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To Study the Efficacy of Inhaled Budesonide Vs Oral Montelukast in Control of Mild Persistant Asthma in Children between 5-18 Years of Age

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Abstract: ***Asthma guidelines in children recommend the use of inhaled budesonide and montelukast to control asthma symptoms and reduce inflammation in patients with mild persistent asthma. This study was undertaken to compare the efficacy of both. Children with mild persistent asthma, aged 5 to 18 years, were included. A prospective, controlled study design was used. Patients received either inhaled budesonide [GROUP A] or oral montelukast [GROUP B] for 90 days. Parameters included improvement in the number of asthma attacks, percentage improvement in the absolute eosinophil count, percentage predicted of normal force expiratory volume in 1 second and percentage improvement in the Peak Expiratory Flow Rate after treatment.Significant improvement in the frequency of asthma attacks, % improvement in the AEC, FEV1%, % improvement in the PEFR in both, group A and B were seen. More significant improvement in asthma attacks (p = 0.05) and FEV1% (p = 0.002), was seen in group A whereas Oral montelukast was better in terms of % improvement in the AEC (p = 0.002). Inhaled Budesonide is superior to oral Montelukast in treatment of mild persistent asthma in 5 to 18 years children in terms of improvement in terms of studied parameters over 12 weeks period.***

Keywords: Inhaled budesonide; mild persistant asthma; oral montelukast

1. Introduction

Bronchial Asthma is a chronic inflammatory disease characterized by airway hyper-responsiveness and respiratory symptoms (breathlessness, wheezing, chest tightness and coughing) [1, 2] and the involvement of numerous cell types in triggering airway inflammation[3].

A clinico-physiological definition is more appropriate for routine diagnosis and management of this disorder. For practical purposes Asthma may be described as disorders of the airways characterized by:

1) Paroxysmal and/or persistent symptoms such as dyspnoea, chest tightness, wheezing and cough with or without mucous production.
2) Variable airway limitation demonstrated by chest auscultation and/or repeated measurement of peak expiratory flow (PEF) volume or other spirometric indices.
3) Airway hyper-responsiveness to a variety of specific and non specific inhalational stimuli[4].

Mild persistent asthma is defined as the asthmatic attacks occurring <1/day >1/week or more than 2/month with FEV1 or PEF>80% of predicted value and PEF variability 20-30%.[5]

Asthma is a leading cause of both acute and chronic illness in children and accounts for almost one third of all chronic conditions occurring annually in children. It is responsible for nearly one fourth of days lost from school because of chronic illness.[4]

In India according to ICMR (Indian council of medical research), the incidence of Asthma is approximately 2.4% with low prevalence in Secundrabad (0.37%) and rural Mumbai(0.74%) and high prevalence in Kolkata (rural 4.52% and urban 5.52%) and Trivandrum(4.45%) in adults above 15yrs in 2010.[4]

Budesonide inhalation suspension and the leukotriene receptor antagonist i.e. montelukast have demonstrated efficacy in treating children with mild persistent Asthma and are both recognized as first-line treatment, but comparative study is needed to determine the efficacy and selection of the treatment of choice in children suffering from mild persistent asthma for which this study has been conducted.

2. Methodology

This study was conducted in the Out-Patient department of Pediatrics, Subharti Medical College, Meerut. The study was conducted between October 2014 to February 2016. A prospective, controlled study design was used.

Subjects

Patients with Asthmatic attacks less than once a day, but more than once a week or more than twice a month with FEV1 % predicted of normal, 80% above of personal best were included in the study.

Patients with a history of chronic pulmonary disease other than Asthma, patients treated in an emergency department within 1 month, hospitalized for Asthma within 3 months, or having unresolved symptoms and signs of upper respiratory tract infection within 3 weeks and also the patients with history of taking the following medications i.e. oral, inhaled or parenteral corticosteroids within one month and inhaled long-acting β2-agonist were excluded from the study.

A total of 60 patients aged 5–18 years, diagnosed as mild persistent Asthma, completed the 12 week run in period. They were divided randomly into 2 groups on the basis of their serial number into Odd and Even group. 30 patients who received inhaled Budesonide were classified as group A and 30 patients who received Montelukast were classified as group B and were analyzed for the study.

Methods

A detailed history was taken along with the number of attacks per month were noted and a thorough physical examination was done. These children were further subjected to pulmonary function test (to determine the FEV1% predicted of normal). Those falling in the category of mild persistent Asthma on the basis of the history, clinical examination and pulmonary function test, were enrolled in the study.

Group A patients were given inhaled BUDESONIDE 200µgm once a day by a metered dose inhaler for 3 months, whereas in Group B, oral MONTELUKAST was given in a dose of 5 mg (age 5-14yrs) or 10mg (age>14yrs) once a day, at night for 3 months.

On the day of enrolment, patients were subjected to Absolute eosinophil count and Peak expiratory flow rate was analysed by a peak flow meter. Patients were reviewed after 2 weeks and peak expiratory flow rate was re-examined to assess the improvement. After 1 month of treatment, the patients were reviewed regarding the improvement in the total number of attacks in that month. After 3 months of treatment, the patients were re-evaluated and pulmonary function tests (FEV1 % predicted of normal by spirometry), Absolute eosinophil count and Peak Expiratory Flow Rate were done.

Clinical parameters, Forced Expiratory Volume in 1 second percentage predicted of normal, Peak Expiratory Flow Rate and Absolute eosinophil counts were compared after completion of 3 months of treatment.

Statistical Analysis

The results were expressed as mean and standard deviation, separately for group A and group B. Results were compared using non parametric test i.e. Chi square test and unpaired t-test was used for intergroup comparisons, p-value of ≤ 0.05 was considered as statistical significant. Data was analyzed by appropriate statistical software like SPSS.

3. Results

Children of age group 5 – 18 years of age were included in our study. The mean age of the children in our study was 12.7 ± 3.51 years in group A and 14.07 ± 3.36 years in group B.

The gender wise distribution showed slight male preponderance in this study as there were a total of 56.7% males overall and with male: female ratio of 1.3:1. There were 60% males, with a male: female ratio of 1.5:1 in group A and there were 53.3% males in group B, with a male: female ratio of 1.1:1.

This was probably due to the stunted female: male ratio in the general population and more over the subjects in our study belonged to the lower socio economic status who usually gives greater importance to the male child.

4. Asthma Attack Frequency

In our study we found that both Montelukast and Budesonide were effective in reducing the number of Asthma exacerbations occurring per month over the 12 weeks period of the study. The percentage improvement in Asthma attack frequency per month at the end of 12 weeks treatment was 91.45 ± 11.85 in the Budesonide group and 84.28 ± 15.9 in the Montelukast group.

The difference in the percentage improvement of Asthma attacks was statistically insignificant when the two groups were compared on the basis of improvement at the end of 1 month time but statistically significant results were obtained between them favoring inhaled Budesonide at the end of 3 months of treatment.

Table 1: % Improvement in Attacks between Groups A & B

% Improvement Asthma Attack Frequency	*Group A*		*Group B*		*P-Value*
	Mean	*SD*	*Mean*	*SD*	
Day 1 – 1 Month	52.45	14.06	48.78	12.37	0.29
1 Month – 3 Month	85.01	20.69	72.78	25.71	0.05
Day 1 – 3 Month	91.45	11.85	84.28	15.90	0.05

SD – standard deviation

Absulute Eosinophil Count

The absolute eosinophil counts in our study were reduced significantly after 12 weeks of treatment in both, the Budesonide group as well as the Montelukast group (p value<0.001). The net improvement in the AEC values were 14.54 ± 4.85 and 17.94 ± 3.28 in group A and group B respectively and the difference was statistically significant favouring the Montelukast group (p value<0.002).

Table 2: NET AEC Improvement after 3 Months of Treatment Among Groups

Variables	*Group A*		*Group B*		*P-Value*
	Mean	*SD*	*Mean*	*SD*	
AEC	14.54	4.85	17.94	3.28	<0.002

SD – standard deviation

FEV1 % Predicted of Normal

The net improvement in the FEV1 % predicted of normal values were 14.73 ± 2.18 and 13.14 ± 1.60 in group A and group B respectively and the results were statistically significant from the base line. A statistically significant difference was also seen when both the groups were compared to each other, favoring the Budesonide group (pvalue<0.002).

Table 3: Comparison of FEV1 % Predicted of Normal Improvement after 3 Months of Treatment

Variables	*Group A*		*Group B*		*P-Value*
	Mean	*SD*	*Mean*	*SD*	
FEV1	14.73	2.18	13.14	1.60	0.002

SD – standard deviation

Peak Expiratory Flow Rate

PEFR was significantly improved in both the groups i.e. Montelukast and Budesonide groups, from the baseline day1. The percentage improvement from baseline PEFR on day1 was significant in both groups when compared to the PEFR values on day14 and day 90.

The net % improvement in the PEFR values was 30.86 ± 6.78 between day 1 and day 90 in group A, whereas it was 29.62 ± 9.48 in group B.

Though the improvement in both the group was significant standing alone, the difference between the Montelukast and the Budesonide group was statistically insignificant on comparison.

Table 4: Inter Group Comparison of PEFR Improvement %

Pefr	*Group A*		*Group B*		*P-Value*
	MEAN	*SD*	*MEAN*	*SD*	
1day - 14 Day	10.42	3.90	9.50	3.33	0.330
14 Day – Day 90	18.49	4.48	18.31	7.18	0.909
1day – Day 90	30.86	6.78	29.62	9.48	0.563

SD – standard deviation

5. Discussion

Mild persistent Asthma is defined as the Asthmatic attack occurring in children >2/week, but <1/day and >2/month with FEV1 or PEF>80% of predicted and PEF variability 20-30%.[5]

Recommendations for Treating Mild Persistent Asthma

According to the Established Guideline of Daily Controller Medication i.e. national asthma education and prevention program (NAEPP)[6], Global initiative of asthma (GINA)[7] and the British thoracic society[8], recommends the use of low-dose inhaled corticosteroids in all children and alternatives drugs that can be used are sustained released theophylline, cromolyn and LTRAs.

In our study we found that both Montelukast and Budesonide were effective in reducing the number of Asthma exacerbations occurring per month over the 12 weeks period of the study. The percentage improvement in Asthma attack frequency at the end of 12 weeks treatment was 91.45 ± 11.85 with Budesonide and 84.28 ± 15.9 with Montelukast. Though the difference in the percentage improvement of Asthma attacks was not statistically significant (p value=0.29), when the two groups were compared on the basis of reduction at the end of 1 month time, statistically significant results were obtained between them (pvalue=0.05) favoring inhaled Budesonide at the end of 12 weeks of treatment. Thus we concluded that Inhaled Budesonide was more efficacious than Montelukast in terms of Asthma free days and reduction in the Asthma exacerbations per month and was also better in reducing the night time symptoms.

These results were similar to the study conducted by Szefler SJ et al (2007)[9] in which the rate of acute severe exacerbations requiring treatment with oral corticosteroids was lower in the Budesonide group compared with the Montelukast group (0.52 vs 0.67, respectively; P value 0.149), with an estimated reduction in the number of courses of additional oral corticosteroid therapy of 22.7% in the BIS group compared with the Montelukast group.

Ostrom et al (2005)[10] compared Montelukast with Fluticasone Propionate and found significantly increased percentage rescue-free days (P=.002), and there was significant reduced night time symptom scores (P <.001) and mean total (P=.018), and night time (P <.001) albuterol use in the FP groups and thus it was concluded that FP was more efficacious than MLK.

Our results were similar to the study done by Shah MB et al[11] that showed significant improvements in PEFR, FEV1/FVC, day time and night time symptoms and frequency of exacerbations in both groups. However, more significant improvement in FEV1/FVC (p = 0.029) and day time symptoms (p = 0.002) was seen in Budesonide group compared to Montelukast group. Garcia Garcia et al[12] also concluded significantly better results with ICS compared to oral montelukast on several secondary measures including PEF variability %, FEV1 or PEF % predicted.

In the study done by NG DKK et al[13], Budesonide provided significantly greater improvement in FEV-1 compared to montelukast after 4 weeks and 6 weeks of treatment (p0.03 and p0.02 respectively). Montelukast group had more asthma exacerbation than the budesonide group (p=0.04). Budesonide achieved faster improvement of FEV-1 and less asthma exacerbation than montelukast and was similar to our study.

Statistically significant results between the Montelukast and inhaled corticosteroid group were also seen in Carlsson LG et al[14] who showed statistically significant differences in favour of Budesonide over Montelukast in the percentage of patients requiring oral steroids over 52 weeks (21.9% vs 37.1%; P = .022), the rate of additional courses of medication (1.35 vs 2.30; P = .003), the rate of additional oral steroid therapy (0.44 vs 0.88; P = .008).

Similarly, Jean Bousquet et al (2005)[15] showed that patients taking Fluticasone had 6.44% (95% confidence interval [CI] 2.24, 10.64) more Asthma-free days than patients taking Montelukast (<2 days/month/patient) and thus found ICS superior to MLK.

Thus, in our study there was significant improvement in PEFR, FEV1 % predicted of normal, day time and night time symptoms and frequency of Asthma exacerbations in both groups. However, more significant improvement in FEV1% predicted of normal (pvalue<0.002) and % improvement in the number of attacks per month were seen in Budesonide group compared to Montelukast group.

In contrast to our study, similar improvement between the Montelukast and the Inhaled steroid group were seen in Kooi EM et al (2008)[16] which revealed no differences between ICS and MLK group in terms of rescue medication free days.

Kumar V et al (2007)[17] observed that there was no statistically significant difference between the groups (ICS and MLK) in the need for rescue drugs in their study.

Stelmach et al (2002, 2005, 2007)[18, 19, 20] also found that there was no statistically significant difference between ICS and MLK in terms of reduction in attack frequency and rescue free days.

Williams Busse et al (2001)[21] also observed that improvements in daytime symptom scores were generally comparable among treatment groups of ICS and MLK.

An important issue to consider in the treatment of children of this age group with Asthma were the ease of drug administration and the long-term tolerability of therapy, because treatment is typically chronic.

Inhalants are the most commonly prescribed controller therapies; however, young patients may have difficulty in using inhaled corticosteroids and dose delivery can be variable. Moreover, reduced compliance with inhalants for Asthma compared to orally administered therapy has been reported. One potential advantage of MLK is the ease of administering a once-daily chewable tablet.

6. Conclusion

In our study we found that the goals for deciding a mono-therapy have been successfully achieved by inhaled Budesonide in terms significant reduction in the number of Asthma exacerbations per month, improvement in the PEFR and significant improvement in the FEV1 % predicted of normal when compared to oral Montelukast.

However, Montelukast was significantly better in reducing AEC when compared to inhalational Budesonide. More over Montelukast had the potential advantage of ease in administering a once-daily chewable tablet and being more socially acceptable.

Although it is important to recognize that the use of ICSs is currently the recommended first-line treatment for children with Asthma, Montelukast is an alternative, safe, orally administered, non steroidal agent for treating mild persistent Asthma, especially in younger children unable to use ICS, those not compliant and where social stigma may lead to an increase in the fallout rate of the treatment.

Thus, taken together, the results of the current study and the other comparative trials, suggest that ICSs such as inhaled Budesonide, are the most effective single-agent controller medications for children suffering from mild persistent Asthma of 5 – 18 years of age.

7. Future Scope

Though our study is by no means exhaustive due to the sample size taken, it does provide us a glimpse about the better efficacy of budesonide over montelukast. We recommend further studies of the similar kind to be carried out with a larger sample size.

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