Original Article

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Paediatrics Section

Efficacy of Episodic Use of Montelukast in Preschool Children with Intermittent Wheezing

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ABSTRACT

Introduction: Acute intermittent wheezing illnesses are frequent occurrences in preschool children and need better management strategies. Montelukast, a leukotriene receptor antagonist has potent anti-inflammatory property with rapid onset of action and may be effective in reduction of asthma symptoms.

Aim: To examine the effectiveness of episodic use of montelukast in modifying the severity of an acute wheeze episode in preschoolers.

Materials and Methods: Children aged 1-5 years with acute wheezing were included in an observational prospective case control study. Montelukast, 4mg orally, was started on admission and continued until symptom resolution, maximum upto 14 days. Primary outcomes were duration of respiratory symptoms, severity of respiratory illness by Paediatric Respiratory Assessment Measure (PRAM) score and duration of hospital stay. Secondary outcomes were need for number of doses of bronchodilator, inhaled or systemic steroid or other medication (MgSO4 and/or Aminophylline). Chi-Square test, unpaired, two sided student t-test and Mann-Whitney U test were applied wherever applicable.

Results: Total 107 patients were enrolled, out of which 53 patients were given montelukast and 54 patients served as control. Montelukast resulted in early reduction in symptom of breathlessness (p=0.0226), sleep disturbance (p=0.0214), feeding difficulty (p=0.011), significant improvement in PRAM score at 24 hour (p=0.046) and significant reduction in hospital stay (p=0.0448) compared to control group. There was significant increase in number of doses of systemic steroid ($p < 0.00001$) and need for other medication (p=0.027) in control group as compared to cases. There was no significant difference in proportion of patients requiring systemic steroid between two groups.

Conclusion: Episodic use of short course montelukast is effective in reduction of symptoms, hospital duration and systemic steroid use.

Keywords: Hospital stay, Intermittent Wheeze, PRAM score, Preschool, Systemic steroid

INTRODUCTION

Asthma is the most common chronic disease of the airways in young children. Around 40% of all preschool children suffer from wheeze [1]. Wheezing episodes in this age group are recurrent in nature and are commonly triggered by viral respiratory infections and accounts for the majority of paediatric emergency department attendances and hospital admissions for asthma [2-4]. Intermittent use of inhaled β2 agonists and anticholinergics has been suggested for symptom control of preschool wheezers. The next treatment options are either intermittent inhaled corticosteroids or intermittent leukotriene receptor antagonist or both [5]. Study on use of inhaled corticosteroid showed that regular use of low dose Inhaled Corticosteroid (ICS) in children with intermittent asthma does not reduce the frequency or severity of the episodes [6]. Studies on use of intermittent ICS for acute episodes showed benefit but at a very high dose and so there is a concern of safety in children [7-10]. Montelukast is a leukotiene receptor antagonist having anti-inflammatory and bronchoprotective effect [1].

Montelukast does not suppress the growth [11,12], so its use in the treatment of wheeze in young children is of clinical interest. This study was planned to assess the efficacy of short course of montelukast in preschoolers with wheeze.

MATERIALS AND METHODS

Study Setting & Ethical Consideration: This was an observational prospective case control study done in paediatric department of tertiary care hospital over a period of one year (October 2016 – September 2017). The study was approved by Institutional Ethical Committee (SMIMER/IEC/OUT/No.2768; date 19/10/2016). A written informed consent was obtained from parents.

Patients (inclusion & exclusion criteria): Eligible patients were children aged between 1 to 5 years (preschooler) who were admitted for wheezing episode with or without associated clinical evidence of a viral respiratory tract infection and having previous history of at least one reported episode of wheezing.

Patients were excluded from the study if they did not meet the inclusion criteria. Patients with any underlying disease like chronic lung disease, Congenital Heart Disease (CHD), neurological disease; radiological evidence of pneumonia, persistent symptoms, on long term corticosteroid in the past or took discharge against medical advice were also excluded from the study.

Treatment: Eligible patients were grouped into two groups by simple randomisation (upon enrollment, patients with even number were put in group 1 and with odd number were put in group 2). Group 1 (case) patients were given montelukast tablet at the dose of 4 mg orally, started within six hour of admission and continued until symptoms had resolved for 48 hours up-to maximum of 14 days. Patients in both groups could receive inhaled β2 agonist (Salbutamol), inhaled anticholinergic (Ipratropium bromide), inhaled corticosteroid (Budesonide), systemic corticosteroid or other medication as per set protocol. Detailed clinical history including socio demographic profile, immunisation status and exclusive breast feeding status was noted. Other points in the history included history of allergic condition, allergic rhinitis or atopy, positive family history

for asthma, number of previous episodes in past one year, duration of symptoms before admission, type of wheeze and severity of respiratory illness on admission. For type of wheezing, patients were considered as Episodic Viral Wheezer (EVW), if wheeze was seen in association with clinically diagnosed viral Upper Respiratory Tract Infection (URTI) and Multiple Trigger Wheezers (MTW), if wheeze was associated with viral URTI as well as other triggers between URTIs such as excited behaviour and allergen exposure [13]. Severity of respiratory illness was assessed by PRAM score [14]. All patients were subjected to laboratory investigation in form of CBC, absolute eosinophil count and X-Ray chest. Clinical monitoring for symptoms and PRAM scoring [14] was done at 6 hour, 12 hour, 24 hour and thereafter, 24 hourly daily till discharge.

Primary outcomes included duration of reduction in symptoms, severity of respiratory illness determined by PRAM score and duration of hospital stay. Secondary outcomes were reduction in number of doses of bronchodilator, need for systemic steroid or other medication.

STATISTICAL CONSIDERATION

A sample size of 107 was estimated by considering the population of patients of wheezing admitted in the hospital in previous year and calculated by using SPSS 16 based on the alpha error 6%, beta error 9.1%, power of the study 90.9% and level of significance 95%. Categorical qualitative data between two groups were compared by chi-square test. Quantitative data were expressed as mean and standard deviation and compared by unpaired, two sided student t-test. For continuous data comparison between two groups, nonparametric Mann-Whitney test was applied and so median and interquartile ranges were reported.

RESULTS

The point prevalence of wheezing patients in hospitalised children during study period was 13.4% in present study. Among 53 patients who received oral montelukast therapy, the drug was started within two hours in 42% of patients and rest were given within 2-6 hour. Mean duration of Montelukast therapy was 7±2.10 days. None of the patients reported any side effects of montelukast.

Mean age of the study cohort was 2.32±1.19 years, Male: Female ratio was 1.5, positive family history and eosinophillia were seen in 20.56% patients and 76% of the patients were episodic viral wheezers. There was no statistically significant difference noted between two groups for baseline characteristics as shown in [Table/Fig-1].

The primary outcome of the study was reduction in the following: (a) duration of symptom; (b) severity of respiratory illness determined by PRAM score; and (c) duration of hospital stay.

There was significant improvement in symptom of breathlessness, sleep disturbance and feeding difficulty among cases. At 24 hours 42% patients had moderate PRAM score and none of the patients had severe PRAM score among cases while 55% patients had moderate and 6% had severe PRAM score among controls. With regard to duration of hospital stay, 35% control group patients had stay for 5-7 days and 5% required stay for more than seven days which was significantly more as compared to cases (p=0.024).

Comparison of primary outcome between two groups showed significant reduction in duration of breathlessness (p = 0.0226), sleep disturbance (p = 0.0214) and feeding difficulty (p= 0.011), statistically significant improvement in severity of respiratory illness (PRAM score) at 24 hours (p = 0.046) and 48 hours (p = 0.036) and statistically significant reduction in duration of hospital stay (p = 0.0448) among cases as compared to controls [Table/Fig-2-4].

All patients received inhaled β2 agonist and inhaled anti-cholinergic in both groups. 36% of cases and 40% of controls required inhaled steroids. Systemic steroids were required in 32 % and 33% patients among cases and controls, respectively. There was no significant difference seen with regard to number of patients requiring inhaled steroid and systemic steroid between two groups. Use of step up medication in form of inj.MgSO4 and/or inj. Aminophylline was significantly more among controls as compared to cases (33% Vs 15%, p = 0.027).

Comparing requirement of number of doses of different medication between cases and control showed no significant difference in mean number of doses of β2 agonist and inhaled steroid. However, control group patients needed more number of doses of systemic steroid as compared to cases which was statistically significant (4.55±6.68 Vs 3.16±2.05, p <0.00001) [Table/Fig-5].

Variable	Case (n=53) (%)	Control (n=54) (%)	p-value
Age in years (mean±SD)	2.3±1.18	2.28±1.21	0.85
Male: female	1.78	1.25	0.36
Type of wheezing			0.77
Episodic Viral Wheezer (EVW)	40(75)	42(78)	
Multiple Trigger Wheezer (MTW)	13(25)	12(22)	
Positive Family history	10(19)	12(22)	0.66
Number of patients having eosinophillia	10 (19)	12 (22)	0.66
Number of episodes in past one year (mean±SD)	3.8±1.18	4.5±1.20	0.57
Duration of symptoms before admission (mean±SD)	4.7±0.97	4.9±1.09	0.66
Eosinophil Count/cmm (mean±SD)	207.2±74.66	192.5±76.96	0.84
Respiratory rate/min on admission	43.2±10.07	47.67±9.27	0.94
PRAM score on admission (Number of patients)			
Mild	20 (38)	21 (39)	0.97
Moderate	25 (47)	24 (45)	
Severe	8 (15)	9 (17)	

[Table/Fig-1]: Baseline characteristics of study participants.

Symptom	Symptom duration in days (Median IQR))		
	Case	Control	p-value
Cough	4(2-6)	4(2-7)	0.49
Breathlessness	2(1-4)	3(1-5)	0.0226
Sleep disturbance	2(1-3)	3(2-4)	0.0214
Feeding difficulty	2(1-4)	3(2-5)	0.011

[Table/Fig-2]: Comparison of outcome based on Symptom duration (in days) between Two Groups.

Time since admission (in hours)	Case (n=53)(%)			Control (n=54)(%)			p-value
	Mild	Moderate	Severe	Mild	Moderate	Severe	
6 hour	21 (38)	26 (49)	6 (11)	21 (39)	24 (44)	9 (16)	0.71
12 hour	27 (51)	24 (45)	2 (4)	21 (39)	28 (52)	5 (9)	0.31
24 hour	31 (58)	22 (42)	0	21 (39)	30 (55)	3 (6)	0.046
48 hour	30 (57)	23 (43)	0	21 (39)	30 (55)	3 (6)	0.036

[Table/Fig-3]: Comparison of outcome based on PRAM score between two groups.

Duration (in days)	Case (n=53)(%)	Control (n=54)(%)	p-value
3 – 5	43 (81)	32 (59)	0.024
5 – 7	10 (19)	19 (35)	
7 – 10	0	3 (5)	
Mean duration (mean±SD)	3.79±0.96	4.36±1.18	0.0448

[Table/Fig-4]: Comparison of duration of hospital stay.

Treatment parameter	Case (n=53)(%)	Control (n=54)(%)	p-value
Inhaled steroid use	19 (36)	22 (40)	0.6
Systemic steroid use	17(32)	18(33)	0.88
Other medication (inj MgSO4/Aminophylline)	8 (15)	18 (33)	0.027
Number of doses of β2 agonist use (mean±SD)	19.6±3.97	22.4±3.08	0.069
Number of doses of inhaled steroid use (mean±SD)	2.15±0.25	2.5±0.23	0.54
Number of doses of systemic steroid use (mean±SD)	3.16±2.05	4.55±6.68	<0.00001

[Table/Fig-5]: Comparing treatment between two groups.

DISCUSSION

The present study demonstrated that a short course of montelukast significantly improved the clinical outcome in the preschool children having acute attack of wheezing. Oral montelukast given on admission resulted in reduction in median duration of breathlessness (p=0.0226), sleep disturbance (p=0.0214) and feeding difficulty (p= 0.011) among cases as compared to controls. The PRAM score was significantly improved (p=0.046) at 24 hours among cases. The numbers of patients with moderate to severe PRAM score were reduced by 19% at 24 hours among cases as compared to controls. Hospital stay was significantly longer among controls as compared to cases (p=0.0448). Out of the total patients,16% more patients had hospital stay up-to seven days and 5% more patients had stayed up to 10 days among controls as compared to cases.

The issue of whether intermittent montelukast is effective in treating preschool wheeze has been addressed by four larger studies. The PREEMPT study by Robertson CF et al., recruited >100 children and compared intermittent Montelukast with placebo and showed 14% reduction in asthma symptoms, 8.6% reduction in sleep disturbance [2]. A North American study by Bacharier LB et al., compared intermittent montelukast, intermittent nebulised budesonide and placebo [15]. They found significant reduction in wheezing, trouble breathing and activity limitation in montelukast group and reduction in trouble breathing and activity limitation in budesonide group as compared to placebo. The primary end point was episodes culminating in an asthma attack in a large multicentric study done by Valovirta E et al., and they didn't find improvement in primary end point but statistically significant reduction in use of β agonist as secondary end point was seen with both daily and intermittent montelukast as compared to placebo [16]. The WAIT trial also showed no clear benefit of intermittent Montelukast in young children [11]. However, subgroup analysis in their study showed the 5/5 ALOX5 genotype subjects as montelukast responsive.

The study outcome was different in different studies; some had considered hospital stay and episode free days while some considered doctor visits and school absenteeism as study outcome. We had studied effect of montelukast for single episode, so we considered duration of hospital stay as one of the outcome. Robertson CF et al., showed 7.8% reduction in doctor visits (p = 0.026) and 37% reduction in school absenteeism (p=0.003) [2]. Bacharier LB et al., found 54% reduction in emergency care visits in patients with positive Asthma Predictive Index [15]. The WAIT trial [11] recorded 20% reduction in unscheduled medical attendance for wheeze in children having 5/5 ALOX5 genotype in montelukast group.

The present study found significantly lesser number of patients requiring step up treatment and significantly lower mean number of doses of systemic steroid in montelukast group as compared to control. In the WAIT trial [11], they found decrease in mean number of courses of rescue oral corticosteroid in montelukast group (p= 0.03) but no difference in the proportion of children requiring at least one course of rescue oral corticosteroid. Cumulative incidence of step up treatment was significantly lower in study by Nagao M et al., (p=0.033) [17].

The beneficial treatment effect shown in present study may not be very large but it has clinical relevance, because acute exacerbations cause a considerable burden on children and their families in terms of emotional trauma and work days loss by parent or caregiver.

LIMITATION

This study has some limitations. First, it was a hospital based open labelled design with small sample size. Second, we studied effect of montelukast for single episode. Third, we have not studied the predictive factor for favourable response to montelukast.

CONCLUSION

The present study found beneficial effect of montelukast in preschool wheezers in terms of reduction in duration and severity of symptoms, reduction in hospital stay and reduction in need for number of dose of systemic steroid and need for step up treatment. We may conclude that episodic use of intermittent short course montelukast may provide clinically beneficial alternative approach in the management of preschool wheezers.

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