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COMPARISON OF MONTELUKAST AND KETOTIFEN AS ADD ON THERAPY IN MODERATE AND SEVERE PERSISTENT BRONCHIAL ASTHMA

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Abstract

Background: Asthma is chronic debilitating disease, various treatment modalities including inhaled steroids in combination with other drugs are widely used ,therefore to compare efficacy as well as safety of montelukast / ketotifen as add-on therapy in moderate and severe persistent asthma is done in present study **Methods:** Asthmatic patients receiving treatment of inhaled steroids and long acting b-agonist (base line treatment) get add on treatment of montelukast and ketotifen and assessed for PEF, ACT, Improvement in shortness of breath and improvement in nocturnal awakening over period.**Results:** Combination therapy of ICS, LABA and monelukast is showing better results in patient compliance, improvement in shortness of breath (113%) compared to base line treatment (77%) and combination with Ketotifen (59%). A significant increase in PEF was observed in add on montelukast group (99%) as compared with add on ketotifen (6%) at the end of study. At the end of treatment 80% patients shows better status of control with add on montelukast therapy in comparison with patients on kitotifen (28%).**Conclusion.** Present study suggest that the addition of montelukast as add-on therapy in moderate persistent asthma is defiantly beneficial in comparison with add on ketotifen therapy.

Keywords: Asthma, Inhaled corticosteroids, Montelukast, Ketotifen, Peak Expiratory Flow

INTRODUCTION:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role .The chronic inflammation causes an associated increase in airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly t night or in the early morning. These episodes are usually associated with widespread with widespread but variable airflow obstruction that s often reversible either spontaneously or with treatment (1).

Majority of patients have mild disease that can be controlled inhaled short acting beta 2 agonist alone or in combination with low to moderate doses of inhaled corticosteroids (ICS) Approximately 20% patients have more severe asthma and despite multiple drug treatment these patient experience considerable morbidity including frequent exacerbation .

There are two approaches to treat asthma patient who continue to experience symptoms on ICS first Increase the dose of ICS, second add another therapeutic agent such as long acting beta 2 agonist (LABA), oral leukotriene antagonist , ketotifen.

Higher doses of ICS may cause higher degree of adverse effects like adrenal suppression growth retardation in children, osteoporosis, cataract,

skin thinning and easy bruising etc. Recent studies suggested that even LABA may causes development of tolerance, even in those patients treated with ICS. Another potential concern is the risk of masking underlying inflammation thereby allowing an exacerbation to go unrecognized.

Therefore the challenge is to achieve good asthma control for adults with moderate to severs persistent disease by improving current management and by developing new improved treatments.

Recent researches into asthma pathogenesis has led to greater understanding of the role of specific anti – inflammatory mediators and this , in turn has improved the development of more focused specific anti asthma therapies (2).

Although becomethasone had a larger means effect than montelukast, both drugs provided clinical benefit to patients with chromic asthma (3). But data regarding the use and efficacy of LTRA / ketotifen as an add on therapy in moderate and severe persistent asthma to achieve good asthma control are insufficient. therefore the presented study was conducted to find out that the addition of LTRA / ketotifen as add – on therapy in moderated persistent asthma is beneficial or not .

MATERIAL AND METHODS

This presented study was a prospective study carried out in 75 patients of moderated to severe asthma, attending the department of Respiratory medicine at tertiary health care institution

Cases of asthma were selected on the basis of clinical diagnosis and confirmed by PEFF with reversibility more then 15%. We exclude the patient having acute episode of asthma, infants, children less then 15 year old adults older than 85 year pregnancy, and person with other respiratory diseases.

Detailed history, including wheezing chest tightness, difficulty in respiration nocturnal cough and awakening, occupational history, history of GERD, rhinitis and allergy family history and previous treatment and response, was taken. General physical examination and proper respiratory system examination and proper respiratory system examination were done. Hypertensive patients were excluded from study.

Chest X-RAY, TLC, DLC AEC, and sputum examination were done. Patients with negative sputum examination and normal chest X_ RAY finding were included in the study.

Baseline PEFR was done and repeated again on 15^{th} and 30^{th} day of treatment and response was noted. PEFR was selected for objective assessment because it is an outdoor procedure, cost effective, best for follow – up and instrument is very handy.

For subjective assessment of response to treatment used ACT at the time of diagnosis as well as during follow – up because the revised guidelines of GINA 2006 to implement asthma management are based on asthma control rather than asthma severity .

Severity of asthma was decided on the basis GINA guidelines according to this the moderate persistent asthma is:

PEFR or FEV1 value 60-80%.

PEF variability > 30%

Symptoms of asthma occurring daily.

Nocturnal symptoms occurring for more than once in a week

Frequent exacerbation.

After diagnosis and categorization of patient into moderate persistent asthma patients were **randomly kept into three groups.**

- Group A: 25 patient in ICS + LABA group
- Group B: 25 patient in montelukast along with ICS + LABA group
- Group c: 25 patients in along with ICS + LABA group.

Doses of the given were:

Fluticasone 100 microgram rotacaps / inhaler.

Salmeterol 50 microgram rotacaps / inhaler.

Montelukast 10 microgram once in evening orally.

Ketotifen 1 milligrams twice in a day orally.

All patients were assessed on first fifteen and thirtieth day on the clinical basis with

PEFR and asthma control test score (which is a questionnaire filled by the patient himself) and side effects .Laboratory investigations were asked whenever possible. Two patients on montelukast did not show any improvement in symptoms and levocetrizine was also added after which the symptoms were improved. Statistical analysis was done.

Comparisons of the change from base line between treatment groups were performed using an analysis – of – covariate model involving treatment as a factor and baseline value as a covariate model involving treatment as a factor and baseline value as a covariate. Within group comparisons of the values at each time point with baseline were also performed using students t – test for the least squares means

Clinical assessment. This include patient's symptoms, sleep disturbances, effort tolerance of daily activities and the frequency of bronchodilator drugs and / or rescue course of steroid used (Table 1).Measuring peak expiratory flows (PEF). This was measured by Wright peak flow meter.

PEF Measurement: This allows measurement of patient's best PEF value which will provide the severity grading and follow up Date 15th and 30th day. As PEFR measurement is easy, feasible, outdoor procedure, recommended for follow up during in attack PEF fairly accurately measure the degree of attack of asthma PEF fairly accurately measures the degree of bronchospasm. Measurement was taken before short acting inhaled bronchodilator treatment and them after bronchodilator them reversibility is calculated as the difference between post bronchodilator and divided by the pre bronchodilator reading expressed as percentage reversibility.

Applications of the ACT score

As a screening test for poorly controlled asthma, the cut-off point of 19 provides the optimum balance of sensitivity (71%) and specificity (71%) for detection of such a patient. If the desire is to pick out patients with a greater specificity (fewer false positive results), what cut-point score should be used? Since the higher the score, the better the control, a cut-point score of less than 19 might be appropriate in this instance. A score of 15 or less will be poorly controlled asthma or asthma that is controlled at all. The higher the ACT scores on the range of 5 to 25, the better the control. A score of 19 or less signal a need for further evaluation to determine whether adjustments to asthma treatment regimen or other measures are required to improve asthma control. A score of 15 or less is of particular concern because it predicts asthma that is poorly controlled or not controlled at all.

RESULTS

Study population shows age and sex wise distribution age group, after that majority (32.01%) of patients fall into 25-54 years age group. Only 3 (4%) patients were belonged to 65-74 year age group.

Similarly, out of 34 female 21 patients are from 25-44 years (21%) age group and only 3 (4%) patients were belonged to 15-24 years age group.

In early age group males (9 patients) out numbered the females (3 patients) while in 25-54 year age group the number in both sexes is nearly equal (male 24, female 25) of studied patients. Out of 41 male patients, 9 (12%) belonged to 15-24 years. family history of asthma is present in 49.33% cases and absent in 50.67% cases and most of the patients were belonged to urban area (54.66%).In majority of patients i.e. 38 (50.67%) out of 75, the disease was between 1-10 years of duration, in 20 (20.77%) patients it was between 11 – 20 years.

Most common symptom of asthma is cough which is present in 69 cases (92%). After that dyspnoea (76%), wheezing (64%), and chest tightness (42.66%) were present. Nocturnal awakening was present in 52 cases (69.33). Rhinitis was present in 54 cases (72%) and GERD was seen in 24 (32%) cases of asthma.

Dust was the most common aggravating factor which is present in 55 cases (57.33%). Smoke, cold air and pollen were associated with asthma in 57.33%, 42.66%, and 20% cases respectively.

Mean percentage change from baseline in PEFR for three study groups over the 4 week treatment period that. With montelukast group, there was a significant improvement in PEFR at the end of study as mean percentage change from baseline was 37.93%. Ketotifen group produced 28.03% change in PEFR over the baseline i.e. evens less improvement than ICS+LABA group. In ICS+LABA group, the mean percentage change from baseline in PEFR was 30.36% (Table 1)

With Montelukast group, there was a significant improvement in ACT at the end of study as mean percentage change from baseline was 113.79%, Ketotifen group produced 59.47% change in ACT over the baseline i.e. even less improvement than ICS+LABA group. In ICS+LABA group, the mean percentage change from baseline in ACT was 77.75%. (Table 2)

Comparison from baseline in Shortness of Breath for three study groups over the 4 weeks treatment period. Montelukast group, there was a significant improvement in Shortness of Breath at the end of study as mean percentage change from baseline was 75.00%. While Ketotifen group produced 27.27% change in Shortness of Breath over the baseline i.e. even less improvement than ICS+LABA group and in ICS+LABA group, the mean percentage change from baseline in Shortness of Breath was 29.03% (Table 3)

Nocturnal Awakening improvement, comparison from baseline among all study groups over the 4 weeks treatment period. in montelukast group, there was a significant improvement in Nocturnal Awakening the end of study as mean percentage change from baseline was 76.54% while in ketotifen group produced 36.84% change in Nocturnal Awakening over the i.e. even less improvement than ICS+LABA group .In ICS+LABA group, the mean percentage change from baseline in Nocturnal Awakening was 33.33%.(Table 4)

According to Act score in Montelukast group 80% patient were in control status, whereas in Ketotifen group 28% in ICS+LABH group 24% patient were controlled. In Ketotifen group 28% patient were in were in control status, whereas in both Montelukast group and in ICS+LABA group 4% patient were in uncontrolled status.

Similarly in partially, controlled status in ICS+LABA group patient were in majority, in Montelukast group only 4% and in Ketotifen group 44% patient were in partially controlled status.

Thus ketotifen group showed uncontrolled status and Montelukast group showed controlled status in majority. (Table 5)

DISCUSSION

The present study is a prospective study, comparing the efficacy and safety profile of Montelukast and Ketotifen as an add-on therapy to ICS + LABH.

Present study results are comparable with results reported by De Macro R, Locatilli F (2002) et al assessed that during Child hood girls have Lower risk to developing Asthma. Around puberty the risk was almost equal in two sexes. It suggested that during puberty hormonal factors may play an important role.(4) This is also supported by Toren K, Gislason T et al that incidence rate was higher amongst females (2.9 Case / 1000 person / year) than amongst males (1.5 Cases / 1000 person / year.)(5)

Majority of patient residing in Urban Areas and most of them were literate (43.47%).

Aggrawal AN, Choudhary et al also reported in their study that females sex Urban area, Low socio economic status and family H/o of Asthma are risk factor influencing disease prevalence. In present study family history was present in 49.33% patients. (6)

Paul Vanden Brandel et al (2006) reported that there was significant improvement (9.97%) in allergic rhinitis with Bronchial Asthma patient given the combination of ICS+LABA+Montelukast. (7)

Present study showed that adding Montelukast to ICS+LABA resulted in 7.32% better improvement in PEFR as compare to ICS+LABA alone

These result were comparable with Vaquerizo, Casan Castello eo al, they concluded in their study that patient with Montelukast had fewer norurnal awakenings and improvement in morning PEFR.(8)

Kannis et al conducted a study which compare the effect of dose reduction of ICS on lung function and clinical scores during treatment with Montelukast they showed that ICS dose reduction up to 50% caused no further deterioration in PEV1 and symptom of Asthma in Montelukast group, however the placebo group (without Montelukast) showed a deterioration in lung function and clinical score(9)

Crabs et al in their study reported that biological effect of Ketotifen may be relevant to its therapeutic activity – the inhibition of release of myotonic mediators, inhibition of SRS induced bronchoconstriction, Ca-antagonistic property and prevention of decrease Beta 2 receptor sensitivity(10)

Canny and Reisman et al reported during their 12 weeks study that ketotifen treated patients were symptomatically better control and ketotifen did not had grater steroid sparing effect than placebo. (11)

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Table 1.Change in Mean PEFR from Baseline to End of Study

Treatment group	PEFR (Litres / min.			% change from baseline in PEFR
	Baseline (Mean±SD)	On 15th day (Mean±SD)	End of study (Mean±SD)	
ICS+LABA	280.84 ±108.96	338.08 ±114.38	366.12 ±116.36	**30.36**
ICS+LABA + Montelukast	311.24 ±116.59	371.28 ±118.59	429.32 ±99.41	**37.93**
ICS+LABA +Ketotifen	**275.64 ±108.21**	**338.08 ±101.53**	**352.92 ±6.93**	**28.03**

TABLE 2. Change in Mean ACT from Baseline End of study

Treatment group	ACT Litres / min		% change from baseline in ACT
	Baseline (Mean±SD)	End of study (Mean±SD)	
ICS+LABA	10.28±2.96	17.92±1.730	**77.75**
ICS+LABA + Montelukast	9.28±2.97	19.84±1.93	**113.79**
ICS+LABA+Ketotifen	**10.76±3.71**	**17.16±2.88**	**59.47**

TABLE 3. Comparative status of improvement in Shortness of Breath

Treatment group	Baseline (Mean±SD)	End of study (Mean±SD)	% change from baseline
ICS+LABA	1.32±0.4	1.86±0.32	**29.03%**
ICS+LABA + Montelukast	1.44±0.64	2.52±0.28	**75%**
ICS+LABA+Ketotifen	**1.28±0.25**	**1.76±0.4**	**27.27%**

TABLE 4.Comparative status of improvement in Noctural Awakening

Treatment group	Baseline (Mean +/- SD)	End of study (Mean +/- SD)	% change from baseline
ICS+LABA	1.44±0.4	1.92±0.32	**33.33%**
ICS+LABA + Montelukast	1.62±0.8	2.86±0.38	**76.54%**
ICS+LABA+Ketotifen	**1.52±0.65**	**2.08±0.5**	**36.84%**

TABLE 5.Comparative status of control of patients At the end of treatment

Status of control	ICS + LABA	%	ICS + LABA + Montelukast	%	ICS + LABA + Ketotifen	%
Controlled	6	24	20	80	7	**28**
Partial Controlled	18	72	4	16	11	**44**
Uncontrolled	1	4	1	4	7	**28**
Total	**25**	**100**	**25**	**100**	**25**	**100**