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 Ipratropium bromide 2 - 4 puffs 6 hourly or Tiotropium bromide 1 rotacap once a day. The patients were analysed by improvement in clinical symptoms, breathlessness and forced expiratory volume in 1 second. 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 (SPO_2), FEV_1 (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.

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BACKGROUND

Asthma is a condition that affects the airways. It is characterised by bronchoconstriction and underlying inflammation.[1] Infiltration of bronchial airways with eosinophils and neutrophils with release of inflammatory mediators is characteristic of asthma. Asthma is a disease that has become increasingly common over last century.[2] Although, it is variable in severity, it is now a common cause of disability. The incidence of asthma has increased dramatically over last 25 years in industrialised nations as a result of exposure to air pollution. Also, other factors include obesity, decreased exercise, change in diet and increased viral respiratory infection.

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The cysteinyl leukotrienes are considered as the most potent inflammatory mediators in asthma. They are produced by the 5-lipoxygenase pathway of the arachidonic acid metabolism.[3] These mediators stimulate the production of airway secretions, cause microvascular leakage and enhance eosinophilic migration in the airways; thus, leukotrienes are believed to play a pivotal role in mediating bronchoconstriction and inflammatory changes in the pathophysiology of mild-to-moderate asthma.[4]

All recent consensus statements on acute attack of asthma advocate aggressive treatment of airway inflammation.[5] Although, several drugs such as ketotifen, sodium cromoglycate and sodium nedocromil have anti-inflammatory properties, inhaled glucocorticoids remain the cornerstone of asthma management because of their efficacy, tolerability and rapid onset of action. Prolonged low-dose administration of inhaled corticosteroids is generally considered safe, although there is considerable concern about the long-term effects of steroids among some consumers.[6] However, when moderate or high doses are required to control symptoms, adverse effects such as growth stunting in children, suppression of the adrenal axis and osteopenia may be observed.[7]

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.[8] In studies of outpatient asthma patients who were treated with Tiotropium bromide they experienced a significantly greater increase in FEV_1, a longer duration of action and fewer side effects.[9] 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.[10] 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 1st 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.[11]

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.[10]

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.[12]

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, β_2-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 C_4 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 1st 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

Asthma Category	Mild	Moderate	Severe
Asthma Score	5-7	8-11	12-15
% FEV_1	< 80%	50 - 65%	< 50%

Table 1. Type of Asthma

Assessment	1 Point	2 Point	3 Point
Respiratory Rate 20-24 yrs. 24-28 yrs. 28-32 yrs. > 32 yrs.	 ≤34 ≤30 ≤26 ≤23	 35-39 31-35 27-30 24-27	 ≥40 ≥36 ≥31 ≥28
O2 Saturation in Room Air	>95%	90-95%	≤90%
Auscultation	No to Mild End-Expiratory Wheezing	Expiratory Wheezing	Ins+Exp Wheezing or Diminished BS
Retraction	None or Intercostal	Intercostal+ Substernal	Intercostal, Substernal+ Supraclavicular
Dyspnoea	Speaks in Sentences or Coos and Babbles	Speaks in Partial Sentences, or Utter Short Cries	Speaks in Single Words or Short Phrases or Grunt

Table 2. Severity of Asthma

Assessment	Group 1 (50)	Group 2 (50)	P value
Age (years) Sex Male/Female	39.57 ± 3.60 28/ 22	38.77 ± 4.05 27/23	p>0.05 p>0.05
Emergency visits within 1 year 0 ≥1	 11 19	 13 17	 P>0.05 p>0.05
Hospitalization within 1 year 0 ≥1	 23 7	 24 6	 P>0.05 P>0.05
Duration of illness years mean ± SD	4.15 ± 2.17	3.95 ± 2.54	p>0.05

Table 3. Characteristic of Patients in the Two Groups

Parameters	Pre-Treatment	Post-Treatment	P-value
Respiratory Rate	29.53 ± 5.12	27.63 ± 0.60	<0.05
Heart Rate	95 ± 11.20	109.43 ± 13.25	>0.05
SPO_2	94.57 ± 14.81	96.43 ± 11.12	<0.05
FEV_1	49.50 ± 10.12	63.80±12.50 19%	<0.05
Serum K^+	4.58 ± 0.80	3.93 ± 0.59	>0.05
Asthma Score	6.80 ± 1.25	7.6 ± 0.79	<0.05

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

Parameters	Pre-Treatment	Post-Treatment	P-value
Respiratory Rate	29.7 ± 4.15	28.37 ± 3.50	< 0.05
Heart Rate	99.52 ± 18.56	112.52 ± 16.02	< 0.05
SPO_2	96.78 ± 13.52	98.12 ± 7.20	< 0.05
FEV_1	49.12 ± 10.90	58.99±13.12 18%	< 0.05
Serum K^+	4.85 ± 0.70	4.61 ± 0.51	> 0.05
Asthma Score	9.42 ± 1.20	7.26 ± 0.71	< 0.05

Table 5. Pre- and Post-Treatment of Ipratropium 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.[13] Ralston et al compared Levosalbutamol 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.[14] It has shown consistent benefit in bronchodilation in all subgroups. Increasing evidence shows the benefit of anticholinergic agents in moderate-to-severe asthma including recent studies evaluating tiotropium as add-on therapy in uncontrolled asthma along with corticosteroids and beta-2 agonist.[15]

Peters et al showed that the addition of tiotropium to low-dose Salbutamol resulted in significant improvements in morning and evening PEF, and pre-bronchodilator FEV_1. The combination of tiotropium and low-dose Salbutamol was very effective.[16] 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.[17]

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.

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