Original Research Article **Pharmacology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

A COMPARATIVE STUDY TO ASSESS THE EFFICACY AND SAFETY OF MOMETASONE / FORMOTEROL AND BUDESONIDE/ FORMOTEROL AS COMBINATION THERAPY IN MODERATE BRONCHIAL ASTHMA PATIENTS – A PROSPECTIVE, OPEN LABEL COMPARATIVE STUDY

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ABSTRACT

Fixed dose combination of an inhalational long acting beta-2 agonist with corticosteroids provide better asthma control as they modify the pathophysiology of bronchial asthma, i.e. smooth muscle dysfunction and airway inflammation. Moreover, it minimizes systemic side effects and improves patient adherence rather than administering as monotherapy. This 12 week prospective comparative study was conducted to evaluate the efficacy and safety of mometasone / formoterol with budesonide / formoterol as combination therapy in 200 moderate bronchial asthma patients.. Group I patients received mometasone 400µg / formoterol 6µg and group II received budesonide 400 µg/ formoterol 6 µg for a period of 12 weeks. Forced expiratory volume in one second and asthma symptom score were used as outcome parameters.The FEV1 values and the symptom scoring were found to be improved in both the groups with mometasone group have shown a better improvement than the budesonide group and was statistically significant. The adverse reactions were mild and treated symptomatically.To conclude,the present study emphasized that inhalational mometasone combination is slightly superior to budesonide combination.

KEYWORDS: **mometasone, budesonide, bronchial asthma, forced expiratory volume, asthma symptom score.**

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INTRODUCTION

Bronchial asthma, a chronic reactive airway disease characterised by recurrent episodes of wheezing, cough and breathlessness with reversible bronchoconstriction and remodelling of the bronchial mucosa.[1] It affects all the ages but usually starts in the early childhood. The estimated prevalence is about 20 million in India when compared to 300 million worldwide.[2] Inadequate control of the disease leads to asthma exacerbations would make the patients in utilizing expensive medical resources, leading on to economic burden.[3,4] Recent data reveals that poor quality of life with the economic burden of individuals are responsible for poor compliance.[5,6] The major goal of treatment is to provide symptom free periods, minimizing the asthma exacerbation with minimal adverse effects.[7, 8] In the management of mild to moderate asthma, a combination of an inhaled long-acting β_2-agonist (LABA) and an inhaled corticosteroid (ICS) will be the mainstay according to Global initiative for Asthma (GINA) guidelines. These combinations improve the patient adherence and produce synergistic interaction [9,10,11,12] Formoterol furoate is a long- acting specific β_2-adrenergic receptor agonist. It stimulates intracellular adenylcyclase thereby increases cAMP levels, causing relaxation of bronchial smooth muscles. Hence, inhibition of mast cells occurs which releases of mediators responsible for Type I hypersensitivity reaction.[13] Mometasone furoate is a potent anti-inflammatory corticosteroid. Mometasone furoate has high receptor affinity when compared to fluticasone and budesonide.[14, 15, 16] The effect of budesonide as ICS is also documented.[8] The inhalational corticosteroid act on the glucocorticoid receptor to inhibit the release of cytokines and inflammatory mediators which would lead on to decrease in eosinophil and mast cell recruitment and it thereby suppresses the adhesion molecule function and induces nitric oxide synthase [9]. These cellular effects would causes significant improvements in the pulmonary functions and the symptoms of asthma which would help in the reductions of exacerbations of acute severe asthma. [10] The combination of inhaled LABA and corticosteroid provides a synergistic role than monotherapy, which are available as Metered dose inhaler [MDI] and Dry Powder Inhaler [DPI]. Combinations like formoterol furoate & fluticasone propionate, formoterol furoate & budesonide, formoterol furoate & ciclesonide and salmeterol & fluticasone are widely used. Inhalational steroids have a lower potential to produce systemic side effects. But suppression of hypothalamic – pituitary- adrenal (HPA) axis occurs only on long term treatment[17]. There are few theoretical advantages of adding mometasone over budesonide which will be combined with LABA. Many studies were conducted in western countries to compare the efficacy and safety of inhalational corticosteroids along with a beta agonist but only few reports obtained in Indian population. The data related to the efficacy and safety of the combination of mometasone/formoterol and budesonide/formoterol in the management of bronchial asthma is minimal, hence we planned for this study. The aim of the study was to compare the efficacy and safety of mometasone (400µg)/ formoterol (6µg) with budesonide (400µg)/formoterol (6µg) as combination therapy in moderate bronchial asthma patients.

MATERIALS AND METHODS

A prospective comparative study was conducted in moderate bronchial asthma patients for a period of 6 months between June 2015 and Dec 2015 at two different tertiary care centres in Salem. The study was performed after getting an approval from Institutional Ethics Committee.(No-VMKVMC/IEC/14/40) The severity and grading of asthma was done based on GINA guidelines and Pulmonary Function Test (PFT) criteria. Patients of either sex, aged 18-65 years with demonstrable Forced Expiratory Volume in one second (FEV1) of 60-85% of predicted normal values at screening and baseline were included in the study. Those patients with severe life threatening bronchial asthma / Chronic obstructive pulmonary disease, patients requiring nebulised therapy or oral corticosteroids and patients with a clinically proven respiratory tract infection were excluded from the study. During the screening visit, eligible patients were selected and enrolled in the study. Baseline evaluations were performed for all the patients prior to give the first dose of the study drug. In addition, patients were explained about all the aspects of the study procedure, including the study visit schedule, methods to use inhalational therapy with rotahaler and pulmonary function tests. Written Informed consent was obtained from all the patients who had undergone the trial. About 200 patients were selected and divided into 2 groups. Group I received formost [mometasone 400µg and formoterol 6µg, Dry powder inhalation (DPI), twice daily] and group II received formonide respicaps [budesonide 400µg and formoterol 6µg, DPI, twice daily]. Both the drugs were given in a fixed dose combination and they were administered through rotahaler. If asthma symptoms were not controlled an inhaled, short-acting beta-2 agonist salbutamol was utilized as rescue medication. For patients who did not respond adequately to the starting dosage of even after 2 weeks of therapy, higher doses of steroid were given to provide additional improvement in asthma control and they were excluded from the study. The efficacy and safety of the study drug combination were assessed periodically through monitoring the primary and secondary efficacy variables throughout the study period.

Efficacy assessment

The efficacy assessment was done by using pulmonary function tests (serial spirometry readings) and 4-point scale.

Primary efficacy variable

The primary efficacy variable was assessed by measuring the Forced expiratory volume in 1 second (FEV1) by using Spirometer. Spirometry reading was measured at baseline, at the end of 4th week and at the end of 12th week.

Secondary efficacy variables

The secondary efficacy variables were measured by using the day-time and the night-time asthma symptom scores. The symptoms of asthma are cough, wheeze,

chest tightness and shortness of breath. The degree of improvement in the day-time and night-time symptoms was graded by using a 4 point scale.

0- no symptoms
1- Symptoms, but not affecting any activities during the day/ sleep at night
2- Symptoms affecting at least one activity during or disturbing sleep
3- Symptoms affecting ≥2 activities or disturbing sleep all night or most of the night. Asthma symptom scoring was done at baseline, at 4th week and at the end of the study.

Safety assessments

Safety assessments were made at the end of each visit and adverse reactions were noted regularly. Clinically significant changes in symptoms, abnormal laboratory results and hypersensitivity reactions were considered to be an adverse effect.

Statistical methods

Data were entered and tabulated. Statistical analysis was done by using latest version of SPSS software. Results were analysed by using Chi-square test, Student's t-test and Analysis of covariance. Demographic data of the study population, asthma symptom score and adverse drug reactions were analysed by Chi-square test. Other variable like FEV1 (%predicted value) was analyzed in terms of percentage change from baseline to 4th week and 12th week by using Student's t-test and Analysis of Co variance. A p value of <0.05 was considered as statistically significant.

RESULTS

A total of 200 patients were enrolled, out of which 184 patients participated throughout the study with 16 were lost to follow up as they experienced worsening of symptoms. Among the dropouts 6 belong to group I and 10 belong to Group II, thereby we had 94 patients in group I and 90 patients in group II. Group I patients were given mometasone and formoterol and group II with budesonide and formoterol.

Baseline demographics

Table 1
Age and sex wise distribution of the study population

Age group	Group I (n=94)		Group II (n=90)		P value
	Male	Female	Male	Female	
20 – 30	9 (17.6%)	7 (16.2%)	8 (16.3%)	6 (14.6%)	
31 – 40	11 (21.5%)	13 (30.2%)	12 (24.4%)	13 (31.7%)	
41 – 50	10 (19.6%)	7 (16.2%)	9 (18.3%)	7 (17%)	
51 – 60	13 (25.4%)	7(16.2%)	9 (18.3%)	12 (29.2%)	0.785
>60	8 (15.6%)	9 (20.9%)	11 (22.4%)	3 (7.3%)	
Total	51 (100%)	43 (100%)	49 (100%)	41 (100%)	
Mean age	42.5±3.6		39.8±4.2		

P value derived by applying chi-square test

The age and sex distribution of the study population was shown in table 1 with males and females were almost equal in number in both groups. Majority of the patients were in the age group of 30 – 50 years in both the groups, with a mean age being 42.5 years in group I and 39.8 years in group II. There were no statistical significant difference in age and sex distribution in both treatment groups (p=0.785). The mean weight, height and BMI of both the groups did not show any statistical significant difference. The mean BMI in group I was 29.34 and for group II was 29.05 (table2).

Table 2
Mean weight, height and BMI among the two groups

Parameters	Group I		Group II		P value
	Mean	SD	Mean	SD	
Weight (Kgs)	70.33	6.78	71.25	7.10	
Height (Cms)	153.36	11.74	157.54	12.83	0.718
BMI	29.34	2.52	29.05	3.25	

P value derived by applying chi-square test

The objective measure in assessing the severity of asthma includes a forced expiratory volume in 1 second (FEV1) as measured by spirometry reading. A total of 3 measurements were taken with one at the baseline, two others at 4 and 12 weeks respectively.

Table 3
FEV1 measured by spirometer among the two groups at the start of the treatment and during the follow-up period

FEV1 measurements	Group I		Group II		P value (by applying T test)
	Mean	SD	Mean	SD	
Baseline value of FEV1(% of the predicted value)	1.853 (60.8%)	0.43	1.853 (60.82%)	0.41	1.000
FEV1 at end of 4 weeks (% of the predicted value)	2.036 (70.2%)	0.78	2.044 (70.8%)	0.69	0.874
FEV1 at end of 12 weeks (% of the predicted value)	2.203 (83.5%)	0.94	2.095 (79.9%)	0.91	0.007
P value (by applying ANOVA)	<.001		<.001		

It was predicted from table 3 that there was a gradual improvement in the FEV1 from baseline to 12 weeks of treatment in both the groups and the difference was found to be statistically significant (p<.001). The patients treated with mometasone showed a further improvement in FEV1 when compared to budesonide treated patients and the different was found to be statistically significant (p=0.007). The

subjective assessment of the severity of asthma was shown in table 4. The global initiative for asthma (GINA) had scored the symptoms of asthma on a 4 point scale, and this scale was utilized in our patients. The four major symptoms which were considered were cough, wheeze, chest tightness and shortness of breath.

Table 4

Asthma scoring based on the symptoms at the start of the treatment and at the end of 12 weeks of treatment

Asthma score	Group I (n=94)		P value	Group II (n=90)		P value
	At baseline	At end of 12 weeks		At baseline	At end of 12 weeks	
1	10 (10.6%)	31 (32.9%)	<.001	10 (11.1%)	23 (25.5%)	<.001
2	42 (44.6%)	53 (56.3%)		41 (45.5%)	48 (53.3%)	
3	37 (39.3%)	10 (10.6%)		35 (38.8%)	19 (21.1%)	
4	5 (5.3%)	0		4 (4.4%)	0	
Mean score	2.98±0.45	2.03±0.08		2.97±0.48	2.39±0.06	

P value derived by applying chi-square test

It was inferred that both the groups had an improvement in symtomatology as they were better from 3-4 to 1-2 points. Among this Mometasone/Formoterol is found to be slightly better than budesonide/formoterol and found to be statistically significant. With respect to the adverse events, there were no major adverse events reported in both the groups, except pharyngitis, tremor, palpitation and headache which were experienced by few patients in both the groups and they were treated symptomatically (table 5).

Table 5

Occurrence of various adverse events among the two groups of patients

Parameter	Group I (n=94)	Group II (n=90)
Adverse events	Total number of patients = 5 (5.3 %)	Total number of patients = 8(8.8%)
Pharyngitis	2 (2.1%)	3 (3.3%)
Oral candidiasis	0	0
Tremor	1(1.1%)	2 (2.2%)
Palpitation	0	1(1.1%)
Headache	2 (2.1%)	1 (1.1%)
Dysphonia	0	1 (1.1%)

P value = 0.5 P value derived by applying chi-square test

DISCUSSION

Various studies have reported the effectiveness and safety of combining LABA with ICS in the management of bronchial asthma. Each compound was found to be better when given alone or combined with other drugs. Few studies are carried out to document the efficacy of mometasone alone or with formoterol which improves lung function there by reducing asthma symptoms and need for rescue medication.[18] but a combination of mometasone /formoterol was not compared with budesonide/formoterol. Hence, we planned to carry out this study in our population. The steroids used in this study were mometasone and budesonide at a dose of 400µg, with the long acting beta-2 agonist formoterol at 6µg. This dosage is optimal and recommended in various guidelines. In the present study, there is a significant improvement in FEV1 at the end of 12th weeks in both the groups. The treatment arm with mometasone/formoterol shows much better outcome as there is significant improvement of FEV1, when compared to budesonide/formoterol. This is in coherence with Jorge Maspero et al who proved that mometasone is superior to Fluticasone by an improvement in pulmonary function tests.[18] A study by comparing mometasone furoate with other long acting steroids like budesonide, fluticasone, beclomethasone has proved that mometasone has better efficacy by an improvement in FEV1. This supports our data that mometasone combination is better than budesonide combination in terms of both the variables.[14, 19, 20] In our study, the subjective assessment was made based on the symptom score, which was designed by GINA guidelines, and the symptom score was improved at the end of 12 weeks in both the groups. A better positive outcome is noted in the mometasone group than the budesonide group and this matches with Zeilder et al and Kemp et al where mometasone proven better improvement in lung function tests and symptom scores.[21,7] In general the potential benefits overweigh the risk and hence the adverse effects in common were tremor, pharyngitis, candidiasis, dysphonia, headache and palpitation with the use of inhalational steroids and beta-2 agonists. Minor and transient side effects were seen in both groups and there was no statistically significant difference. In our study population about 2.7% of the patients had experienced pharyngitis, 1.6 % of them had a headache and 1.6% experienced tremor. The tolerance was good and minor adverse effects were treated symptomatically and observations were better than the similar studies by Bousquetetal and Chervinskyetal.[22, 23] This study had proved that an inhalational steroid with the long acting beta-2 agonist had shown a statistically significant improvement in symptoms as well as improvement in FEV1 and symptom score in patients of bronchial asthma.

CONCLUSION

This study has demonstrated the effectiveness of inhalational mometasone /formoterol over budesonide/formoterol in moderate bronchial asthma patients in terms of improved pulmonary function tests especially increased FEV1. A marked change in FEV1 and symptom score with few adverse effects is noted in mometasone group. Hence, this combination which has a positive impact in the treatment of moderate bronchial asthma has to been given much consideration when optimal results are needed. As this study is restricted to a small group of patients, large scale trials have to be carried out to prove the effectiveness of this combination.

ACKNOWLEDGMENT

We wish to express our gratitude to the reviewers for their helpful comments and suggestions and the patients

who participated in this study. Also we are thankful to the statistian and technical persons helped for this study.

CONFLICT OF INTEREST

There is no conflict of interest .

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