COMPARATIVE EFFICACY AND SAFETY OF IPRATROPIUM BROMIDE VERSUS TIOTROPIUM BROMIDE FOR MAINTENANCE THERAPY OF MILD-TO-MODERATE BRONCHIAL ASTHMA IN ADULTS

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ABSTRACT

BACKGROUND
Anticholinergic drugs are commonly used for maintenance therapy of bronchial asthma. Selective beta-2 agonist like Salbutamol is associated with undesirable side effects like tachycardia and hypokalaemia. The objective of this study is to compare the efficacy and safety of Ipratropium bromide versus Tiotropium bromide for maintenance therapy of bronchial asthma.

MATERIALS AND METHODS
A randomised double-blind clinical study was conducted including 100 known asthma patients. After adequately treating the acute attack, these study medicines were given. Spirometry was performed three times and the best of the three values were recorded. The following parameters were recorded: Asthma score, Heart Rate (HR), Respiratory Rate (RR), Oxygen Saturation (Spo2), FEV1 (Forced Expiratory Volume in 1 second) and Serum potassium level was determined.

RESULTS
In Ipratropium group, there was significant increment in FEV1 and Spo2 (p < 0.05) with decreased tachypnoea and asthma score, while no significant difference was found in pre- and post-treatment HR and serum K+ levels. In the Ipratropium bromide group although there was clinical improvement in terms of FEV1, Spo2 and asthma score, it resulted in significant tachycardia and decrease in K+ levels. This study showed both Tiotropium and Ipratropium are effective bronchodilators in mild-to-moderate asthma patients.

CONCLUSION
Tiotropium bromide is equally effective as compared to Ipratropium bromide in terms of asthma parameters for maintenance therapy of mild-to-moderate asthma, but in terms of dosage schedule it is convenient to patient.

KEYWORDS
Ipratropium Bromide, Tiotropium Bromide, Mild-to-Moderate Asthma.

HOW TO CITE THIS ARTICLE: Mujeeb MMA, Ahmed SM, Chudiwal TB. Comparative efficacy and safety of ipratropium bromide versus tiotropium bromide for maintenance therapy of mild-to-moderate bronchial asthma in adults. Journal of Evolution of Research in Medical Pharmacology 2017; Vol. 3, Issue 1, Jan-June 2017; Page:1-4
Studies have shown that in mid-to-moderate asthmatic patients, treatment with anticholinergic drugs decreased hypersensitivity to methacholine to a greater degree and with longer duration of action. In studies of outpatient asthma patients who were treated with Tiotropium bromide they experienced a significantly greater increase in FEV₁, a longer duration of action and fewer side effects. Earlier studies showed that Tiotropium bromide has equal efficacy and safety as compared to Ipratropium bromide, but is good in terms of dosing schedule and convenience to patient. The purpose of the present study is to evaluate the impact of Tiotropium bromide on clinical effectiveness and assess the patient outcome in maintenance therapy of mild-to-moderate asthma after adequate control of acute attack.

**Objectives**

1. To assess improvement in symptoms of patients suffering from bronchial asthma with Ipratropium bromide.
2. To assess improvement in symptoms of patients suffering from bronchial asthma with Tiotropium bromide.
3. To compare the improvement in symptoms of the two modalities of treatment.
4. To compare pulmonary function test abnormalities in the two groups.

**MATERIALS AND METHODS**

This was a randomised, double-blind clinical study that included 100 known mild-to-moderate asthmatic patients of both sexes. All the eligible patients were randomly assigned with the random number table. Severity of asthma was assessed using the asthma score illustrated in Table 1.

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 on room air SPO₂, asthma score and serum K⁺ level. Forced expiratory volume at 1 s second (FEV₁) was measured using manual Spirometer. Patients had spirometry 3 times and best of the three values were recorded.

**Study Design**

The study was conducted according to the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the clinical treatment protocol was approved by the Ethical Committee. A randomised, double-blind comparative study was used to find out the effects of these drugs. A sequenced number was assigned to each of these sealed envelope, thus blinding was ensured.

**Ethical Approval**

The study was carried out in the Respiratory Medicine OPD and indoor patients after approval from Ethical Committee.

**Study Population**

**Group I**

Tiotropium bromide group n= 50, 1 rotacap once a day.

**Group II**

Ipratropium bromide group n= 50, 2 - 4 puffs 6 hourly.

**Inclusion Criteria**

Mild-to-moderate asthma patient.

**Exclusion Criteria**

Age below 5 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.

**Duration of Study**

Each patient was followed for 1 year.

**Primary Outcome**

The primary outcome was the number of patients with at least one exacerbation requiring systemic corticosteroids.

**Secondary Outcomes**

1. Other clinical outcomes reflecting the severity of asthma exacerbations (e.g. Hospital admissions, acute care visit).
2. Clinical or physiologic outcomes reflecting chronic asthma control (e.g. Pulmonary function tests, symptom score, β₂-agonist use, measures of functional status, quality of life, patient’s and physician’s satisfaction, etc.).
3. Biological markers of inflammation (e.g. Eosinophil count in blood and sputum, leukotriene C₄ in biological samples, expired nitric oxide, etc.).
4. Clinical and biochemical adverse effects (e.g. Elevation of liver enzymes, growth).

Withdrawal rates (Overall withdrawals, withdrawals due to poor asthma control and withdrawals due to adverse effects).

**Data Collection and Evaluation**

Parents or caretakers were given a detailed briefing about the purpose of the study. Informed consent forms were signed by the subject or the subjects legally authorised representative before his/her participation in the study. Before and after giving Ipratropium bromide or Tiotropium bromide 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.

**RESULTS**

Baseline characteristic age, sex, diagnosis, duration of mild-to-moderate asthma were comparable between the two groups (p value > 0.05) (Table 2). 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 on room air SPO₂, FEV₁ (Forced Expiratory Volume at 1 s second), asthma score and serum K⁺ level. In Ipratropium group, there was significant increment in FEV₁ and SPO₂ (p < 0.05) with decreased tachypnoea and asthma score, while no significant difference was found in pre- and post-treatment HR and serum K⁺ levels. In the Ipratropium bromide 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). This study showed both Tiotropium and ipratropium are effective bronchodilators in mild-to-moderate asthma patients. Although, statistically overall response to Tiotropium bromide appears to be superior.

Severity Assessment

<table>
<thead>
<tr>
<th>Asthma Category</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma Score</td>
<td>5-7</td>
<td>8-11</td>
<td>12-15</td>
</tr>
<tr>
<td>% FEV1</td>
<td>&lt; 80%</td>
<td>50 - 65%</td>
<td>&lt;50%</td>
</tr>
</tbody>
</table>

Table 1. Type of Asthma

<table>
<thead>
<tr>
<th>Assessment</th>
<th>1 Point</th>
<th>2 Point</th>
<th>3 Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Rate 20-24 yrs</td>
<td>≤34</td>
<td>35-39</td>
<td>≥40</td>
</tr>
<tr>
<td>24-28 yrs</td>
<td>≤30</td>
<td>31-35</td>
<td>≥36</td>
</tr>
<tr>
<td>28-32 yrs</td>
<td>≤26</td>
<td>27-30</td>
<td>≥31</td>
</tr>
<tr>
<td>&gt; 32 yrs.</td>
<td>≥23</td>
<td>24-27</td>
<td>≥28</td>
</tr>
<tr>
<td>02 Saturation Room Air</td>
<td>&gt;95%</td>
<td>90-95%</td>
<td>≤90%</td>
</tr>
<tr>
<td>Auscultation No to Mild End-Expiratory Wheezing</td>
<td>Expiratory Wheezing</td>
<td>Ins+Exp Wheezing or Diminished BS</td>
<td></td>
</tr>
<tr>
<td>Retraction None to Intercostal</td>
<td>Intercostal+ Subternal</td>
<td>Intercostal, Subernal+ Supraclavicular</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea Speaks in Sentences or Coos and Babbles</td>
<td>Speaks in Partial Sentences, or Utter Short Cries</td>
<td>Speaks in Short Words or Short Phrases or Grunt</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Severity of Asthma

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Group 1 (50)</th>
<th>Group 2 (50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.57±3.60</td>
<td>38.77±4.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Sex Male/Female</td>
<td>28/22</td>
<td>27/23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Emergency visits within 1 year</td>
<td>11</td>
<td>13</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>≥1</td>
<td>19</td>
<td>17</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hospitalization within 1 year</td>
<td>23</td>
<td>24</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>≥1</td>
<td>7</td>
<td>6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Duration of illness years mean±SD</td>
<td>4.15±2.17</td>
<td>3.95±2.54</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 3. Characteristic of Patients in the Two Groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-Treatment</th>
<th>Post-Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Rate</td>
<td>29.53±5.12</td>
<td>27.63±0.60</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heart Rate</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>
<tr>
<td>Serum K+</td>
<td>4.58 ± 0.80</td>
<td>3.93 ± 0.59</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Asthma Score</td>
<td>6.80±1.25</td>
<td>7.6 ± 0.79</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 4. Pre- and Post-Treatment of Tiotropium Bromide

DISCUSSION

The objective of this study was to evaluate whether Ipratropium bromide/Tiotropium bromide inhaler provides more effective relief of bronchospasm in maintenance therapy of mild-to-moderate asthma. The addition of tiotropium to low-dose Salbutamol resulted in significant improvements in morning and evening PEF, and pre-bronchodilator FEV1. The combination of tiotropium and low-dose Salbutamol was very effective. The addition of tiotropium significantly improved lung function; however, no significant differences were observed in asthma-related health status or rescue medication use in this crossover and short-term setting the design of which may have impacted the clinical outcome.

Bateman et al showed that adding tiotropium to medium-dose Salbutamol was non-inferior to salmeterol and superior to placebo in patients with moderate asthma. These studies support a potentially important therapeutic role for the long-acting anticholinergic tiotropium as maintenance therapy in the treatment of patients with asthma. In this study, the overall safety profile of Tiotropium was similar to Ipratropium. As previously observed with short-acting anticholinergics, patients receiving Ipratropium reported more cough. Therefore, in this population with poor asthma control, exacerbations are expected to be more frequent.

CONCLUSION

Tiotropium bromide is equally effective as compared to Ipratropium bromide in terms of asthma parameters for maintenance therapy of mild-to-moderate asthma, but in terms of dosage schedule it is convenient to patient.

REFERENCES


