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Original Research Article

Effectiveness of montelukast in childhood asthma: a prospective observational study

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ABSTRACT

Background: Asthma is characterized by hyperresponsiveness of airways to various stimuli, manifested by widespread narrowing of airways causing paroxysmal dyspnoea, wheezing or cough. Most asthma medications are inhalational and compliance is difficult. So, development of an orally active and once daily drug with additional bronchodilator properties would lead to a major advance for managing young patients with asthma.
Methods: Children between 6-18 years with not well controlled asthma on daily controller therapy were enrolled. Their personal data and history regarding the duration of asthma symptoms, frequency and severity of exacerbations was noted. Diagnosis and grading of severity of asthma was confirmed by spirometry. Then subjects were started on montelukast as add on to their daily controller therapy and were reassessed at 4, 8 and 12 weeks by clinical symptoms and PEFR. The change in frequency of symptoms and PEFR at the end of 12 weeks gave the outcome of efficacy of montelukast. Side effects of montelukast were also assessed.
Results: Among total 64 subjects, at 4 weeks, 52 improved to well-controlled asthma. The remaining 12 did not improve, so required an increase in dose of their daily controller medication. Out of those 12 subjects, 10 subjects improved to well-controlled asthma at 8 weeks and 2 subjects still did not improve, so, their inhaled corticosteroids (ICS) dose was further increased. All 64 subjects showed improvement at 12 weeks. No serious side effects were observed.
Conclusions: 81.25% subjects showed improvement at the 1st follow up itself and no serious complications were observed. So, it can be suggested that montelukast is a safe drug.

Keywords: Asthma, Montelukast, Inhaled corticosteroids

INTRODUCTION

Asthma is one of the most common and highly prevalent chronic diseases having a substantial impact on quality of life and is a major cause of morbidity and mortality.[1] It is characterized by hyperresponsiveness of the airways to various stimuli, manifested by widespread narrowing of airways causing paroxysmal dyspnoea, wheezing or cough. Obstruction of airway is caused by oedema and inflammation of mucus membrane, excessive secretion of mucus inflammatory cells and cellular debris and spasm of bronchial smooth muscles. This obstruction is reversible in majority of cases either spontaneously or in response to treatment.[2]

It was believed that the inflammation was confined only to the central airways; but now it is accepted that also the peripheral airways are of at least equal importance in the pathophysiology of asthma.[3] Also, there is an association with atopy. Asthma and allergic rhinitis are totally different disease entities, but they are closely linked to each other.[4] Many studies have also explained the systemic nature of asthma, expressed by blood eosinophilia, atopic dermatitis, cognitive disorders and asthenia.[4-6]

Asthma classification based on severity (intermittent and persistent) helps in initiating asthma therapy and classification based on asthma control (Well controlled, not well controlled, and very poorly controlled) helps in adjusting therapy. Among the risk factors, genetic predisposition and environmental exposures are main. But environmental exposures to endotoxin and infections may be protective or may act as risk factors, depending on the timing of exposure in childhood.[7]

Management goals of asthma therapy are to control asthma so that the child can lead a normal life without any asthma exacerbations. The 2 classes of drugs used most commonly for childhood asthma are β2 agonists bronchodilators and inhaled corticosteroids (ICS). Development of tolerance due to their continuous use, compliance to inhaled medication and their increased side effects are the main reasons of poor quality of life of asthmatics. So, development of an orally active drug with additional bronchodilator properties would lead to a major advance for managing young patients with asthma.[8,9]

Montelukast may be used as a monotherapy or as an add-on therapy to ICS for improving clinical symptoms as it will increase the anti-inflammatory effects. Montelukast is an oral preparation, easier to administer in young children and its once daily dosing encourages compliance.[10,11] Studies show that the LTRAs have a wide therapeutic window with low toxicity at therapeutic concentration, thus having a good safety profile.

METHODS

A prospective observational study was conducted at Geetanjali Medical College and Hospital, Udaipur. Study was conducted during one-year period (January 2019 to December 2019) after obtaining permission from the ethical committee of institute.

Inclusion criteria

Asthmatic children aged between 6-18 years with not well controlled asthma on daily controller therapy were included in the study.

Exclusion criteria

Children with any other systemic disease, children already on montelukast therapy, and children having very poorly controlled asthma were excluded from the study.

All eligible children were consecutively enrolled in the study after taking prior informed consent from the parents. Their personal data was noted and detailed history regarding the duration of asthma symptoms, frequency and severity of exacerbations was taken. Diagnosis and grading of severity of asthma was confirmed by spirometry. Then the subjects were started on montelukast therapy as add on to their daily controller therapy (ICS/ICS+LABA). Subjects were reassessed at 4, 8 and 12 weeks by clinical symptoms and PEFR.

The change in frequency of symptoms and PEFR at the end of 12 weeks gave the outcome of efficacy of montelukast. Side effects of montelukast were also assessed. Statistical analysis was done using SPSS statistical software. Descriptive data was expressed as mean, standard deviation (SD), frequency and proportions. Categorical data was analyzed using chi-square test. Quantitative data was analyzed using student t-test (unpaired). A p value <0.05 was considered statistically significant.

RESULTS

We enrolled 64 eligible children having not well controlled asthma in our study. Data was collected for each subject in pre-designed proforma.

Table 1 shows distribution of children according to the gender, age and area of residence. Out of the total 64 subjects, 49 (76.6%) were males and 15 (23.4%) were females (p value <0.001). 28 (43.75%) were among 6-11 years and 36 (56.25%) were among 12-18 years (p value >0.05). 47 (73.4%) were living in urban areas and 17 (26.6%) were living in rural areas (p value <0.0001).

Table 1: Distribution of socio-demographic factors among children with not well controlled asthma.

Factors	Number (%)
Gender	
Male	49 (76.6)
Female	15 (23.4)
Total	64 (100)
P value	<0.001
Age group (years)	
6-11	28 (43.75)
12-18	36 (56.25)
Total	64 (100)
P value	0.15
Residence	
Urban	47 (73.4)
Rural	17 (26.6)
Total	64 (100)
P value	<0.0001

Table 2 shows that after starting montelukast, at 4 weeks follow up, out of 23 subjects with family history of asthma, 19 (82.6%) were found to improve and out of the 41 subjects without family history of asthma, 33 (80.5%) were found to improve (p value >0.05). Similarly, at 4 weeks, out of 13 subjects with history of passive smoking, 11 (84.6%) were found to improve asthma and out of the 51 subjects without history of passive smoking, 41 (80.3%) were found to improve (p value >0.05).

In Table 3, frequency of asthma symptoms, PEFR and overall grading of asthma control at 4 weeks follow up is

shown. In 6-11 years age group, out of 28 subjects, 23 (82.2%) improved to having impairment symptoms ≤2 days/week and 5 (17.8%) still had impairment symptoms >2 days/week (p value <0.0001). Among subjects of 12-18 years, out of 36, 31 (86.2%) improved to having impairment symptoms ≤2 days/week and 5 (13.8%) still had impairment symptoms >2 days/week (p value <0.0001).

Table 2: Asthma control at 4 weeks in relation to presence of family history of asthma and history of passive smoking in study cases.

Asthma control classification	With family history (%)	Without family history (%)	H/o passive smoking (%)	No H/o passive smoking (%)
Well controlled	19 (82.6)	33 (80.5)	11 (84.6)	41 (80.3)
Not well controlled	4 (17.4)	8 (19.5)	2 (15.4)	10 (19.7)
Total	23 (100)	41 (100)	13 (100)	51 (100)
P value	0.83		0.7	

Table 3: Frequency of asthma symptoms, PEFR and overall grading of asthma control at 4 weeks follow up among study subjects.

Symptoms	6-11 years	12-18 years
Impairment symptoms (days/week)		
≤2	23 (82.2)	31 (86.2)
>2	5 (17.8)	5 (13.8)
Total	28 (100)	36 (100)
P value	<0.0001	<0.0001
Night time awakenings		
≤1/month	21 (75)	-
≥2/month	7 (25)	-
≤2/month	21 (75)	31 (86.2)
1-3/week	-	5 (13.8)
Total	28 (100)	36 (100)
P value	<0.0001	<0.0001
Requirement of SABA (days/week)		
≤2	22 (78.5)	32 (88.8)
>2	6 (21.5)	4 (11.2)
Total	28 (100)	36 (100)
P value	< 0.0001	< 0.0001
Grade of interference in normal activity		
None	23 (82.2)	32 (88.8)
Some limitation	5 (17.8)	4 (11.2)
Total	28 (100)	36 (100)
P value	<0.0001	<0.0001
PEFR		
Green zone (>80%)	21 (75)	31 (86.2)
Yellow zone (50-80%)	7 (25)	5 (13.8)
Total	28 (100)	36 (100)
P value	<0.0001	<0.0001
Grading of overall asthma control		
Well controlled	21 (75)	31 (86.2)
Not well controlled	7 (25)	5 (13.8)
Total	28 (100)	36 (100)
P value	<0.0001	<0.0001

In 6-11 years age group, out of 28 subjects, 21 (75%) improved to having night time awakenings ≤1/month and 7 (25%) still had night time awakenings ≥2/month (p value <0.0001). Among subjects of 12-18 years, out of 36, 31 (86.2%) improved to having night time awakenings ≤2/month and 5 (13.8%) still had night time awakenings 1-3/week (p value <0.0001). In 6-11 years age group, out of 28 subjects, 22 (78.5%) improved to having SABA requirement ≤2 days/week and 6 (21.5%) still had SABA requirement >2 days/week (p value <0.0001). Among subjects of 12-18 years, out of 36, 32 (88.8%) improved to having SABA requirement ≤2 days/week and 4 (11.2%) still had SABA requirement >2 days/week (p value <0.0001).

In 6-11 years age group, out of 28 subjects, 23 (82.2%) were found to have no limitation in normal activity and 5 (17.8%) still had some limitation in normal activity (p value <0.0001). Among subjects of 12-18 years, out of 36, 32 (88.8%) were found to have no limitation in normal activity and 4 (11.2%) still had some limitation in normal activity (p value <0.0001). In 6-11 years age group, out of 28 subjects, 21 (75%) improved their PEFR to >80% (green zone) and 7 (25%) still had their PEFR between 50-80% (yellow zone) (p value <0.0001). Among subjects of 12-18 years, out of 36, 31 (86.2%) improved their PEFR to >80% (green zone) and 5 (13.8%) still had their PEFR between 50-80% (yellow zone) (p value <0.0001).

Among total of 64 subjects, at 4 weeks, 52 improved to well-controlled asthma from not well controlled asthma. The remaining 12 still remained not well controlled. So, they required an increase in dose of their daily controller medication. Once daily montelukast was still continued for these 12 participants. Further analysis was done separately as group 1 consisting of 52 subjects who improved by 4 weeks and group 2 consisting of 12 subjects who required increase in the dose of their daily controller medication.

In Table 4 frequency of asthma symptoms, PEFR and overall grading of asthma control at 8 weeks follow up is shown. In group 1, all 21 (100%) subjects from 6-11 years and all 31 (100%) subjects from 12-18 years, who had improved to having impairment symptoms for ≤2 days/week, night time awakenings for ≤1/month and ≤2/month respectively, SABA for only ≤2 days/week, no interference in normal activity, >80% (green zone) of predicted PEFR and who had improved to well controlled

asthma at 4 weeks, had no deterioration in their symptoms, PEFR or asthma control.

In group 2, for age 6-11 years, out of 7, 6 (85.7%) subjects improved to having impairment symptoms for≤2 days/week, night time awakenings for≤1/month, requirement of SABA for≤2 days/week, no limitation in normal activity, PEFR >80% (green zone) and improved to well controlled asthma while 1 (14.3%) subject still had impairment symptoms for>2 days/week, night time awakenings for≥2/month, required SABA for>2 days/week, some limitation in daily activity, PEFR between 50-80% (yellow zone) and still had not well controlled asthma (p value<0.05).

Similarly for age 12-18 years in group 2, out of 5, 4 (80%) subjects improved to having impairment symptoms for≤2 days/week, night time awakenings for≤2/month, requirement of SABA for≤2 days/week, no limitation in normal activity, PEFR >80% (green zone) and improved to well controlled asthma while 1 (20%) subject still had impairment symptoms for>2 days/week, night time awakenings for≥2/month, required SABA for>2 days/week, some limitation in daily activity, PEFR between 50-80% (yellow zone) and still had not well controlled asthma (p value <0.05).

Therefore, it was observed that the 52 subjects that had achieved asthma control at 4 weeks, had their symptoms and PEFR persistently controlled at 8 weeks also. Out of those 12 subjects, who had not achieved asthma control at 4 weeks, and their ICS dose was increased, 10 subjects improved to well-controlled asthma at 8 weeks. Among the total 64 subjects, 62 improved to well-controlled asthma by 8 weeks. 2 subjects, who were still not well controlled at 8 weeks, their ICS dose was further increased and they were followed up later at 12 weeks to assess their asthma control. All 64 subjects showed improvement to well controlled asthma at 12 weeks, out of which 52 were controlled only by adding montelukast and 12 required hike of conventional asthma controller medication.

Table 5 shows the side effects observed in the subjects during 12 weeks study period. In the age group of 6-11 years, 4 (14.3%) subjects presented with head ache and no subjects had any rash. Out of those 4 with headache, 2 (7.1%) presented within first 4 weeks, 1 (3.6%) presented between 4-8 weeks, and 1 (3.6%) presented between 8-12 weeks of follow up. In the age group of 12-18 years, 3 (8.3%) subjects presented with rash. Out of those 3, 1 (2.8%) presented within first 4 weeks and 2 (5.5%) presented between 8-12 weeks.

In the same age group, 7 (19.4%) subjects presented with head ache. Out of those 7, 3 (8.3%) presented within first 4 weeks, 2 (5.5%) presented between 4-8 weeks, and 2 (5.5%) presented between 8-12 weeks of follow up. No other complications/adverse effects were observed.

Table 4: Frequency of asthma symptoms, PEFR and overall grading of asthma control at 8 weeks follow up among study subjects.

Symptoms	Group 1		Group 2	
	6-11 years	12-18 years	6-11 years	12-18 years
Impairment symptoms (days/week)				
≤2	21 (100)	31 (100)	6 (85.7)	4 (80)
>2	0	0	1 (14.3)	1 (20)
Total	21 (100)	31 (100)	7 (100)	5 (100)
P value	<0.0001	<0.0001	0.009	0.04
Night time awakenings				
≤1/month	21 (100)	-	6 (85.7)	-
≥2/month	0	-	1 (14.3)	-
≤2/month	-	31 (100)	-	4 (80)
1-3/week	-	0	-	1 (20)
Total	21 (100)	31 (100)	7 (100)	5 (100)
P value	<0.0001	<0.0001	0.009	0.04
Requirement of SABA (days/week)				
≤ 2	21 (100)	31 (100)	6 (85.7)	4 (80)
>2	0	0	1 (14.3)	1 (20)
Total	21 (100)	31 (100)	7 (100)	5 (100)
P value	<0.0001	<0.0001	0.009	0.04
Grade of interference in normal activity				
None	21 (100)	31 (100)	6 (85.7)	4 (80)
Some limitation	0	0	1 (14.3)	1 (20)
Total	21 (100)	31 (100)	7 (100)	5 (100)
P value	<0.0001	<0.0001	0.009	0.04
PEFR				

Symptoms	Group 1		Group 2	
	6-11 years	12-18 years	6-11 years	12-18 years
Green zone (>80%)	21 (100)	31 (100)	6 (85.7)	4 (80)
Yellow zone (50-80%)	0	0	1 (14.3)	1 (20)
Total	21 (100)	31 (100)	7 (100)	5 (100)
P value	<0.0001	<0.0001	0.009	0.04
Grading of overall asthma control				
Well controlled	21 (100)	31 (100)	6 (85.7)	4 (80)
Not well controlled	0	0	1 (14.3)	1 (20)
Total	21 (100)	31 (100)	7 (100)	5 (100)
P value	<0.0001	<0.0001	0.009	0.04

Table 5: Side effects of montelukast at 4, 8 and 12 weeks follow up among study subjects.

Follow up time	Age group (6-11 years), N=28 (100%)		Age group (12-18 years), N=36 (100%)	
	Headache	Rash	Headache	Rash
4 weeks	2 (7.1%)	0	3 (8.3%)	1 (2.8%)
8 weeks	1 (3.6%)	0	2 (5.5%)	0
12 weeks	1 (3.6%)	0	2 (5.5%)	2 (5.5%)
Total	4 (14.3%)	0	7 (19.4%)	3 (8.3%)

DISCUSSION

At 4 weeks follow up, out of the 23 subjects with family history of asthma, 19 (82.6%) were found to improve and out of the 41 subjects without family history of asthma, 33 (80.4%) were found to improve with p value=0.83, which is not significant, suggesting that the presence/absence of family history of asthma, does not have a substantial effect on the effect of montelukast. These results are consistent with a study conducted by Harmanci K, which explained that characteristics predictive of asthma prognosis like family history of asthma, eosinophilia or personal history of allergy were not predictive of response to montelukast therapy.[12]

Out of the 13 subjects with history of passive smoking, 11 (84.6%) were found to improve and out of the 51 subjects without history of passive smoking, 41 (80.3%) were found to improve with p value=0.7 which is not significant. According to a study conducted by Lazarus et al to evaluate how smoking affects response to ICS or LTRA in asthma in adults, it has been explained that in subjects with mild asthma, who smoke, the response to ICS is attenuated, but greater improvements were seen in smokers treated with montelukast.[13] This suggested that, addition of leukotrienes may be important in such cases. Such studies are limited in pediatric age group. In current study, the results show that the difference in the asthma control between the passive smokers and non-passive smokers is not statistically significant.

At the 4 weeks follow up, in 6-11 years age group, out of the 28 subjects, number and percentage of subjects whose frequency of impairment symptoms decreased were 23 (82.2%) (p value <0.0001), decreased night time awakenings were 21 (75%) (p value <0.0001), decreased use of β agonist were 22 (78.5%) (p value <0.0001), no limitation in daily activity were 23 (82.2%) (p value <0.0001), improvement in PEFR values were 21 (75%) (p value <0.0001) and improvement in overall asthma control were 21 (75%) (p value <0.0001).

At 4 weeks, in 12-18 years age group, out of the 36 subjects, number and percentage of subjects whose frequency of impairment symptoms decreased were 31 (86.2%) (p value <0.0001), decreased night time awakenings were 31 (86.2%) (p value <0.0001), decreased use of β agonist were 32 (88.8%) (p value <0.0001), no limitation in daily activity were 32 (88.8%) (p value <0.0001), improvement in PEFR values were 31 (86.2%) (p value <0.0001) and improvement in overall asthma control were 31 (86.2%) (p value <0.0001).

These results are consistent with a study conducted by Knorr, in which montelukast demonstrated significant decrease in requirement of SABA (p value=0.01) and decrease in limitation in daily activity (p value <0.001) over a period of 8 weeks.[14] The improvement in impairment symptoms and PEFR was not found to be statistically significant, but numerically, it was in favour of montelukast. Another study by Laviolette et al also has shown a significant improvement in the impairment symptoms (p value=0.041), night time awakenings (p value=0.027) and PEFR (p value=0.0004) on addition of montelukast to ICS over a period of 16 weeks.[15]

Another study conducted by Virchow et al to evaluate the effect of add-on montelukast in asthmatic adults, who were inadequately controlled on ICS/ICS+LABA has shown significant improvement in overall asthma control after addition of montelukast.[16] So, the results of current study are almost similar to other studies conducted over the years in a larger sample size.

At 8 weeks follow up, it was found that, all subjects of both age groups, who had shown improvement at 4 weeks (group 1) in their symptoms, PEFR and over all asthma control, consistently had this improvement at 8 weeks also. These results are consistent with the study conducted by Knorr showing that the treatment effects of montelukast are maintained consistently over time, with no evidence of tolerance.[14] Similar results have also been explained in a study conducted by Reiss TF et al on adults.[17]

In the current study, the side effects of montelukast observed during the study period were only headache and rash. This headache was transient, no subject had it persistently and it subsided on its own without alteration in montelukast therapy. Also the rash disappeared spontaneously within 3-4 days without any alteration in montelukast therapy. The results of the current study are consistent with studies conducted by Virchow et al, Joos et al, Nayak et al and Ducharme et al on montelukast as no significant side effects were reported.[16,18-20] Also, a study conducted by Bisgaard et al in 2009 on more than 2700 asthmatic children and adolescents on montelukast, concluded that clinical and laboratory safety profile of montelukast was good, without any significant side effects and safety profile of montelukast did not change even with long term use.[21] So, it can be suggested that montelukast is safe to use in children.

CONCLUSION

Among total 64 subjects, at 4 weeks, 52 improved to well-controlled asthma. The remaining 12 still remained not well controlled. So, they required an increase in dose of their daily controller medication. 52 subjects that had achieved asthma control at 4 weeks, had their symptoms and PEFR persistently controlled at 8 weeks also. Out of those 12 subjects, who had not achieved asthma control at 4 weeks, and their ICS dose was increased, 10 subjects improved to well-controlled asthma at 8 weeks. Among the total 64 subjects, 62 improved to well-controlled asthma by 8 weeks. 2 subjects, who were still not well controlled at 8 weeks, their ICS dose was further increased and they were followed up later at 12 weeks to assess their asthma control. All 64 subjects showed improvement to well controlled asthma at 12 weeks. No serious side effects were observed in any subjects.

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