbutamol and 100% in those who received salbutamol and ipratropium bromide.

A study of 125 children with severe asthma found that the forced expiratory volume in one second (FEV1) improved to a greater extent in children receiving salbutamol and ipratropium than in those receiving salbutamol and placebo, but there was no effect on overall rates of hospitalisation. In a subgroup analysis of children in whom FEV1 was less than 30 percent of the predictive value, the hospitalisation rate among those receiving the combination therapy was significantly lower than the rate with salbutamol alone. But the small number of patients limited the extent to which these observations could be
generalised. A study of 434 children with moderate and severe asthma exacerbation showed that the addition of ipratropium bromide had a significant effect on improvement of the asthma score, but there were no significant difference in improvement of the peak expiratory flow rate (PEFR). A study in 2004 showed that frequent combined nebulisation with salbutamol and ipratropium bromide significantly improved percentage of PEFR starting at 30 minutes and lasting for 4 hours in 50 children (6-14 years) with moderate asthma exacerbation in India.

In both groups, efficacy was high in male children; 59.5% boys in GA and 48.4% in GB. Although no significant benefit of combining ipratropium with salbutamol was found in the present study, ipratropium appears to be an effective bronchodilator in patients with acute severe asthma.

Conclusion
The combination of nebulised ipratropium bromide and salbutamol in a child with acute severe asthma exacerbation was associated with significant reduction of clinical asthma score.

Reference