VOLUME-7, ISSUE-1, JANUARY-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

Physiology

A COMPARATIVE STUDY ON ORAL MONTELUKAST VERSUS INHALED LOW DOSE BUDESONIDE IN ADULT MILD PERSISTENT ASTHMA PATIENTS.

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ABSTRACT Management of asthma by inhaled corticosteroids (ICS) is prevalent and quite effective. But there exists some apprehension among patients regarding use of steroid inhaler. Till date most of the studies which have compared oral montelukast against ICS, has worked on the paediatric age group. In the present study we intend to compare these two agents in adults (age>14 years), having mild persistent asthma. A total 60 patients in a tertiary care hospital were enrolled and divided into two equal groups, Group-A to receive single dose oral Montelukast (10 mg/day) and Group-B inhaled Budesonide (400 µg DPI /day) as twice daily inhalation with turbuhaler. The study period of 06 weeks have 03 obligatory visits to judge the patients – symptomatically by Asthma Control Questionnaire (ACQ), spirometry, peripheral blood absolute eosinophil count (AEC) and induced sputum eosinophil count (SEC). Statistical analysis used by SPSS version 20. The groups were statistically comparable. Patients of both groups have improved gradually. Intergroup comparison shows no significant difference regarding improvement of Spirometric parameters (p> 0.05), ACQ score (p=0.7332), AEC comparison (p=0.1126) but SEC shows significantly (p=0.0117) more reduction in the montelukast group. Montelukast may be considered a valid alternative as orally administered, non-steroidal, singe agent in treatment of mild persistent asthma in adults, but Budesonide is more efficacious in sputum eosinophil count reduction.

KEYWORDS : asthma treatment, mild persistent asthma, montelukast, inhaled budesonide.

Introduction:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning [1]. The characteristic symptoms of asthma are wheezing, dyspnoea, and coughing which are variable. Simple spirometry confirms airflow limitation with a reduced FEV_1, FEV_1/FVC ratio, and PEFR. Asthma is classified as Intermittent and Persistent. Persistent asthma is again divided into mild, moderate and severe [2]**.** Many cells play a role in Asthma, in particular, lymphocyte, eosinophils, mast cells, macrophages, neutrophils and epithelial cells [3]**.** Eosinophils and their products are known to play an important role in asthma, and the measurements of blood and sputum level of such markers of inflammation may provide information reflecting the evolution and control of disease [4]. A consistent finding of asthmatic airways is the presence of increased numbers of activated eosinophils or their release products which correlate broadly with the severity of disease as reflected in symptoms, bronchial hyper-reactivity and lung function [1].

This study compared adult patients (age >14 years) diagnosed as mild persistent asthma (MPA) and treated with single dose oral Montelukast (10 mg/day) vis-à-vis inhaled low dose Budesonide (400µg/day) as dry powder inhaler (DPI) with turbuhaler, by - clinical improvement, lung function, peripheral blood absolute eosinophil count (AEC) and sputum eosinophil count (SEC); in R. G. Kar Medical College, Kolkata. Till date most of the studies have compared these two treatment options among the paediatric age group. Moreover this study also attempted to take a demographic account of adult MPA patients who have attended during the study period.

Materials and Methods:

An observational, cross sectional study on asthma was done in R.G.Kar Medical College, a tertiary care hospital in Kolkata involving the departments of Respiratory Medicine and Physiology. It was approved by the "Institutional Ethical Committee". Asthma symptomatic patients of both gender, aged above 14 years, having clinical symptoms of asthma for more than 01 year, reported asthmatic attacks in < 1/day, >1/week or >2/month and whose FEV1>80% of predicted – thus satisfying the criteria of Mild Persistent Asthma (MPA) [2]; were recruited consecutively from the Respiratory Medicine Out Patient Department during a period of one year.

After initial evaluation, 24 patients among the total 84 recruited cases were excluded from study having any of the following - suffering from other respiratory or cardiac diseases like – uncontrolled hypertension, valvular heart disease, cardiomyopathy, recent myocardial infarction, ischaemic heart disease, active tuberculosis, post tubercular fibrosis, bronchiectasis, interstitial lung disease, recent history of pneumonia etc. Patients who are currently using corticosteroids or long acting beta agonists, pregnant, lactating mother, known mental illness, unwilling to consent and hypersensitive to medications were also excluded.

Thus, total 60 patients were finally enrolled after exclusion. They were then divided into two equal groups based on serial numbers in even or odd sequence, Group-A with 30 patients to receive single oral Montelukast (10 mg/day) and Group-B with 30 patients inhaled dry powder inhaler (DPI) Budesonide (400 µg /day) as twice daily inhalation with turbuhaler.

After recruitment the patients enter a wash-out period of 48 hours, during which only rescue Salbutamol inhalation was allowed. Then they are placed in the study period of 06 weeks which include 03 obligatory visits at – initial "0 day", mid study "21st.day" and concluding "42nd.day". In these 03 visits the patients were judged – (1) symptomatically by Asthma Control Questionnaire (ACQ), scores range from 0–6 (higher is worse) [5]. A score of 0.0–0.75 is classified as well-controlled asthma, (2) spirometry with reversibility testing with inhaled Salbutamol 200 µgm, (3) peripheral blood absolute Eosinophil count (AEC), (4) induced sputum Eosinophil count (SEC).

Lung function test was conducted by Helios computer mounted Spirometer Model No. 702 of the Recorders and Medicare system. Three consecutive tests were taken and the best result was accepted. After baseline spirometry, reversibility testing was done

by giving 200*µgm* Salbutamol from pressurised metered dose inhaler (pMDI) and measurements repeated after 15 minutes.

For AEC 2ml.of peripheral venous blood was drawn by phlebotomy with aseptic precautions, Eosinophil counting was done under compound microscope in an improved Neubaur's Chamber in the Physiology Department.

For sputum induction patients were pre treated with inhaled salbutamol 200 *µgm* by pMDI and 10 minutes later nebulised with hypertonic saline (3%) solution for 05 minutes by an air-driven nebulizer and expectorated sputum was collected. After initial procedure with the sputum, smears were prepared, fixed with 95% ethyl alcohol and stained with Haematoxylin-Eosin (H&E) and examined in the Physiology Department.

Objectives of this study were. To compare efficacy of oral Montelukast versus inhaled Budesonide in adult patients of mild persistent asthma and correlate the clinical improvement, lung function, blood and sputum eosinophil count during treatment. To assess the demographic parameter in respect of asthma in the sub-population of North Kolkata and North 24-PGS district of West Bengal, who are attending R. G. Kar Medical College, Respiratory Medicine OPD.

Statistical analysis was done by SPSS version 20. Appropriate analysis of results was done by Chi square test, unpaired t- test for intergroup comparison.

Results:

This study comprises of 60 adult (age > 14yr.) mild persistent asthma patients who were divided into two groups, each comprising of 30 patients. Group-A patients received 10mg Montelukast orally daily and Group-B patients inhaled 400µg Budesonide daily by DPI. Clinical examination including Asthma Control Questionnaire (ACQ), spirometry, blood and sputum eosinophil count was done in 1st. 3rd and 6th week. Following results emerge after tabulation -

Table 1: showing the basic characteristics of the patients in two groups.

Parameter	Group-A Mean ± SD	Group-B Mean ± SD	p value
Age(years)	41.03±16.23	41.4±17.23	0.9326
Sex	**Male-** 53.33% **Female-** 46.67%	**Male-** 56.67% **Female-** 43.33%	—
Height(cm)	155.87±7.71	157.8±9.04	0.3765
Weight(kg)	52.27±13.99	52.83±14.28	0.8771
BMI(kg/m^2)	21.32±4.39	21.11±4.83	0.7287
Smoking	1.4±0.4982	1.37±0.49	0.7948
F/H of Asthma	1.43±0.504	1.47±0.5074	0.7994
H/O allergy	1.63±0.4901	1.57±0.5040	0.6055
Levels of asthma control	2.7±0.466	2.73±0.449	0.779

So, both the groups (A and B) are matched (p>0.05) regarding different parameters.

Table 2: Comparison of clinico-physiological characteristics of Group-A & Group-B patients.

Parameter	Group-A Mean ±SD	Group-B Mean ±SD	p-value
FVC PP	85.97±10.34	87.133±8.97	0.6424
FEV_1PP	67.07±7.26	68.27±6.36	0.4986
FEV_1/FVC PP	78.07±2.85	78.2±3.07	0.8624
PEFRPP	48.7±21.58	53.13±16.72	0.3774
FEF_{25-75} PP	38.46±19.64	36.4±11.56	0.6212
AEC	448.33±67.89	452.5±88.17	0.8382
SEC	8.47±2.27	8.47±1.94	1
ACQ score	2.7±0.47	2.73±0.45	0.7790

Here, the groups are matched (p>0.05) in terms of - levels of asthma control, h/o allergy, h/o smoking, family h/o asthma etc.

Table 3: comparison of parameters of initial (1st.week) and concluding (6th.week) visit of Group-A (oral Montelukast) patients.

Parameter	1st visit Mean ±SD	3rdvisit Mean ±SD	P value
FVC PP	85.97±10.34	98.93±12.90	0.0001
FEV_1PP	67.07±7.26	90±15.38	0.000
FEV_1/FVC PP	78.07±2.85	90.47±7.62	0.001
PEFR PP	48.7±21.58	70.53±20.27	0.000
FEF_{25-75} PP	38.46±19.64	63.07±23.14	0.000
AEC	448.33±67.89	326.67±51.67	0.000
SEC (%)	8.47±2.27	2.97±0.85	0.0001
ACQ score	2.7±0.47	1.33±0.35	0.000

It has been observed that in the patients of Group-A, after 6 weeks all parameters was improved from its baseline value.

Table 4: comparison of parameters of initial (1st.week) and concluding (6th.week) visit of Group-B patients (inhaled Budesonide).

Parameter	1st visit Mean ±SD	3rdvisit Mean ±SD	P value
FVC PP	87.133±8.97	104.73±8.87	0.0001
FEV_1PP	68.27±6.36	92.23±14.98	0.000
FEV_1/FVC PP	78.2±3.08	87.53±8.60	0.001
PEFR PP	53.13±16.72	74.73±23.61	0.000
FEF_{25-75} PP	36.4±11.56	65.37±23.61	0.000
AEC	452.5±88.17	348.33±52.50	0.000
SEC (%)	8.47±1.94	3.5±0.73	0.000
ACQ score	2.73±0.45	1.66±0.38	0.0001

In Group-B patients also, after 6 week all parameters was significantly (p<0.05) improved from baseline value.

Table 5: comparison of parameters of the final (6th.week) visit of Group-A (oral Montelukast) & Group-B (inhaled Budesonide) patients.

Parameter	Group-A 3rd visit (Mean ±SD)	Group-B 3rdvisit (Mean ±SD)	P value
FVC PP	98.93±12.90	104.73±8.87	**0.0470**
FEV_1PP	90±15.38	92.23±14.98	0.5710
FEV_1/FVC PP	90.47±7.62	87.53±8.6	0.1675
PEFR PP	70.53±20.27	74.73±23.61	0.4628
FEF_{25-75} PP	63.07±23.14	65.37±23.61	0.7046
AEC	326.67±51.67	348.33±52.50	0.1126
SEC (%)	2.97±0.85	3.5±0.73	**0.0117**
ACQ score	1.33±0.35	1.66±0.38	0.7332

The inter group comparison is showing that both Montelukast and Budesonide are equally effective in improving spirometric parameters and clinical level of asthma control in mild persistent asthma. However, inhaled budesonide appears more effective in controlling airway inflammation as evident by statistically significant reduction of SEC in comparison to Montelukast.

Discussion:

The different established guidelines including – GINA, National Asthma Education and Prevention Programme (NAEPP) and BTS recommends low-dose ICS, LTRA (leukotriens receptor antagonist), Cromolyn in the management of mild persistent asthma (MPA) [1, 2, 6]. Among these options this study compared between oral montelukast versus inhaled budesonide. Both the groups of present study are statistically comparable (Table-1) and have improved gradually in the study period (Table- 3, 4).

The oral montelukast group (Group-A, Table-3) showed following improvements between 1st. and final (3rd.) visits – (a) significant spirometric improvement: FEV1 (p=0.000), FEV1/FVC (p< 0.001), FVC (p< 0.001), PEFR (p=0.000). (b) Significant reduction of eosinophil counts: AEC (p=0.000), SEC (p=0.000). (c) Significant improvement of ACQ score (p= 0.000).

Previous studies by Theodore F.et al observed significant increase of FEV1 (p<0.001), PEFR, asthma exacerbation control days and peripheral AEC (p<0.001) compared to placebo [7]. Kenji M.et al found decreased SEC from baseline 24.6 ±12.3% to 15.1 ±11.8% and AEC decreased to 314 ±236.6 in comparison to placebo (423.1±232.2/ml; p<0.005) after montelukast treatment [8]. Goutam G.et al conducted a 4 week study on oral montelukast monotherapy and found significant improvement (p<0.001) of PEFR and FEV1/FVC [9]. Abadoglu O. et al showed that oral montelukast decreased significantly the ratio of SEC (p=0.02) [10].

The inhaled budesonide group (Group-B, Table-4) also show following improvements between 1st. and final (3rd.) visit – (a) significant spirometric improvement: FEV1 (p=0.000), FEV1/FVC (p= 0.001), FVC (p= 0.0001), PEFR (p=0.000). (b) Significant reduction of eosinophil counts: AEC (p=0.000), SEC (p=0.000). (c) Significant improvement of ACQ score (p=0.0001).

Previous studies by D.Peroni et al. found budesonide prevents fall of FEV1 and SEC in asthmatic children [11]. Gibson P.G. et al found SEC significantly reduced after budesonide use (25%, 4.5) compared with placebo (37%, 6.2; p<0.05) and 2.2 fold (95%Cl 1.45 to 3.33) improvement in airway responsiveness [12].

Intergroup comparison between oral montelukast and inhaled budesonide (Table-5) shows the following – (a) Spirometric parameters (FEV1, FEV1/FVC, PEFR etc.) show no significant difference (p> 0.05). (b) Improvement of ACQ score also show insignificant difference (p=0.7332), (c) Eosinophil counts: AEC comparison shows insignificant (p=0.1126) but SEC shows significantly (p=0.0117) more reduction in the montelukast group.

Some studies with montelukast and budesonide showed similar results. Stelmach et al. found no significant difference between them in respect of use of rescue medications and attack frequency [13]. Kumar V.et al also observed no difference in the need for rescue drugs with groups of montelukast and ICS [14]. William Busse et al. observed comparable betterment of daytime symptom scores in both montelukast and ICS groups [15]. Kooi EM et al. also found similar comparable response among these two drugs, concerning "rescue medication free days" [16]. Vikram Kumar et al. from AIIMS in 2007 found that montelukast and ICS has similar effectivity in improving PEFR and FEV1. They concluded as montelukast is as effective as budesonide in 5 to 15 year aged children having M.P Asthma.[17] A recent study by N.Raghava, A.Dubey et al (2017) comprising efficiency of inhaled Budesonide vs. oral Montelukast, has reported Montelukast as significantly better in reducing AEC. But in our study, the level of AEC reduction among the two groups are statistically insignificant (p= 0.1126), while regarding SEC reduction, Budesonide group has scored over Montelukast group with statistical significance (p=0.0117) [18].

With this present study on adult patients we like to conclude that - montelukast may be considered a valid alternative orally administered, non-steroidal, singe agent in treatment of mild persistent asthma in adults. Both for clinical and functional benefits, but Budesonide is more efficacious on sputum eosinophil count reduction in adult patients. Moreover lung function, blood and sputum eosinophil count which are known as important indicators of Asthma assessment, can be used to judge response to treatment as well.

A prospective follow up of these asthma patients regarding adherence to treatment, to quantitate their usage of rescue medication and accounting asthmatic attacks may be the future scope for this study. Main limitations of our study are – small sample size, un-blinded and non-placebo controlled design. We recommend much longer period, prospective, multicentric studies for circumventing these limitations.

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