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### EFFICACY OF ORAL MONTELUKAST AND INHALED BUDESONIDE AS FIRST LINE PREVENTIVE THERAPY IN MILD PERSISTENT ASTHMA IN CHILDREN: A COMPARATIVE STUDY AT A TERTIARY CARE CENTRE IN NORTH WESTERN PART OF INDIA

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#### ABSTRACT

Background- Bronchial asthma is a chronic inflammatory airway disease and is more prevalent in children. Inhaled corticosteroids (Budesonide) and leukotriene receptor antagonist (Montelukast) are the drugs of choice for asthma in children. The present study was aimed to compare the efficacy of oral montelukast and inhaled budesonide as first line preventive therapy in mild persistent asthma in children at tertiary care hospital in north western part of Rajasthan, India. Materials and methods- It was a hospital based prospective randomized open label comparative clinical study. The duration of study was 6 months. Total 70 patients of 6 to 14 years age group included in the study. Patients were randomized into two groups of 35 each and accordingly medications were given. Group A patients were given Montelukast 5mg/day for 1 Month and Group B patients were given metered dose inhaler (MDI) Budesonide 100µg 1 puff BD for 1 month. Data collected were entered in a specially designed proforma. To evaluate the efficacy of the drug ISAAC questionnaire, Asthma control test and Pulmonary function test was done of each patient at the first visit and every follow up. Results and conclusion- Montelukast oral as well as Budesonide inhalational both drug were effective as first line preventive therapy in mild persistent asthma in 6 to 14 years of age children. Both drugs show significant effect with individual groups. When we compared effect of both drugs to each other between two groups, Budesonide was found significantly more effective than Montelukast as first line preventive therapy in mild persistent asthma in 6 to 14 years of age children in our study.

**Keywords:** Asthma, Montelukast, Budesonide.

#### INTRODUCTION

Asthma is a chronic, reversible, inflammatory disease of the airways; whose incidence is increasing worldwide [1]. Asthma is the most common chronic illness of childhood, affecting approximately 10% of children. Worldwide, the prevalence of childhood asthma and hospitalizations for it are increasing [2]. Asthma affects approximately 7 million children in United States,

accounting for 9.4% of the paediatric population. Incidence of asthma in India is also increasing [3]. It reduces the quality of life for children as it leads to growth retardation, inability to exercise and nocturnal bouts of wheezing resulting in loss of sleep that may also impair daytime concentration at school [4]. So management of asthma is largely directed towards symptoms relief and improving quality of life.

Quality of life has been found to be impaired both in patients with asthma and in patients with allergic rhinitis, but the relative burden of these diseases has not been investigated [5]. Asthma is defined by the history of recurrent respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation [6]. The basic pathophysiology of asthma consists of chronic inflammation of airways. Cysteinyl leukotrienes are inflammatory bioactive lipids produced by various cells [7]. Leukotrienes are important mediators of asthma leukotrienes are produced and released from inflammatory cells, including eosinophils and mast cells. They cause bronchoconstriction, mucous secretion and increased vascular permeability [8]. The 2002 National Asthma Education and Prevention Program (NAEPP) guidelines recommend the use of long term inhaled corticosteroids (ICSs) as the preferred treatment for persistent asthma in children of all ages, because very young children may lack the coordination or the ability to use dry powder inhalers or metered dose inhalers correctly, nebulized delivery of Inhaled corticosteroids may facilitate treatment adherence. Budesonide inhalation suspension is the first and only nebulized Inhaled corticosteroid approved in the United States for the management of asthma in children 1 to 8 years of age [9].

Montelukast (MON), a leukotriene antagonist, is an alternative treatment option to inhaled corticosteroid. Montelukast works by blocking cysteinyl leukotrienes, a class of pro inflammatory mediators, which decrease eosinophil migration, broncho- constriction & mucous hypersecretion [10]. Inhaled corticosteroids (ICS) are regarded as the corner stone of effective anti-inflammatory therapy for the treatment of asthma. Regular long term inhaled corticosteroid therapy significantly reduces asthma mortality, asthma exacerbation, airway inflammation, and asthma symptoms, and significantly improves lung functions in subjects with asthma [11].

The use of leukotriene receptor antagonists is an alternative to inhaled corticosteroid therapy for the treatment of mild to moderate persistent asthma in children [12].

Montelukast is a safe drug with modest benefits in bronchial asthma. It is useful in mild persistent asthma where ICS administration may-be impractical due to compliance issues, and also in patients with co morbidities like allergic rhinitis. It is also found to decrease the episodes of viral-induced wheeze in young children [13]. In this study, we tried to compare the clinical efficacy of oral montelukast with Inhaled budesonide considering symptom control as main outcome [14].

## MATERIAL AND METHODS

The study was conducted at Sardar Patel Medical College, Bikaner. It was a hospital based prospective

randomized open label comparative clinical study. The duration of study was 6 months. Total 70 patients of 6 to 14 years age group included in the study. Patients with symptoms suggestive of recurrent airflow obstruction like recurrent wheeze, recurrent isolated cough, recurrent breathlessness, nocturnal cough, tightness of chest and patients having more than 3 episodes of airflow obstruction were included in this study. Patients with age >14 year, non cooperative patients, and those patients with age <6 years, recurrent respiratory tract infections, and chronic respiratory disease (eg. Cystic fibrosis, tuberculosis). congenital anomalies of respiratory tract (eg. Laryngomalacia), congenital heart disease, mentally retarded or unconscious patients and patients who were on other anti asthmatic agents were excluded from study. Permission from the institutional ethical committee was taken for this study. Children recently diagnosed with mild persistent asthma that attended paediatric department in PBM Hospital & associated group of Hospital Bikaner, Rajasthan were taken for this study. Patients were randomized by using computer generated random number sequence into two groups of 35 each and accordingly medications were given.

Group A: patients were given Montelukast 5mg/day for 1 Month

Group B: patients were given metered dose inhaler (MDI) Budesonide 100µg 1 puff BD for 1 month.

A written/informed consent was taken from all patients before subjecting them for study. Data collected were entered in a specially designed proforma. ISAAC questionnaire was used to take patients history in which eight questions were asked to the patient [15]. Asthma control test was done to evaluate efficacy of the drug budesonide and montelukast. This questionnaire had five questions [16]. Pulmonary function test was done by the physician at the time of every follow up [17]. Full information concerning the name, dosage and duration of other concomitant therapy was recorded in Proforma. On the day of enrolment, general examination and base line investigation like complete blood count with absolute eosinophilic count, chest X-Ray, pulmonary function test (whenever feasible mostly 6 years of age) were done by the physician. The follow-up for this was taken in every 15 days. Total three follow-up was done during this study. Patients were advised to keep diary in which columns are made including cough, wheeze, breathlessness, limitations of daily activities, sleep disturbance, emergency department visit, hospitalization for acute exacerbation and the treatment received for the exacerbations (number of oral steroid doses/course, number of days nebulisation required). Daily records of these days were maintained by parents in diary and analyze monthly on their visit. Data analysis was done by primer and Microsoft excel with the help of tables and figures.

## RESULTS

Total 70 patients were recruited in this study. Patients were divided in two groups of 35 each. Group A was given oral montelukast and group B was given inhaled budesonide. In Group A 15 cases were from age group 11-14 years followed by 11 cases from age group 9-11 years. In Group B age group 9-11 years and 11-14 years both included 13 patients followed by 9 cases from 6-8 years age group. In Group A, 19(54.29%) cases were male and 16(45.71%) cases were female. Group B, 9 (25.71%) cases were male and 26(74.29%) cases were female.

Table1: Shows Comparison of effect of montelukast in Group A at base line and final visit on basis of ISAAC questionnaire the mean at base line was 7.14 and mean value at final visit was 2.37. Paired t-test value was 29.966 and P-value was 0.0001. When we compared the effect of drug at base line and at final visit we found statistically significant difference.

Table2: Shows Comparison of effect of Budesonide in Group B at base line and on final visit on basis of ISAAC questionnaire. Where 7.20 mean at base line and 2.03 mean at final visit. Where paired t-test value was 33.144 and P-value was 0.0001. When we compared the effect of drug at base line and final visit we found statistically significant difference.

Table3:Shows the comparison of effect in both group –A and Group B having 35 Cases each, where Z-test value was 2.107 and p-value was 0.039 in both group A and group B after applying Z-test at final visit so at last visit we found statistically significant difference. Group B drug is significantly effective.

Table4: Shows Comparison of effect of group A and group B patients according to Asthma control test (ACT). As shown in table numbers of well controlled patients were 19 in group A and 21 in group B. The numbers of completely controlled patients were 5 in group A and 6 in group B where P value was 1.000 after applying  $\chi^2$  test statistically insignificant.

Table5: Shows Efficacy of Montelukast among Group A on basis of Pulmonary function test. In group A 1.19 was mean of FEV1 at baseline and 1.47 was mean of FEV1, at final visit where P-value was 0.0001 after applying t-test statistically significant within the group. 1.29 was mean of FVC at baseline and 1.62 was mean of FVC at final visit where P-value was also 0.0001 after applying t-test statistically significant within the group.

Table6: Shows efficacy of Budesonide among Group B on basis of pulmonary function test (PFT). In Group B 1.21 was mean of FEV1 at baseline and 1.70 was mean of FEV1, at final visit where P-value was 0.0001 after applying t-test statistically significant within the group. 1.35 was mean of FVC at baseline and 1.85 was mean of FVC at final visit where P-value was also 0.0001 after applying t-test statistically significant within the group.

Table7: Shows Efficacy in between group A (Montelukast) and Group B (Budesonide) on basis of Pulmonary function

test (PFT). As shown in above table 1.19 was mean of FEV1 in Group A and 1.21 was mean of FEV1 in Group B at baseline where P-value 0.603 was statistically not significant. At final visit 1.47 was mean of FEV1 in group A and 1.70 was mean of FEV1 in Group B. Where P-value 0.0001 was statistically significant in comparison of both Group A and Group B. 1.29 was mean of FVC in Group A and 1.35 was mean of FVC in Group B at baseline where P-value 0.110 was statistically not significant. At final visit 1.62 was mean of FVC in group A and 1.85 mean of FVC in Group B where P-value 0.0001 was statistically significant in comparison of both Group A and Group B.

## DISCUSSION

The present prospective randomized open label comparative clinical study was done with an aim of comparing Montelukast to Budesonide as a first line preventive therapy in mild persistent asthma in patient with 6 to 14 years of age. The study was conducted in Paediatric Department at PBM and Associated Group of Hospital S.P. Medical College, Bikaner, after obtaining permission from institutional ethical committee. Children recently diagnosed with mild persistent asthma that attended paediatric department during the course of study were evaluated.

In the present study we found that maximum number of cases were above 11 year of age in both group A and group B. Similar results were observed in Peat et al [18] study that there was a larger proportion of continuing asthmatics among boys than girls after the age of 12 years.

A study conducted by Ranbir et al [19] in Sikkim concluded that boys (male sex) had a significantly higher prevalence of asthma as compared to girls (female sex) 12.8% and 10.7% respectively. In the present study found that both male and female have equal prevalence of asthma. In similar study conducted by Monil Bharat shah et al [20] observed that out of the study groups comprising of 30 patients each, male to female ratio was 23/7 and 19/11 respectively adding to the increased risk of asthma in male gender.

In present study on the basis of ISAAC questionnaire we found that the mean value of group A (Montelukast) was 7.14 at baseline and 2.37 at 3<sup>rd</sup> follow up In Group B (Budesonide) the mean value at baseline was 7.20 and 2.03 at 3<sup>rd</sup> follow-up it shows the improvement in symptoms in asthmatic patients.

In our study we compared the effect of the drug Montelukast within the same group A. So when we compared the effect of the drug at base line and at the end of the time of 3<sup>rd</sup> follow-up we found statistically significant difference which shows significant improvement in the effect of drug. In similar study Knorr et al [21] demonstrated that Montelukast once daily is effective therapy in 6-to14 year old patients with asthma. Montelukast was well tolerated and demonstrated a safety

profile generally similar to placebo. The results of this study suggest that Montelukast would be a well-tolerated and effective therapeutic option to current asthma therapies in 6 to 14 year old patients.

In present study, we also compared the effect of the drug B (Budesonide) within the same group. We found statistically significant improvement in the effect of drug at baseline and the time of last visit. In similar study Szeffler et al [22] observed that inhaled corticosteroids such as Budesonide are the most effective single-agent controller medication for preschool and school- age children with mild persistent asthma, even of mild persistent severity.

In our study it was observed that in Group A (Montelukast) and Group B(Budesonide) , the number of well controlled and completely controlled patients were increased at the end of the study. It shows significant

improvement in asthmatic patients on basis of asthma control test. According to Ring et al [23] it was observed that ACT might help the patients to achieve better asthma control by informing them of the ideal asthma control and allowing them to make personal asthma action plans and to self monitor their asthma control conditions.

On comparing the change in FEV1 and FVC from baseline to end of the study within the same group there was improvement in both groups.

In similar study Kumar et al. observed that the mean FEV1 in group A was 1.4 and in group B 1.31) which persisted at second follow up visit at 2 months. However, there was no statistical difference in FEV1 from base line to the end of the study in either group.

**Table 1: Comparison of effect of Montelukast in Group A at base line and final visit on basis of ISAAC questionnaire.**

Visit	Group A (n-35) Mean $\pm$ SD	t-value	P -Value
Baseline	7.14 $\pm$ 0.55	29.966	0.0001
Final Visit	2.37 $\pm$ 0.69		

**Table 2 : Comparison of effect of Budesonide in Group B at base line and on final visit on basis of ISAAC questionnaire.**

Visit	Group B (n-35) Mean $\pm$ SD	t-value	P -Value
Baseline	7.20 $\pm$ 0.72	33.144	0.0001
Final Visit	2.03 $\pm$ 0.66		

**Table 3: Comparison of efficacy between Group A (Montelukast) and Group B (Budesonide) on basis of ISAAC questionnaire.**

Follow Up	Group A (n-35) Mean $\pm$ SD	Group B (n-35) Mean $\pm$ SD	t-value	P –Value
Baseline	7.14 $\pm$ 0.55	7.20 $\pm$ 0.72	0.392	>0.05
3 <sup>rd</sup> follow up(45 Days)	2.37 $\pm$ 0.69	2.03 $\pm$ 0.66	2.107	0.0001

**Table 4: Comparison between Group A (Montelukast) and Group B (Budesonide) on basis of Asthma control test (ACT).**

Asthma control test (ACT)	Group – A (N = 35)	Group – B (N=35)	Total
Not controlled	0	0	0
Poorly controlled	2	1	3
Somewhat controlled	9	7	16
Well controlled	19	21	40
Completely controlled	5	6	11
df	4		
X <sup>2</sup> value	0.774		
P value	1.000		

**Table 5: Efficacy of Montelukast among Group A on basis of Pulmonary function test.**

Parameters	Group – A (n = 35)		t-value	P-value
	Baseline	Final visit		
FEV1	1.19 ± 0.17	1.47 ± 0.15	7.307	0.0001
FVC	1.29 ± 0.15	1.62 ± 0.15	9.203	0.0001

**Table 6: Efficacy of Budesonide among Group B on basis of Pulmonary function test.**

Parameters	Group – B (n = 35)		t-value	P-value
	Baseline	Final visit		
FEV1	1.21 ± 0.15	1.70 ± 0.11	15.584	0.0001
FVC	1.35 ± 0.16	1.85 ± 0.11	15.235	0.0001

**Table 7: Comparison of efficacy between group A (Montelukast) and Group B (Budesonide) on basis of Pulmonary function test.**

Parameters		Group-A	Group B	t-value	P-value
FEV1	Baseline	1.19 ± 0.17	1.21 ± 0.15	0.522	0.603
	Final Visit	1.47 ± 0.15	1.70 ± 0.11	7.315	0.0001
FVC	Baseline	1.29 ± 0.15	1.35 ± 0.16	1.619	0.110
	Final Visit	1.62 ± 0.15	1.85 ± 0.11	7.315	0.0001

## CONCLUSION

Maximum number of cases was from age group of >11 years in both group A (15) and group B (13). After treatment with Montelukast in group A, we observed statistically significant improvement in asthmatic patients in the effect of Montelukast within the same group. In group B it was observed that the effect of Budesonide within the same group B statistically significant, which shows improvement in asthmatic patients. When we compared the effect of Montelukast (oral) and Budesonide (inhaled) to each other we found drug B (Budesonide) was significantly effective. We also found that in the study Montelukast in group A (p-value 0.143) shows insignificant change in effect in relation to pre visit to post visit of the patients. It was observed that in group B Budesonide also

shows significant change in effect in relation to pre visit and post visit of the patients. The groups were comparable in the baseline spirometric parameters FEV<sub>1</sub> and FVC. We observed that FEV1 and FVC were statistically significant at the end of the study. So in this 6 months long study we concluded that Montelukast oral as well as Budesonide inhalational both drug were effective as first line preventive therapy in mild persistent asthma in 6 to 14 years of age children. Both drugs show significant effect with individual groups. When we compared effect of both drugs to each other between two groups, Budesonide was found significantly more effective than Montelukast as first line preventive therapy in mild persistent asthma in 6 to 14 years of age children in our study.

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