Research Paper

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# Efficacy of Inhaled Budesonide Along with Oral Montelukast Compared to Inhaled Budesonide Alone in Patients with Mild-to-Moderate Asthma

Medical Science

**KEYWORDS :** inhaled corticosteroids, Monteleukast, bronchial asthma, add on therapy

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## ABSTRACT

*Background: Inhaled corticosteroids (ICS) are widely used either alone or in combination with other classes of drugs for treatment of asthma. Now-a-days leukotriene antagonists (LTRAs) have also emerged as an important drug in asthma management. Objective: To evaluate the efficacy of inhaled Budesonide along with oral Montelukast in comparison to inhaled Budesonide alone in mild-to-moderate asthmatic patients. Study design: Single blind prospective study Main outcomes: Peak expiratory flow (PEF), Forced expiratory volume in 1st second (FEV1), Forced vital capacity (FVC), and Sputum eosinophils. Method: A single blind prospective study carried at tertiary care teaching hospital. 40 patients of bronchial asthma (Group A) meeting the inclusion criteria, received inhaled Budesonide 400 µg bid, 40 other bronchial asthma patients (Group B) received inhaled Budesonide 400 µg bid along with oral Montelukast 10 mg OD daily for 4-weeks. Patient parameters recorded before and after study period were PEF, FEV1, FVC, and sputum eosinophil count. Results: Both groups showed progressive improvement in several measures of asthma control compared with baseline. Mean FEV1, PEF, and FVC improved significantly ($p<0.05$) in the 4 weeks of treatment compared with baseline in both groups. Both groups showed statistically significant reduction in sputum eosinophil count also. Compared with Group 'A', Group 'B' showed significant improvement in FEV1 and significant reduction in sputum eosinophils, but improvement in PEF, FVC. Conclusion: This study shows that inhaled Budesonide along with oral Montelukast is more effective and well tolerated and provides greater improvements in asthma control compared to inhaled Budesonide alone.*

**INTRODUCTION:**

Bronchial asthma is a chronic inflammatory disease associated with airway hyper-responsiveness and episodic wheezing characterized by breathlessness, chest-tightness, and cough, particularly at night or in the early morning. [1] Various cells i.e. eosinophils, T-cells, mast cells, basophils and neutrophils play an important role in pathophysiology of asthma.[2] Cysteinyl leukotrienes (Cys LTs) and other mediators released by these cells also involved in bronchial asthma. [3-5]

According to Global Initiative for Asthma (GINA) guidelines, inhaled corticosteroids (ICS) are the primary drugs for long term treatment of mild-to-moderate asthmatic patient, while leukotriene receptor antagonists (LTRAs) are considered to be a therapeutic option for add on therapy.[6] This regimen is rational due to two main reasons: first, LTs play an important role in triggering airway inflammation, second- the level of LTE4 is not reduced by corticosteroid, when given by any route i.e. inhaled, oral, or intravenous. [7-10] It has been observed that some asthmatic patients often received higher ICS dose than necessary.[11] In asthmatic patients who are not controlled by ICS, there are two option for management-either to increase the dose of ICS or add on second therapeutic agent. By adding a second drugs there is better asthma control compared to increasing the dose of corticosteroid. [12-13] There is additive effect of LTRAs on inflammatory events, when it is added to corticosteroid, [8, 14,] providing the basis for a therapeutic option in asthma management. Montelukast- a potent LTRA, when given daily, improves asthma symptoms in adults [15-16] and children. [17] It has beneficial effects on exercise-induced bronchoconstriction,[18] and in decreasing sputum eosinophil counts also.[19] ICS are effective for early intervention due to their anti-inflammatory properties. They reach the airway directly [20-22] but shows dose dependent adverse effects, when large amount of drug get deposited in upper respiratory tract. [20,23] Therefore it is recommended to combined a second agent with ICS rather than increasing the dose of ICS. [13,24,25]

**METHODS:**

**Study Population/Subjects:**

This study was conducted over a period of six months.

The patients were selected from those visiting Respiratory Medicine OPD for respiratory complaints. Patients selected were those suffering from mild-to-moderate persistent bronchial asthma according to the GINA guidelines (FEV1 between 60 to 80% of the predicted value) with a clinical history of dyspnea, wheezing, chest tightness, or cough for at least 4 months, with reversible airway obstruction (defined as an increase of FEV1 >12% after inhaled salbutamol administration) at the time of the enrollment visit (V1). Patients of either sex (18 year or above ages) who were able to perform clinical assessment and previously not kept on regular corticosteroids and not suffering from any other chronic disease/condition were include in this study. Patient excluded from the study were those having other acute or chronic pulmonary disease, any cardiovascular disease, tremor, seizure or any CNS disorder, history of carcinoma or drug abuse and unwilling patients. Patient suffering from any hormonal or metabolite disorders, diabetes mellitus or sensitivity to Montelukast and those with unstable asthma or who have to change asthma therapy were also excluded.

The study was approved by the institutional ethical review committee.

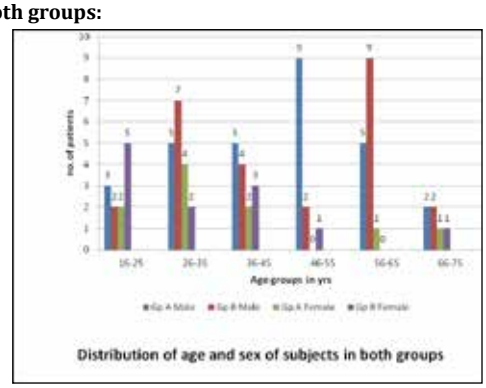
**Study design:**

This single blind prospective study was conducted in a group of 80 asthmatic patients meeting the inclusion criteria, out of which 40 patients (Group A) continued to use inhaled Budesonide (BUD) 400µg twice daily for 4-weeks, while remaining 40 patients (Group B) received inhaled BUD 400µg twice daily along with oral Montelukast 10 mg daily for 4-weeks. During the enrollment visit (V1); all patients underwent a complete clinical examination, spirometry including reversibility testing. Written informed consent was obtained from patients participating in this study. After treatment visit (V2), assessment included clinical examination of the respiratory system, spirometry, evaluation of treatment compliance, adverse drug's reactions if any, and general objective examination. At least three spirometry maneuvers were performed and best reading were recorded & compared with pre-treatment values. Sputum eosinophil count was also monitored and compared with their pre-treatment value. Both group patients were asked about the need for rescue medication (i.e. inhaled salbutamol as and when needed) & nocturnal symptoms if any, during study period.

Statistical analyses: Statistical analyses were performed by the SPSS program, version 10.05 (SPSS, Inc., Chicago, IL, USA). Data were expressed as mean ± SD. Values of $p < 0.05$ were considered statistically significant. Primary end points were the mean values of FEV1 and PEF (expressed as % of the predicted value) measured during the visits (V1 to V2). Secondary end-points were the use of salbutamol, and the drug tolerability profiles.

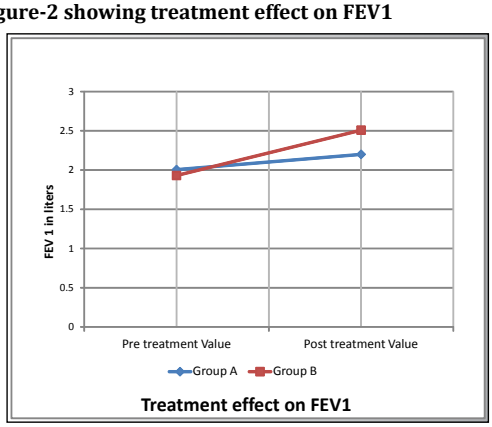
**Results:**
The both treatment groups were comparable in mean age (Group A, 44.425 ± 15.63836 yr; Group B, 44.5±17.39584 yr). Subjects in both groups comprise of 80 cases out of which 58 patients (72.5%) were male and 22 patients (27.5%) female. In Group 'A', the male to female ratio was: 3:1 and in Group 'B' it was 7:3 (Table-1).

**Figure-1: Showing distribution of age and sex of subjects in both groups:**



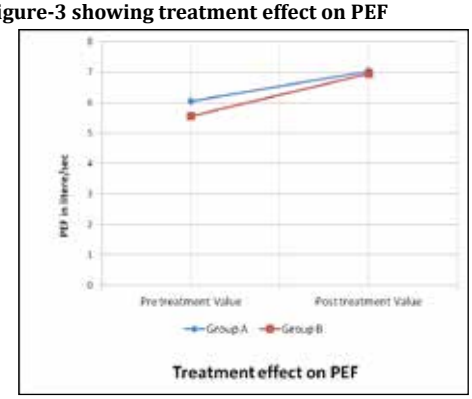

Mean value of FEV1 in-Group A, before treatment was 2.007 (L) ± 0.379 (L) (mean ± SD) and after four weeks of therapy it was 2.200±0.433, its mean of difference was 0.193±0.509 with a 'p' value of less than 0.05, which means that in Group A in which therapy was started with alone inhaled Budesonide, there was significant improvement in FEV1. It was also observed that in Group B, mean value of FEV1 before treatment was 1.930 (L) ±0.370 (L) (mean ± SD) and after therapy it was 2.508 (L) ± 0.451 (L), with mean of difference 0.577±0.557. Its 'p' value was less than 0.05, showing that in group B, where therapy was started with inhaled Budesonide plus oral Montelukast there was also significant improvement in FEV1. In comparison of their pre-treatment value, 'p' value was more than 0.05 showing insignificant difference between both groups before treatment while after therapy 'p' value was < 0.05 that means there was significant and greater improvement or response in Group 'B' compared to group 'A' (Table-2).

**Figure-2 showing treatment effect on FEV1**



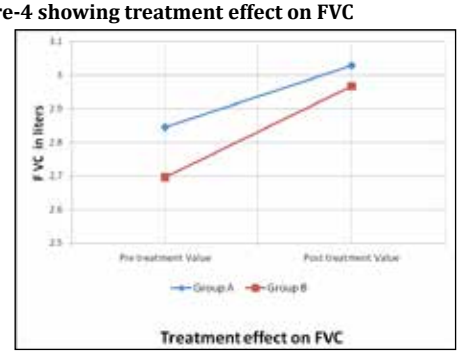

Baseline PEF value was 6.053 (L/s) ± 1.923 (L/s) in Group 'A' and after therapy it was 7.030 (L/s) ± 1.062 (L/s) with mean of difference 0.977 ± 1.626 (L/s) (p value <0.05). Therefore, it was observed that after inhaled Budesonide therapy there was significant improvement in PEF (L/s) among asthmatic patients of Group 'A'. In Group 'B', the base line PEF value was 5.560 (L/s) ± 1.742(L/s) before treatment that improved to 6.955(L/s) ± 1.244 (L/s) after treatment with mean of difference 1.394 (L/s) ± 0.245(L/s) (p value < 0.05), showing significant treatment benefit. There was significant improvement in PEF values individually in both the groups, however, there was greater change in PEF from baseline in Group B compared to Group A, but it was statistically insignificant (p value > 0.05) (Table-3).

**Figure-3 showing treatment effect on PEF**



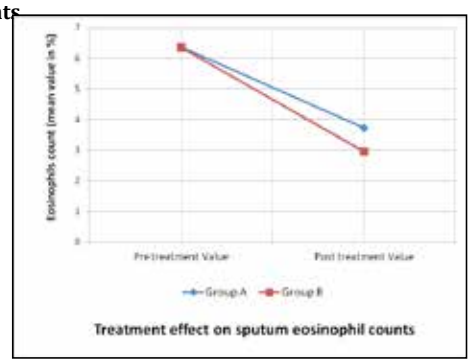

Before treatment, the mean value of FVC was 2.844(L) ± 0.635(L) and 2.696(L) ± 0.513(L) in Group 'A' and Group 'B' respectively and after treatment changed to 3.029(L) ± 0.562(L) and 2.968(L) ± 0.606 (L) in Group 'A' and Group 'B' respectively. Their mean of difference was 0.184(L) ± 0.409(L) in group 'A' and 0.272 (L) ± 0.548 (L) in group 'B'. The improvement in FVC after therapy in both groups was statistically significant (p value < 0.05). Although there was greater improvement in FVC among group 'B' than group 'A' but it was again statistically insignificant (p value > 0.05) (Table-4).

**Figure-4 showing treatment effect on FVC**




The mean value of sputum eosinophil was 6.38(%) ± 0.481(%) & 6.365(%) ± 0.458(%) at the beginning of therapy in Groups A & B respectively. After therapy, it was found 3.72(%) ± 0.498(%) & 2.967(%) ± 0.393(%) in both groups respectively with mean of difference in Group A 2.66(%) ± 0.283(%) and in Group B 3.397(%) ± 0.041(%). Negative sign in mean of difference indicates that there was reduction in sputum eosinophil. In both groups, there was significant reduction in sputum eosinophil count (p value <0.05) but the reduction in sputum eosinophil count was more in Group 'B' than Group 'A' and it was statistically significant (p value <0.05) showing that addition of Montelukast to BUD results in greater reduction in sputum eosinophil count (Table-5).

**Figure-5 showing treatment effect on sputum eosinophil counts**




Clinically observed adverse effects that were reported during study are illustrated in table-6. In both groups there was no sta-

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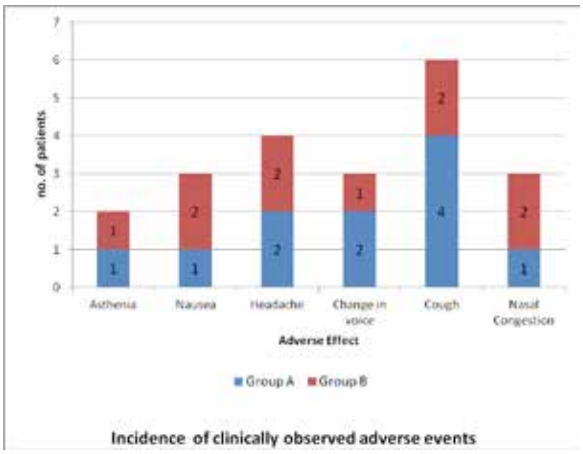
tistically significant difference observed in adverse effects. (p value > 0.05)

**Figure-6 showing the incidence of clinically observed adverse events**




Incidence of clinically observed adverse events

Three patients (7.5%) of Group A needed rescue medication for control of asthma symptoms and 4 (10%) also complained nocturnal awakening due to cough despite regular inhaled BUD therapy. None of the patients of Group B complained nocturnal symptoms or need for rescue medication.

**DISCUSSION:**

There are two options for management of persistent asthma symptoms not controlled by low dose ICS - either by increasing the dose of ICS or by adding second therapeutic agents with ICS. It has been observed that a number of potential side effects occurred with increasing the dose of ICS. [26, 27] and it may not be necessary that all patients show more effective control of asthma in higher dose of ICS.[13,28,29] Therefore international guidelines recommended using ICS in minimum dose whenever possible.[30] Second therapeutic agent with a complementary mechanism of action may be appropriate for adding with ICS. Such therapeutic agents include (a) long acting beta agonist (LABA), (b) sustained released theophylline and (c) LTRAs. It has been observed in clinical studies that, when second therapeutic agents i.e. LABA[12-13,31] or theophylline[32,33] are added with ICS, there is better control of asthma symptoms compared to doubling or increasing the dose of ICS. Therefore addition of another agent may be preferred for better control of asthma symptoms. [12,13]

Theophylline has a narrow therapeutic index, has modest clinical benefit and associated with more drug interaction and serious side effects, [34] so it is no longer commonly used as first line therapy with ICS. Therefore two agents i.e. LABA & LTRAs are left for adding with ICS. In some studies, it has also been observed that Montelukast plus ICS group provide significantly greater effect than Salmeterol plus ICS group, when compared in exercise induced bronchoconstriction for their bronchoprotective effect. [35,36]

Significant effects were found in PEF variation, night-time symptoms score and bronchodialator consumptoms, when Montelukast sodium 10 mg once daily added to 800 µg Budesonide in one study. [37]

Our study indicates the additive effects of Montelukast to inhaled BUD in mild-to-moderate persistent asthma patients, with significant improvement in FEV1 value compared to those patients treated with inhaled BUD alone ($p < 0.05$). Similar results were found by other studies also. [27,28]

In present study, none of the patients of Group 'B' complained of nocturnal symptoms or need for rescue medication, while such complains were reported in few patients of Group 'A', showing that addition of Montelukast to inhaled BUD provides comparatively better control in asthma symptoms with minimal clinical adverse effects and with better tolerance.

Results of our study suggest that inhaled Budesonide along with oral Montelukast therapy is comparatively more effective, well tolerated and provides greater improvements in asthma control compared to inhaled Budesonide alone in patients with mild-to-moderate persistent bronchial asthma.

## REFERENCE

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