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RESEARCH ARTICLE

The Role of Leukotriene Receptor Antagonist as an add on therapy to β2-Agonists in Acute Asthma

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ABSTRACT:

Objective: This study was designed to determine the role of leukotriene receptor antagonist as an add on therapy to β2-agonists in acute asthma. **Methods:** A prospective study carried out in ESIC hospital in which the total number of 100 patients were enrolled. The study has two arms, the group A treated with salbutamol alone and the group B treated with salbutamol and montelukast. The symptomatic changes and variation in pulmonary function test (PFT), pulse rate (PR), respiratory rate (RR) were compared between both the group. The data were collected, compiled, analysed with statistical tools (SPSS – Microsoft Version 6). **Results:** In comparison of force expiratory volume % (FEV1 PRED) between the group A and group B, after 24 hours significant change was noticed in group B. The results of forced expiratory volume/forced vital capacity (FEV1/FVC%) shows a significant difference after 24 hours of the treatment with salbutamol in group A and salbutamol plus leukotriene receptor antagonist (Montelukast) from the baseline measurement. Base line asthma score shows p value (p = 0.58). But after 48 hours, significant change was noticed in both groups. p value was significant (p = 0.05). In group B, asthma score was significantly improved with passage of time. **Conclusion:** The study revealed the effectiveness of leukotriene receptor antagonist in preventing many types of aggravated asthmatic responses. Once-daily treatment with 10 mg of montelukast, as compared with β2-agonists, provided significant protection against severe broncho-constriction. Parameters strongly confirmed the role of leukotriene receptor antagonist when in addition added with β2-agonists.

KEYWORDS: Leukotriene receptor antagonist, acute asthma, β2-agonists.

INTRODUCTION:

Asthma is a chronic reactive airway disorder causing episodic airway obstruction that results from broncho spasms[1], increased mucus secretion, and mucosal edema[2]. It is a type of chronic obstructive pulmonary disease (COPD), a long-term pulmonary disease characterized by increased airflow resistance; other types of COPD include chronic bronchitis[1] and emphysema.

Although asthma strikes at any age, about 50% of patients are younger than age 10, twice as many boys as girls are affected in this age group. One-third of patients develops asthma between ages 10 and 30, and the incidence is the same in both sexes in this age group. Moreover, approximately one-third of all patients share the disease with at least one immediate family member [3].

Asthma is thought to be caused by a combination of genetic and environmental factors. [4] Environmental factors include exposure to air pollution and allergens. [2] Other potential triggers include medications such as aspirin and beta blockers.[2] Diagnosis is usually based on the pattern of symptoms, response to therapy over time, and spirometry. [5] Asthma is classified according to the frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate. [6] It may also be classified as atopic or non-atopic where atopy refers to a predisposition toward developing a type 1 hypersensitivity reaction. [7][8]

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Current clinical practice guidelines from the National Heart, Lung, and Blood Institute and the Global Initiative for Asthma recommend the use of anti-inflammatory controller therapy for the long-term treatment of persistent asthma. [8,19]

Short-Acting β2 Agonists (SABA) given can prevent acute asthma for up to 4 hours,[4] but this bronchoprotective effect has been observed to significantly decrease after 1 week of regular use[5] are recommended and are used widely as first-line controller agents with leukotriene-modifying agents being recommended as alternative or add-on therapies.[17,18]

The long-acting β2 agonists (LABA) formoterol and salmeterol both will inhibit asthma attack for up to 12 hours, but formoterol is more rapidly effective.[4] However, regular use of long-acting inhaled β2 agonists has resulted in tachyphylaxis,[5] as evidenced by diminished bronchoprotection by 6 to 9 hours.[6]

Studies have reported variable results when comparing montelukast with SABA in improving lung function end points such as peak flow and forced expiratory volume in 1 second (FEV1)[7]

Leukotriene receptor antagonists (LTRAs) have been suggested both as suitable monotherapy and add-on therapy to inhaled corticosteroids (ICS) for the treatment of asthma[9]. The cysteinylleukotrienes (LTC4/D4/E4) induce bronchoconstriction, mucus hypersecretion, mucosal edema, enhance airway hyperreactivity, and act as chemoattractants for eosinophils in the airway[10]. Therefore, it is not surprising that LTRAs improve lung function, attenuate bronchial hyper-responsiveness, and reduce the number of exacerbations in patients with mild to moderate asthma[11]. Moreover, addition of LTRAs to LABA results in better control of asthma and can decrease the requirement for LABA. Effects of LTRAs on inflammatory markers are less certain. Treatment with LTRA montelukast has resulted in a significant decrease in serum eosinophil cationic protein and both sputum[12] and peripheral blood eosinophils[13]. Oral leukotrine receptor antagonists increase the control over the disease in both children and adults and can reduce the severity of the asthma. Acute asthma is a common medical emergency that is often poorly managed despite well defined recommendations for its assessment and treatment. However, the effect of the leukotriene receptor antagonists in the treatment of acute attack of asthma is still unknown. The question now is exactly how effective is the leukotriene antagonist (Montelukast), when compared with the other conventional therapy in the treatment of the acute asthma. This study helps us to know the effect of oral leukotriene receptor antagonist in the treatment of acute asthma in comparison with the other therapy.

MATERIALS AND METHODS:

The study was conducted after getting approval from the Institutional Ethical Committee, School of Pharmaceutical Sciences, and Vels University. Patient who are diagnosed with acute asthma based on international guidelines were included in the study. A total number of 100 patients were enrolled in the study after obtaining informed consent. The study has two arms, the group A and the group B. The study was conducted over a period of 7 months. Prospective data was collected from the patients. Together with the data symptomatic changes and variation in PFT, PR, RR were also noted.

The group A treated with Salbutamol alone and the group B with Salbutamol along with montelukast for a period of 30days.The effect of drug was studied by two methods (i) Observational analysis (Symptomatic change) and (ii) Laboratory parameters (FEV1, PR, RR). The data were collected, compiled, analysed with statistical tools (SPSS – Microsoft Version 6). Paired sample T test was be used for comparison of qualitative output response. Student t – test will be used for comparison of numeric output response. Statistical significance will be taken at $p< 0.05$.(* = significant, ** = Moderately significant, *** = Highly significant).

Table 1: NICE criteria for Acute Asthma

Children aged 2–5 years	Children older than 5 years	Adults
• Heart rate ≤140/minute • Respiratory rate ≤40/minute	• Able to talk • Heart rate ≤125/minute • Respiratory rate ≤30/minute	• Heart rate ≤125/minute • Respiratory rate ≤30/minute

Table 2: GOLD Spirometric Criteria for COPD Severity

I. Mild COPD	FEV1/FVC < 0.7 FEV1 >/= 80% predicted	At this stage, the patient is probably unaware that lung function is starting to decline
II. Moderate COPD	FEV1/FVC < 0.7 50% </= FEV1 < 80% predicted	Symptoms during this stage progress, with shortness of breath developing upon exertion.
III. Severe COPD	FEV1/FVC < 0.7 30% </= FEV1 < 50% predicted	Shortness of breath becomes worse at this stage and COPD exacerbations are common.
IV. Very Severe COPD	FEV1/FVC < 0.7 FEV1 < 30% predicted or FEV1 < 50% predicted with chronic respiratory failure	Quality of life at this stage is gravely impaired. COPD exacerbations can be life threatening.

RESULTS:

In the study population ,In Group A 9 patients and Group B 8 patients were in between 5 to 15 years ; 13 from Group A and 16 from Group B were among 16 to 30 years ;18 from group A and 17 from Group B were among 30 to 45 years and 10 patients in Group A and 9 patients in Group B were in the age group above 45 years. The results showed a maximum study population in the age group of 30 to 45 years. (Table 3)

Table 3: Age Distribution of The Study Population

Range	No. of patients		%	
	Group A (n=50)	Group B (n=50)	Group A	Group B
5 to 15 years	9	8	18	16
16to 30 years	13	16	26	32
30 to 45years	18	17	36	34
above 45years	10	9	20	18

Among the study population females were more in both group A 58% and group B 60 % (Table 4)

Table 4: Gender Distribution of Study Population

Gender	No.of patients		%	
	Group A (n=50)	Group B (n=50)	Group A (n=50)	Group B (n=50)
Male	21	20	42	40
Female	29	30	58	60

It was alsofound that 42 % in Group A and 44 % in Group B were with allergy. (Table 5)

Table 5: Allergic Condition

Allergic condition	No. of patients		%	
	Group A (n=50)	Group B (n=50)	Group A	Group B
With allergy	21	22	42	44
Without allergy	29	28	58	56

The Table 6 shows the different types of allergens and most patients are affected due to smoke allergy in both Group A and Group B

TABLE 6: TYPES OF ALLERGENS

Allergens	No.of patients		%	
	Group A (n=21)	Group B (n=22)	Group A	Group B
dust	7	6	33.3	27.2
smoke	9	10	42.8	45.4
weather	5	6	23.8	27.2

The status of Crepts sound before and after treatment between the group A and group B were compared and the number of patients in group B shows improvement. (Table 7)

TABLE 7: EFFECT OF TREATMENT ON CREPTS SOUND

Sound	Before Treatment		After Treatment	
	Group A (n=50)	Group B (n=50)	Group A (n=50)	Group B (n=50)
Crepts	37	39	26	11
Non Crepts	13	11	24	39

In comparison of force expiratory volume % (FEV1 PRED) between the group A and group B, after 24 hours significant change was noticed in group B. The results were significant after 24 hour of the treatment. The results of forced expiratory volume/forced vital capacity (FEV1/FVC%) shows a significant difference after 24 hours of the treatment with salbutamol in group A and salbutamol plus leukotriene receptor antagonist (Montelukast) from the baseline measurement. Similarly, FEV1% PRED was highly significant in group B patients of acute asthma after 04 week of therapy. Comparison of forced expiratory volume/forced vital capacity (FEV1/FVC) showed clinically important results. In group B patients of acute asthma, after 24 hours the result was significantly observed, But, after 48 hours, there was no significant difference noticed in both groups. After 72 hours, again an improvement was notice in group B patients of acute asthma with a significant p value (Table 8).

Table 8: Changes in Spirometric Parameters Over Time

Time Period	Forced expiratory volume (FEV1)			Forced expiratory volume % (FEV1 %)			Forced expiratory volume / Forced Vital Capacity		
	Group A (Mean ±SD)	Group B (Mean ±SD)	P = value	Group A (Mean ±SD)	Group B (Mean ±SD)	P = value	Group A (Mean ±SD)	Group B (Mean ±SD)	P = value
Baseline characters	1.55 ±0.35	1.71±0.45	0.62	66.47 ± 5.08	65.30 ± 4.81	0.83	62.0 ± 5.62	64.3 ± 4.11	0.72
After 24 hours	1.89 ±0.23	2.01±0.29	0.05*	66.43± 5.02	66.45 ± 4.68	0.07	69.0 ± 5.24	69.7± 4.32	0.05*
After 48 hours	2.21±0.21	2.31±0.34	0.06	67.44 ±4.78	67.46± 4.55	0.07	72.3 ±5.21	73.22±4.76	0.06
After 72 hours	2.66± 0.45	2.91± 0.56	0.04	67.56 ± 4.55	69.06 ± 4.44	0.05*	76.53 ±4.34	77.32± 4.22	0.05*
After 1 week	2.89±0.28	3.25±0.35	0.001*	67.56 ± 4.55	72.56 ± 4.02	0.001**	79.92±4.12	84.02± 4.33	0.001*
After 2 week	3.08±0.33	4.24±0.37	0.0001**	69.06 ± 4.81	73.64 ± 3.87	0.05*	81.02±4.22	87.02±4.12	0.05*
After 4 week	3.79±0.32	4.51±0.39	0.0001**	72.64 ± 3.77	89.64 ± 1.57	0.0001***	85.62±2.87	89.96±1.97	0.0001*

* = significant, ** = Moderately significant, *** = Highly significant

Base line asthma score shows p value (p = 0.58). But after 48 hours, significant change was noticed in both groups (Table 9). p value was significant (p = 0.05). In group B, asthma score was significantly improved with passage of time.

TABLE 9: EFFECT OF TREATMENT ON ASTHMA SCORES

Time Period	Group A (Mean± SD)	Group B (Mean± SD)	P = value
Base line character	13.54 ± 2.74	13.36 ± 2.58	0.58
After 48 hour	14.56 ± 2.60	14.75±2.60	0.05
After 1 week	14.75 ± 2.59	17.6± 2.50	0.001 *
After 4 week	17.9 ± 2.53	22.38 ± 1.60	<0.0001 **

* = significant, ** = Moderately significant, *** = Highly significant

Comparison of pulse rate (beats/minute) was observed. At the time of base line measurements, tachycardia was found and base line heart rate was (121.36 ±5.45 beats/minute) in group A and (122.21 ±5.62 beats/minute) in group B. In the first 24 hours mild improvement were observed in heart rate as compare to base line measurement but between the groups there was no significant change was noticed. The p value was observed (p = 0.08). In comparison of pulse rate between group A and group B after 4 weeks was done which showed high significance (p=0.0001).(Table 9)

TABLE 9: CHANGES IN RESPIRATORY RATE, PULSE RATE

Time Period	Respiratory rate (breaths per minute)			Pulse rate (beats per minute)		
	Group A (mean± SD)	Group B (mean± SD)	P = value	Group A (mean± SD)	Group B (mean± SD)	P = value
Baseline characters	31.71 ±5.34	31.12 ±4.12	0.58	121.36 ±5.45	122.21 ±5.62	0.46
After 24 hours	25.27 ±3.41	26.16 ±3.21	0.05*	106.35 ±2.53	114.31 ±4.51	0.08
After 48 hours	23.73 ±2.19	22.61 ±2.44	0.05*	94.55 ±1.63	97.22 ±1.59	0.06
After 72 hours	20.75 ±1.55	19.75 ±2.11	0.001**	91.21 ±1.43	90.37 ±2.13	0.05*
After 1 week	19.85 ±1.12	16.24 ±1.32	0.001**	89.24 ±1.16	86.51 ±1.08	0.001**
After 2 week	18.89 ±1.01	15.43 ±1.12	0.001**	88.19 ±1.43	82.21 ±1.12	0.001**
After 4 week	17.22 ±1.57	14.01 ±1.02	0.0001***	85.76 ±1.11	78.21 ±1.01	0.0001***

* = significant, ** = Moderately significant, *** = Highly significant

DISCUSSION:

In this study the comparison of force expiratory volume % (FEV1 PRED) between the group A and group B, after 24 hours significant change was noticed in group B and FEV1% PRED was highly significant in group B patients of acute asthma after 04 week of therapy which is similar to that reported Syed hyderrazanaqvi et al, Carlos A. Camargo et al.

An interesting feature of most clinical studies is that some patients appear to show better responses than others (Malmstrom, K., et al), suggesting that leukotrienes may play a more important role in some patients. This highlights the importance of individualizing treatment to suit the patient, and ensuring that management guidelines are flexible to allow this.

Our study results and all the parameters that were observed strongly confirmed the role of leukotriene receptor antagonist when in addition added with β2-agonists therapy in the treatment of acute asthma, there were a smooth improvement was noticed. This study also confirmed previous observations from previous trials, that leukotriene receptor antagonists provide additional clinical benefit to patients using constant doses of inhaled corticosteroids but with incomplete asthma control (Altman *et al*., 1998).

CONCLUSION:

The data reviewed here shows that acute asthma shall be treated with leukotriene-modifier drugs alone, and they provide reason to believe that the addition of a leukotriene modifier to a multifaceted asthma-treatment program will have a salutary effect. In patients with acute asthma, leukotriene-modifier therapy can be combined with β2-agonists to maintain and control of asthma with lower doses of β2-agonists, or it can be added to an existing regimen to achieve better control of asthma. Once-daily treatment with 10 mg of montelukast, as compared with β2-agonists, provided significant protection against severe broncho-constriction. The above mentioned parameters strongly confirmed the role of leukotriene receptor antagonist when in addition added with β2-agonists therapy in the treatment of acute asthma, there were a smooth improvement.

CONFLICTS OF INTERESTS:

All authors have none to declare

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