COMPARATIVE EFFICACY & SAFETY OF SALBUTAMOL VERSUS LEVOSALBUTAMOL FOR TREATMENT OF ACUTE EXACERBATION OF BRONCHIAL ASTHMA

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ABSTRACT
Salbutamol is an effective treatment of acute exacerbation of bronchial asthma but its use is associated with undesirable side effects like tachycardia and hypokalaemia. Published studies have showed that levosalbutamol improves pulmonary function more than racemic salbutamol without the known salbutamol side effects.

OBJECTIVE
To compare the efficacy and tolerability of Salbutamol and Levosalbutamol for the treatment of acute exacerbation of bronchial asthma in children aged 5 to 15 years.

METHODS
A randomized double blind clinical study included 100 known asthmatic children aged between 5 and 15 years, who attended the emergency department for an acute exacerbation. The studied medicines were salbutamol 2.5mg and levosalbutamol 0.63mg. The total drug volume was 2.5ml which was nebulized over a period of 8-10 minutes. Forced expiratory volume in 1st second was measured using Manual Prometer. Spirometry was performed 3 times and the best of the three values was recorded. The following clinical parameters were recorded initially and after giving 3 nebulisations at 20 minutes interval in the 1st hour of presentation: respiratory rate (RR), heart rate (HR), oxygen saturation in room air SPO2, FEV1 ( Forced expiratory volume in 1st second), asthma score and serum potassium level.

RESULTS
In the levosalbutamol group there was significant increment in FEV1 and SpO2 (p<0.05) with decreased tachypnea and asthma score while no significant difference was found in the pre and post treatment HR and serum K+ levels. In the Salbutamol group although there was clinical improvement in terms of FEV1, SpO2 and asthma score, there was significant tachycardia and decrease in K+ levels.

CONCLUSION
Levosalbutamol has similar therapeutic effects with salbutamol in acute exacerbation of asthma but has no side effects such as tachycardia and hypokalaemia.

KEYWORDS
Levosalbutamol; Salbutamol; Bronchial Asthma.


INTRODUCTION
Salbutamol, the most commonly used bronchodilator, is a chiral drug with R and S Isomers. The commonly used formulation is a racemic mixture that contains equal amount of both R and S isomer.1 β2-agonist racemic Salbutamol has been the mainstay of treatment for bronchial smooth muscle contraction since 1982.2 β2-agonist are racemic mixture that are composed of a 50:50 ratio of (R) and (S) isomers. The R isomer (Referred to as levosalbutamol) is the therapeutically active bronchodilator by increasing intracellular calcium in airway smooth muscle cell in vitro which promotes smooth muscle contraction opposing bronchodilation. Current evidence indicates that the s-isomer is devoid of any bronchodilator activity.3 Also, levosalbutamol (LEV) the active component of racemic salbutamol (RAC) when administered as the single isomer avoids all of the potential adverse effect of (S) isomer.4

Studies have shown that in asthmatic patients, treatment with levosalbutamol decreased hypersensitivity to methacholine to a greater degree and with longer duration of action than does treatment with racemic salbutamol.5 In studies of outpatient asthma patients who were treated with levosalbutamol they experienced a significantly greater increase in FEV1, a longer duration of action and fewer side effects.6 In the emergency department studies showed levosalbutamol improved pulmonary function significantly more than racemic salbutamol and significantly decreased the number of hospitalizations compared to racemic salbutamol.7 Though Salbutamol is an effective treatment of acute exacerbation, its use is associated with undesirable side effects like tachycardia and hypokalaemia. Search for a more effective drug with fewer side effects is still on. The purpose of the present study is to evaluate the impact of levosalbutamol on clinical effectiveness and assess the patient outcome.8

Formulation of salbutamol containing only R-isomer (Levosalbutamol) has been available on the national and international market for the last few years. So far to our knowledge, efficacy and tolerability of levosalbutamol have not been compared with racemic salbutamol in acute exacerbation asthma in children.9

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OBJECTIVE
To compare the efficacy and tolerability of Levosalbutamol and Salbutamol for the treatment of acute exacerbation of asthma in children aged 5 to 15 years.

MATERIALS AND METHODS
This was a randomized double blind clinical study that included 100 known asthmatic children of both sexes aged 5 to 15 years who attended the emergency department for acute asthma exacerbation. The studied medicines were salbutamol 2.5mg and levosalbutamol 0.63mg concealed in a numbered envelope. All the eligible patients were randomly assigned. The total drug volume was 2.5ml which was nebulized over a period of 8-10 minutes. Severity of asthma was assessed using the asthma score illustrated in Table 1. Children were treated in emergency department for 1 hour.

Randomization effects were performed using randomization sequence, Randomization was performed using random number sequence, a computer and STATA 8.0 software. Two resident doctors responsible for the study prepared the randomization series the assignment was then performed using opaque envelop. A sequence number was assigned to each of these sealed envelope, thus blinding was ensured.

STUDY DESIGN
The study was conducted according to the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) and the clinical treatment protocol was approved by the ethical Committee of the University and departmental review board. A randomized double blind hospital based comparative study was used to assess the effects of the two drugs on the above mentioned parameters. Randomization was performed using a random number sequence, a computer and STATA 8.0 software. Two resident doctors responsible for the study prepared the randomization series the assignment was then performed using opaque envelop. A sequence number was assigned to each of these sealed envelope, thus blinding was ensured.

ETHICAL APPROVAL
The study was carried out in the asthma center (ED) of Paediatrics Department, after approval from ethical committee.

STUDY POPULATION
Group I- Levosalbutamol group n=50
Group II- Salbutamol group n=50

INCLUSION CRITERIA
Asthma patient 5-15 years presenting with acute exacerbation.

EXCLUSION CRITERIA
Age below 5 years and above 15 years, children already on preventive therapy (Inhaled steroids or long acting bronchodilator LABA), first episode of wheezing, congenital heart diseases, cystic fibrosis and other chronic lung diseases were excluded from the study.

DATA COLLECTION AND EVALUATION
Parents or care takers were given a detailed briefing about the purpose of the study. Informed consent forms were signed by the subject or the subjects legally authorized representative before his/ her participation in the study. Before and after giving levosalbutamol or salbutamol baseline clinical parameter RR, HR, SPO2, asthma score and serum K+ level were recorded and compared on a designed proforma. All the values were expressed as mean ± SD for pre and post treatment effects. Comparative analysis of baseline parameters of two groups and within the groups and percentage of improvement between these two groups before and after treatment was done using unpaired “t” test. All the statistical analysis was done by using SPSS package 16 version.

<table>
<thead>
<tr>
<th>Characteristic of patients in the two groups</th>
<th>Group 1 (LEV)</th>
<th>Group 2 (RAC)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10.57±3.60</td>
<td>10.77±4.05</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Sex Boys / Girls</td>
<td>28/22</td>
<td>27/23</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>ED visits (past 12 mths)</td>
<td>11</td>
<td>13</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>0 ≥1</td>
<td>19</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Hospitalization (past 12 months)</td>
<td>23</td>
<td>24</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>0 ≥1</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years mean ± SD)</td>
<td>4.15±2.17</td>
<td>3.95±2.54</td>
<td>P&gt;0.05</td>
</tr>
</tbody>
</table>

Table 1: Scoring severity of asthma Severity Assessment Asthma Score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>29.53±5.12</td>
<td>27.63±6.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HR</td>
<td>95±11.20</td>
<td>109.43±13.25</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>SPO2</td>
<td>94.57±14.81</td>
<td>96.43±11.12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV1</td>
<td>49.50±10.12</td>
<td>63.80±12.50</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
RESULTS
Baseline characteristic age, sex, diagnosis, duration of asthma were comparable between the two groups (p value >0.05) (Table 2). None of the patients were receiving preventive therapy like steroids or LABA before presenting to ED. Patients were either lost to preventive therapy or never initiated on preventive therapy, none was given steroids during their 1 hour stay at ED.

The following parameters were recorded initially and after giving 3 nebulisations at 20 minutes interval in the 1st hour of presentation respiratory rate (RR), heart rate (HR), oxygen saturation in room air SPO2, FEV1 (Forced expiratory volume in 1st second), asthma score and serum K+ level. In levosalbutamol group, there was significant increment in FEV1 and SPO2 (p<0.05) with decrease tachypnoea and asthma score while no significant difference was found in pre and post treatment HR and serum K+ levels. In the Salbutamol group although there was clinical improvement in terms of FEV1, SPO2 and asthma score, it resulted in significant tachycardia and decrease in K+ levels (Tables 3 and 4).

DISCUSSION
It has been established that regular and excessive use of racemic salbutamol (RAC) induces paradoxical reaction in some subject with asthma.10 This has led to development of safer and at least equally therapeutically active agents of the available β2-agonists. Levosalbutamol (LEV), the active component of racemic salbutamol avoids the potential adverse effect of (S) isomer when administered as the single isomer. "Levosalbutamol" was approved by Food and Drug Administration (FDA) in 1999 as a purified single isomer for clinical use in asthma patients.11,12

Levosalbutamol (LEV) has approximately 2-fold greater affinity than the racemic salbutamol for the β2 adrenergic receptor and approximately 100-fold greater binding affinity than S-salbutamol.13,14 LEV elevates intracellular concentration of cyclic AMP (cAMP) by activating adenyl cyclase. In the airways, increased concentration of cAMP relaxes bronchial smooth muscle by reducing intracellular calcium and prevents contraction of hyperresponsive airways. Increased concentration of cAMP also inhibit the release of inflammatory mediators from mast cells and eosinophil.15

Milgrom et al. previously compared LEV to RAC in paediatric population with chronic stable asthma showing that LEV (0.63mg) produces greater change in FEV1 immediately post nebulization (18%) when compared to RAC 2.5mg (15.6%). Our study in acute exacerbation showed the 2 drugs made 19% and 18% increase respectively indicating similar therapeutic effects.16,17 Study assessing the efficacy of LEV in acute exacerbation of asthma have been carried in adults but only one in children done by Punj in India among children aged 5-18 years presenting in the ED with acute exacerbation of asthma. The patients had initial PEFR <80% of predicted and nebulized LEV (0.63mg) at presentation. Results showed efficacy in terms of improvement in SpO2, PEFR and asthma score (P<0.001) and better tolerability, less tachycardia and less hypokalaemia compared to RAC (P<0.001). Our study result shows that both have same therapeutic effect with less significantly less tachycardia and hypokalaemia in the LEV group (P<0.05).18

Another study was conducted in children aged 1-5 years with reactive airway diseases that compared LEV with RAC and assessed hospitalization as outcome measure showing shorter hospitalization with LEV. Although this outcome measure is not same as in the present study it points towards usefulness of LEV similar to the present results. In this study there was no demonstration of reduction of side effects like tremor and tachycardia but then they used a higher dose of LEV (1.25mg) while our patients had a lower dose of LEV (0.63mg).

Ralston et al. compared LEV with a combination of salbutamol and ipratropium bromide in children between 6-18 years presenting with acute asthma and reported that LEV was associated with less tachycardia but showed no other advantage of associating RAC with ipratropium bromide. Our study underlines the fact that while having similar effects with RAC alone, LEV does not cause either tachycardia or hypokalaemia.19

CONCLUSION
Levosalbutamol has equally good effect with salbutamol in improving FEV1, SPO2 and asthma score in acute exacerbation of asthma in children but better tolerability in terms of tachycardia and hypokalaemia compared to salbutamol.

What This Study Adds To Our Knowledge
1. Levosalbutamol has equally good therapeutic beneficial effect with salbutamol in improving FEV1, SPO2 and asthma score in acute exacerbation of asthma.
2. Levosalbutamol has better tolerability in terms of tachycardia and hypokalaemia compared to salbutamol.

REFERENCES