Research Article

Comparative Study Evaluating the Effects of Salmeterol/Fluticasone and Formoterol/ Budesonide Combinations on Lung Functions and Sleep Quality in Adults with Moderate Persistent Asthma

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ABSTRACT

Objectives Asthma is commonly occurring chronic disease with a large number of people having incomplete control of asthma. Now day's combinations of inhaled corticosteroids and long acting β_2 agonists are tried in patients not controlled with steroids and not many studies are available with these combinations. In this study we have evaluated and compared the efficacy of two commonly used combinations on the lung functions and sleep quality in persistent asthma.

Methods 71 patients of moderate persistent asthma were randomized to receive two different treatments i.e. salmeterol/fluticasone and formoterol/ budesonide in an open, randomized, prospective, comparative study of which sixty patients completed the study successfully. Lung functions were measured using spirometry and quality of sleep was assessed using Pittsburgh Sleep Quality Index. Day time sleepiness was assessed by Epworth Sleep Scale.

Results Salmeterol/fluticasone and formoterol/budesonide both significantly increased the forced expiratory volume in first second, forced vital capacity and peak expiratory flow rate, quality of sleep and daytime sleepiness from baseline values. Salmeterol/fluticasone was shown to improve night symptoms better than formoterol/ budesonide combinations.

Conclusions Salmeterol /fluticasone and formoterol/budesonide, both caused significant improvement in lung functions, and an overall improvement in quality of sleep. However salmeterol/fluticasone was more beneficial in improving nocturnal symptoms.

Keywords: Asthma, combination therapies, inhaled corticosteroids, long acting beta2 agonists.

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INTRODUCTION

Asthma is defined as a chronic inflammatory disease of airways characterized by increased responsiveness of the tracheobronchial tree to a multiple of stimuli. Approximately 300 million people worldwide currently have asthma, with estimates suggesting that asthma prevalence increases globally by 50% every decade [1]. Inflammation is the underlying disease process in asthma, leading to a bronchial hyperresponsiveness causing reversible airway obstruction. These can reduce the symptoms of asthma, such as cough, wheezing and dyspnoea, but the inflammatory process continues [2].

Treatment with anti-inflammatory agents and bronchodilators is the cornerstone of asthma therapy. Treatment with inhaled corticosteroids improves lung functions and reduces asthma symptoms in patients with persistent asthma. Many patients remain symptomatic despite using optimal dose of inhaled corticosteroids (ICS). Continued symptoms, airway inflammation and obstruction lead to distress, limitation of activity and interference in activities of daily living and also put a patient at risk of acute exacerbation and hence increased mortality [3].

However it is seen that patients requiring high dose of steroids do benefit by the addition of an inhaled long acting beta2 agonist (LABA). This approach further improves lung functions and quality of life in patients with moderate to severe persistent asthma. The principal advantage of combining inhaled corticosteroid (ICS) and long acting beta2 agonists (LABA) in one inhaler is the simultaneous delivery of two effective inhaled therapies. This may lead users to adhere better to dosing regimens, especially given concerns over the use of LABA therapy without a regular background steroid [4].

Many combinations of steroids and beta2 agonists are available throughout the world for the better management of uncontrolled asthma. The present study intended to evaluate two different combinations available widely and estimate which of the two is better. This study was conducted in a prospective randomized manner to compare the two treatment groups i.e. salmeterol/fluticasone and formoterol/ budesonide in patients with mild to moderate persistent asthma to evaluate the effect on asthma.

MATERIAL AND METHODS

Patients

This was a prospective, randomized, comparative clinical study conducted by the Department of Pharmacology and Department of Medicine, Pt. B.D. Sharma PGIMS, Rohtak. This work was approved by institutional review board. Seventy one male and female asthmatic patients aged 18 years and above participated in this study. Sixty patients completed the study successfully over 6 weeks period (Flow chart I).The patients were included in the study if they satisfied the following criteria:

1. Asthma of at least 6 months duration.
2. Patients receiving 400-800 μg/day of beclomethasone or an equivalent.
3. Reversible increase in forced expiratory volume in first second (FEV_1) of 12% or more and >300ml 15 minutes after inhaling salbutamol 200-400 μg.
4. Asthma symptom score (day and night combined) of atleast 2 (2 or more episodes of symptoms during the day/night).
5. Informed consent.

The patients were excluded according to following criteria:

1. Respiratory tract infection or acute asthma exacerbation (requiring emergency treatment or hospitalization within last 4 weeks).
2. Oral corticosteroids within last 4 weeks, depot steroids within last 12 weeks.
3. Pre-bronchodilator FEV_1 of <50% of predicted value.
4. Smoking history of >10 pack years, any known allergy to the study drugs.
5. Refusal to give informed consent.
6. Any co-morbid illness.
7. Pregnancy and lactation.

STUDY DESIGN

After screening, the patients were randomly allocated to two treatment groups of 30 subjects each and received one of the following treatments as shown in flow chart below. Envelope randomization was done to allocate the patient to a particular group. Group I patients received salmeterol (25 μg b.i.d. by inhalation)/fluticasone (250μg b.i.d. by inhalation) (Cipla Ltd, India) and Group II patients received formoterol (6 μg b.i.d. by inhalation)/budesonide (200 μg b.i.d. by inhalation) (Cipla Ltd, India). Both the groups received the treatment for a period of 6 weeks. Two inhalations were given twice daily.

Age, smoking status, duration of asthma, any comorbidities, chief complaints and treatment history were recorded. After a run in period of 1 week in which all patients underwent haematological check up i.e. haemoglobin, total leukocyte count (TLC), differential leukocyte count (DLC), platelet count, biochemical investigations including random blood sugar, urea, creatinine, serum glutamate oxaloacetate transferase (SGOT), serum glutamate pyruvate transferase (SGPT), routine urine examination and pulmonary function tests i.e. forced vital capacity (FVC), forced expiratory volume in first second (FEV_1), peak expiratory flow rate (PEFR) and ratio of FEV_1/FVC were measured and recorded. Borg dyspnoea score was also recorded. All the patients were also evaluated for the quality of sleep and day time sleepiness.

Clinical evaluation was repeated at 3 weeks and at 6 weeks. Primary endpoints were change from baseline values in FEV_1, FVC, FEV_1/FVC, PEFR and improvement in quality of sleep. Secondary end point was improvement in Borg's dyspnoea score.

DATA ANALYSIS

The data obtained are expressed as Mean ± Standard Error of Mean (SEM) and both descriptive and analytical statistics were applied. Chi-square ($\chi 2$) test was used to analyze categorical variables like sex. The ability of two combinations to cause clinical improvement was assessed by primary comparison of the change in spirometric values from the baseline values. Intragroup analysis was done using Repeated Measures Analysis of Variance (RM-ANOVA) with Bonferroni's correction. Differences among the 2 groups were analysed using one-way Analysis of Variance (one way-ANOVA) followed by post-hoc analysis using Tukey's test. The two questionnaires i.e. Pittsburgh sleep quality index (PSQI) and Epworth sleep scale (ESS) were analyzed using mann whitney U test for intragroup analysis and intergroup analysis was done using wilcoxon signed-rank test. A p-value of < 0.05 was considered as statistically significant. All statistical calculations were performed with SPSS software package (version 16.0).

RESULTS

Sixty patients completed the study successfully with thirty patients in each treatment group as shown in the flow chart below. The baseline characteristics were comparable between the treatment groups (**Table 1**). The mean predose baseline spirometric values were comparable in both the treatment groups ($p > 0.05$).

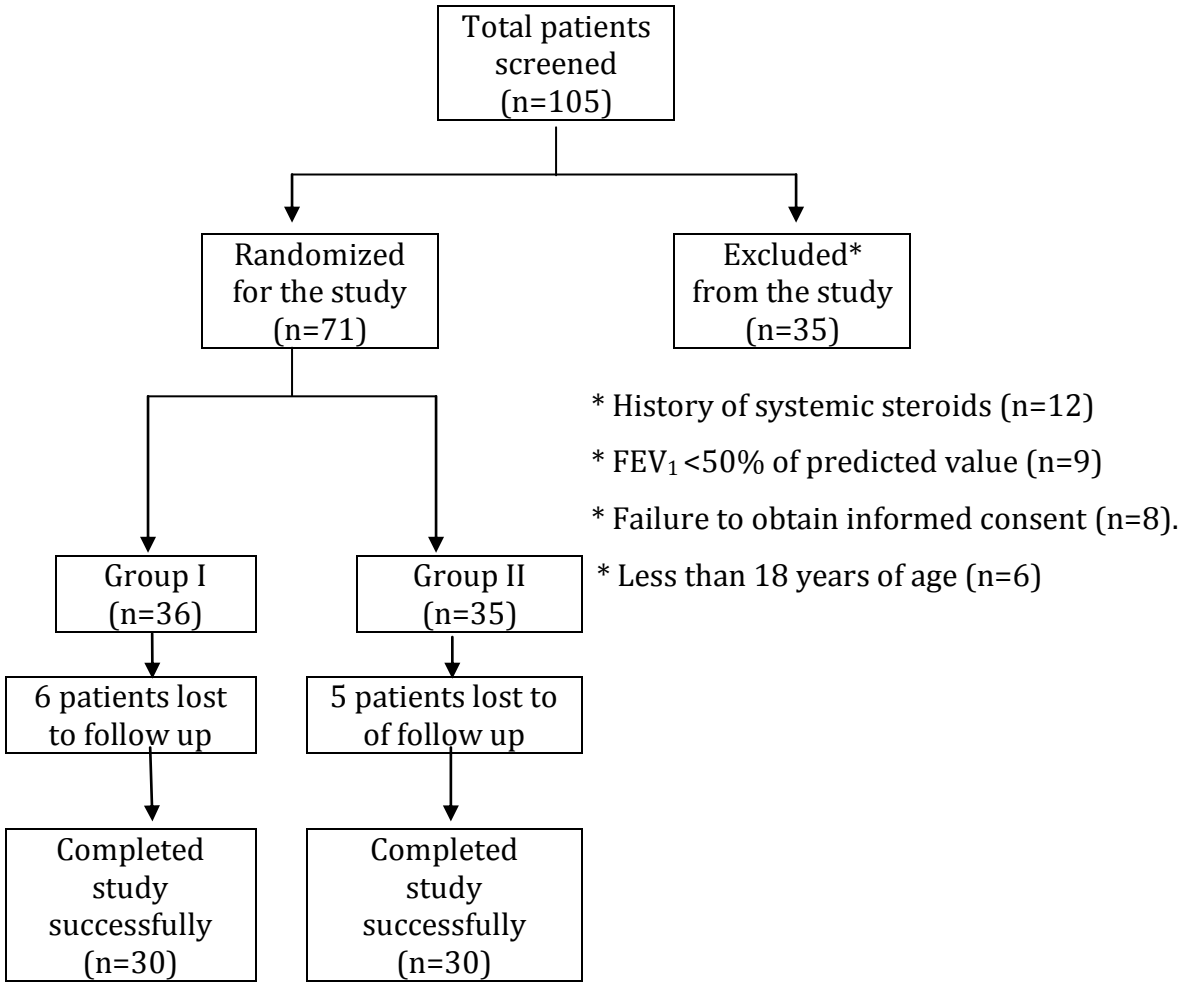

Table 1: Baseline Characteristics of Patients

Characteristics	Group I	Group II
Age (years)	35.63±1.65	36.36±1.80
Sex (F / M)	22 / 8	21 / 9
Height (centimeters)	159.23±1.02	158.56±1.24
Weight (Kilograms)	63.23±2.37	61.40±2.35
Duration of asthma (years)	6.36±0.54	6.13±0.57
History of smoking (pack years)	0.13±0.07	0.10±0.07
FVC (liters)	3.23±0.07	3.21±0.09
FEV_1 (liters)	2.59±0.06	2.56±0.07
FEV_1/FVC (%)	80.17±0.48	80.14±0.53
PEFR (liters/min)	5.84±0.17	5.77±0.18

Values given as mean ± SEM

CHANGES IN VARIOUS PARAMETERS AFTER THE ADMINISTRATION OF TEST DRUGS

1. **LUNG FUNCTION TESTS**

   Lung functions in all the patients were assessed using spirometry. Various lung volumes noted with the help of spirometry were FVC, FEV_1, FEV_1/FVC and PEFR. Changes in the values of above parameters are tabulated in (**Table 2**).

CHANGES IN FEV VALUES

Intragroup analysis has shown significant improvement in group I at 3 weeks (13%) as well as at 6 weeks (14%) after the administration of medication. FEV_1 improved significantly as compared to the baseline values ($p < 0.05$) as shown in (**Table 2**). When the comparison was made between improvement at 3weeks and 6 weeks, it was found to be insignificant ($p > 0.05$). Group II showed similar improvement. There was marked improvement at 3 weeks ($p = 0.000$) while the comparison in the values at 3 weeks and 6 weeks showed no significance ($p > 0.05$). The above results show that there was a marked improvement at 3 weeks and it was sustained at 6 weeks also. On intergroup analysis no significant difference in the different lung volumes was observed at 3 and 6 weeks indicating their equal efficacy.

CHANGES IN FVC VALUES

Intragroup analysis in group I show that there was a significant improvement of 11% both at 3 weeks and at 6 weeks after the administration of medication ($p < 0.05$) as shown in (**Table 2**). Comparison made between improvement at 3weeks and 6 weeks, was statistically insignificant ($p > 0.05$). In group II also there was a marked improvement of 10% both at 3 weeks and 6 weeks. There was marked improvement at 3 weeks while the comparison in the values at 3 weeks and 6 weeks showed no significance. The results showed marked improvement at 3 weeks and it was sustained at 6 weeks also. On intergroup analysis no significant difference in the FVC value was observed at 3 and 6 weeks. It means that both the treatments were equally efficacious.

CHANGE IN FEV /FVC VALUES

Comparing the FEV_1/FVC ratio within the two groups, it was found that in group I there was a significant improvement in the ratio at 3 weeks and at 6 weeks in comparison to the baseline value. Comparison between 3 weeks and 6 weeks showed significant difference statistically ($p = 0.02$). Similar results were seen in group II. Statistical comparison between the improvement at 3 weeks and 6 weeks was also significant ($p = 0.049$). The above results show that there is continuous

improvement till 6 weeks in both the groups. Intergroup statistical comparison of this ratio showed that there was no significant difference at 3 weeks and 6 weeks ($p > 0.05$). It means that similar improvement was seen in both the combination products.

CHANGES IN PEFR VALUES

Both the groups showed marked improvement at 3 weeks and 6 weeks as compared to the baseline values as shown in (**Table 2**). Significant difference was found when the two treatment groups were compared for improvement seen at 3 weeks and 6 weeks. Group I showed significant improvement as compared to group II ($p = 0.180$). Above results revealed that there was continuous improvement at 3 weeks (11%) and at 6 weeks (13%) in group I, while in group II PEFR did not increase significantly after 3 weeks. Intergroup analysis showed that there was no significant difference in improvement at 3 weeks and at 6 weeks.

Table 2: Lung Function Tests in Both the Groups at Different Time Intervals

	GROUP I			GROUP II		
TIME	**Baseline (0 week)**	**3weeks**	**6 weeks**	**Baseline (0 week)**	**3weeks**	**6 weeks**
FVC (ltr)	2.29±0.06 (71%)	2.61±0.06 (81%)*£	2.62±0.06 (81%)*#£	2.25±0.07 (70%)	2.56±0.07 (80%)*£	2.57±0.08 (80%)*#£
FEV1(ltr)	1.71±0.04 (66%)	2.05±0.05 (79%)*£	2.07±0.05 (80%)*#£	1.71±0.05 (67%)	2.01±0.05 (78%)*£	2.03±0.05 (79%)*#£
FEV1/ FVC	75.16±0.62	78.49± 0.51*£	79.27± 0.50*#£	76.2±0.60	78.53± 0.52*£	78.93± 0.47*#£
PEFR (liters/ min)	4.06±0.13 (69%)	4.71±0.13 (80%)*£	4.78±0.14 (81%)*#£	3.90±0.15 (68%)	4.54±0.15 (78%)*£	4.57±0.16 (79%)*#£

All values are expressed as mean ± SEM and in percentages, * Baseline values compared with values at 3 weeks and 6 weeks in both groups ($p<0.05$), # Comparison between values at 3 weeks and at 6 weeks in both groups ($p>0.05$), £ Comparison between 2 groups at 3weeks and at 6 weeks ($p>0.05$)

2. BORG'S DYSPNOEA SCORE

Significant improvement was seen in the scores in group I patients at 3 weeks as well as at 6 weeks ($p < 0.05$) as shown in (**figure 1**). Similar results were seen in the group II patients. When the comparison was made in the values between 3 weeks and 6 weeks, both the groups showed significant improvement at 6 weeks. The above results show that there was a significant improvement at 3 weeks and continued improvement upto 6 weeks. On intergroup analysis, no significant difference was found between the two groups and the improvement seen was found to be comparable both at 3 weeks and at 6 weeks showing thereby that both the drugs cause comparable improvement in the dyspnoea.

3. PITTSBURGH SLEEP QUALITY INDEX

The comparison showed that in group I PSQI improved significantly both at 3 weeks as well as at 6 weeks ($p < 0.05$). The same test was applied to group II also and it was seen that PSQI improved both at 3 weeks and at 6 weeks ($p < 0.05$) when compared with the baseline values. When the sleep quality was compared at 3 weeks and 6 weeks, there was significant improvement in group I ($p = 0.004$) while group II patients did not show further improvement ($p = 0.377$). The above results show that in group I continued improvement occurred upto 6 weeks while in group II the improvement occurred at 3 weeks and was sustained at 6 weeks. There was no significant difference at 0 week and 3 week but at 6 week it was seen that the difference

in two groups was significant (p=0.007). The above results show that in group I it continued to improve. It shows that the treatment in the group I showed a better efficacy in this regards (**Figure 2**).

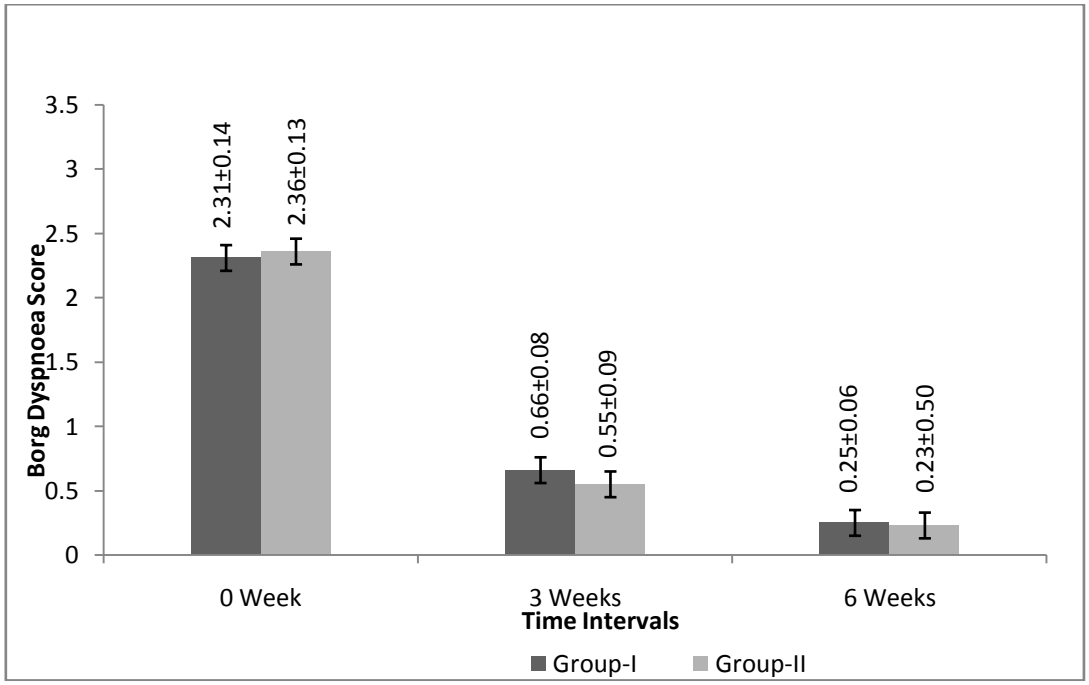

Figure 1: Borg dyspnoea score changes at different time intervals

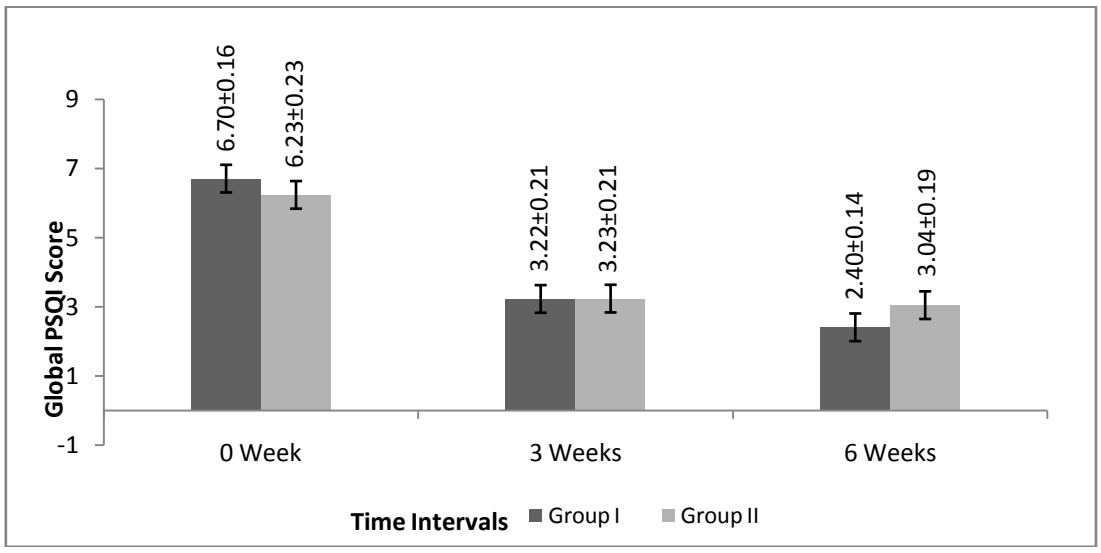

Figure 2: Global PSQI score at different time intervals

4. EPWORTH SLEEP SCORE

Intragroup analysis showed that there was significant improvement seen at 3 weeks as well as at 6 weeks in both the group (p = 0.000). Minimal improvement was seen after 3 weeks, statistical comparison showed that the improvement was not significant after 3 weeks. On intergroup analysis it was found that p value was 0.829 at 0 week which means that the groups were comparable. There was no significant difference in improvement at 3 weeks and 6 weeks (p > 0.05). The above results show that the improvement was seen with both the treatment groups and to the same extent (**Fig. 3**).

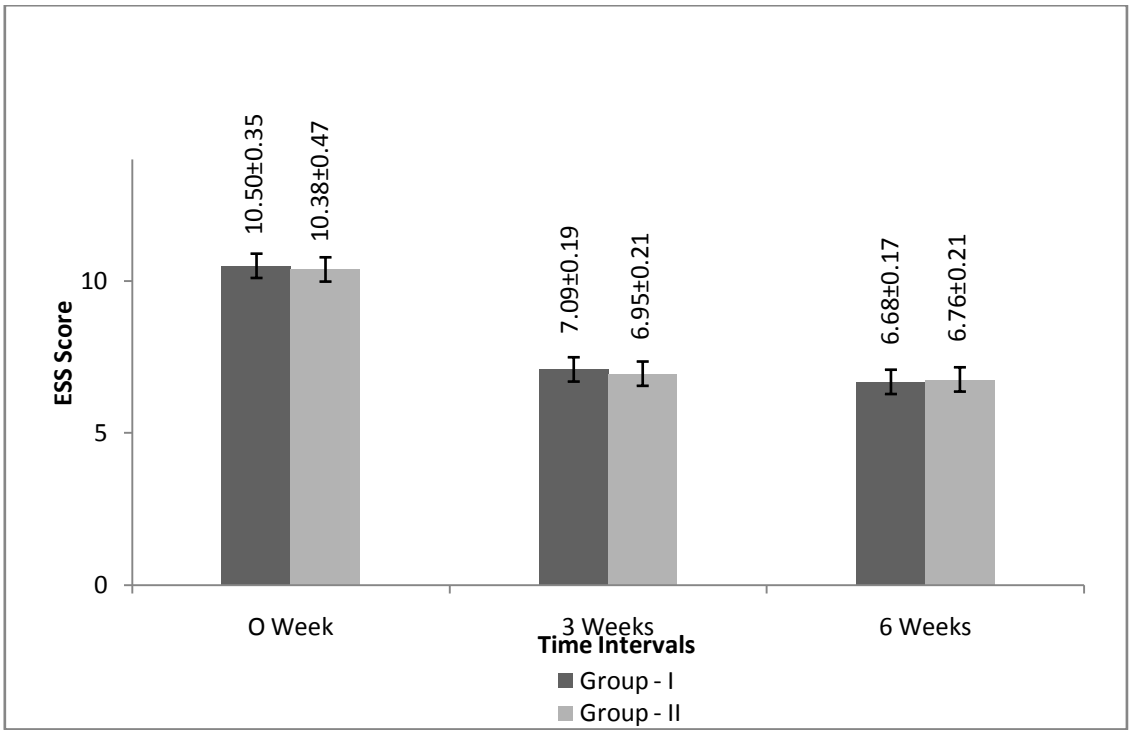

Fig 3: ESS score in both groups at different time intervals

DISCUSSION

The results of this study show that combination of long acting beta2 agonists and inhaled steroids causes significant benefits in pulmonary functions and quality of life in patients suffering from chronic asthma. There is now persuasive evidence that β_2 agonists and corticosteroids target different and complementary aspects of the inflammatory process in asthma and that both the classes of treatment are needed for optimal control in most patients with asthma. LABAs enhance intracellular binding of corticosteroids and potentiate the anti-inflammatory action of corticosteroids. Moreover corticosteroids protect against the loss of β_2 receptors during long term LABA therapy. The fixed dose combinations of ICS and LABA may be more cost-effective than giving the two drugs separately [5, 6].

Many randomized controlled trials have shown the influence of the combined ICS and LABA therapy in asthma like Formoterol and Corticosteroids Establishing Therapy (FACET) study [7], the Oxis and Pulmicort Turbuhaler In the Management of Asthma (OPTIMA) study [8] and the Gaining Optimal Asthma Control (GOAL) study [9].

O'Byrne and colleagues (2005) reported that for patients already receiving an ICS, addition of formoterol proved more effective than doubling the dose of ICS alone, reducing the risk of severe exacerbations by 43% and reducing the number of poorly controlled days by 30% [10]. Having established the efficacy of fixed-dose budesonide/formoterol and salmeterol/fluticasone combination therapies in the treatment of uncontrolled asthma, some studies have performed the direct comparison between the two.

In preliminary results of a fixed-dose, double-blind 24-week trial in patients with persistent asthma, the rate of exacerbations was not significantly different between one inhalation of salmeterol/fluticasone propionate 50µg/250µg twice daily and two inhalations of formoterol/ budesonide 160µg/4.5µg twice daily. Both treatment groups showed similar improvements in lung function and asthma symptoms. However, in a post hoc analysis, the benefits of salmeterol/fluticasone increased over time [11]. A study by Kuna et al, 2007 reported that effects of both fixed-dose

regimens were similar for all the efficacy parameters [12].

In this study it was found that in both the groups lung functions showed a definite improvement at the end of the study period as compared to the baseline values. The results may be attributed to the simultaneous delivery of two potent drugs.

The patients were assessed for sleep disturbances with the help of (Pittsburgh Sleep Quality Index (PSQI) [13] and Epworth Sleep Scale (ESS) [14]. Few studies have been conducted on the pharmacological management of sleep disturbances in asthma. Therapy with salmeterol outperformed that with theophylline in terms of number of awakenings and arousals and in QOL measures [15].

Wcislo et al compared salmeterol / fluticasone and formoterol / budesonide in separate inhalers and found that the salmeterol / fluticasone combination group had significantly more nights without awakening, without symptoms and with asthma symptom score below 2 [16]. There was no significant difference with respect to symptoms of asthma during the day.

In this study we found that salmeterol/fluticasone improved night symptoms more as compared to budesonide/formoterol while the day time symptoms were improved to the same levels in both the groups.

The overall results of the present study show that both the treatments i.e. salmeterol/fluticasone and formoterol/ budesonide were equally effective as far as improvement of the lung functions are concerned while the combination salmeterol/fluticasone was found to be better than formoterol/ budesonide for improving the quality of sleep.

CONCLUSION

The combinations salmeterol/fluticasone and formoterol/ budesonide caused a significant improvement not only in the lung functions and Borg's dyspnoea score but also resulted in an overall improvement in the quality of sleep. Since the LABA's and ICS complement the effect of each other pharmacologically, it may be a good idea to use the fixed dose combinations of the beta2 agonists and inhalational steroids in asthmatic patients to achieve a better therapeutic control with an improved compliance. Salmeterol was more efficacious in improving the nocturnal symptoms as compared to the other combination. So it is prudent to use salmeterol/ fluticasone combination in persons having significant disturbances in sleep because of asthma.

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. Allergy 2004 May; 59: 469-78.
2. Lipworth BJ. Antagonism of long acting beta2- adrenoceptor agonism. Br J Clin Pharmacol 2002 Sep; 54: 231-45.
3. Chabra SK. Assessment of control in asthma: The new focus in the management. Indian J Chest Dis Allied Sci 2008 Oct- Dec; 50: 109-16.
4. Walters EH, Gibson PG, Lasserson TJ, Walters JA. Long acting beta2 agonists for chronic asthma in Adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database Syst Rev 2007, 1: CD001385.
5. Barnes PJ. Scientific rationale for inhaled combination therapy with long acting beta 2 agonists and corticosteroids. Eur Respir J 2002 Feb; 19: 182-91.
6. Chung KF, Adcock IM. Combination therapy of long acting beta2 adrenoceptor agonists and corticosteroids for asthma. Treat Respir Med 2004 Sep- Oct; 3 (5): 279-89.
7. Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. New Eng J Med 1997 Oct; 337: 1405-11.
8. Paul M, O'Byrne PJ, Barnes PJ, Rodriguez roisin R, Runnerstrom E, Sandstrom T, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA Randomized trial. Am J Respir Crit Care Med 2001 Oct, 164: 1392-97.
9. Bateman ED, Boushey HA, Bousquet J. Can guideline defined asthma control be achieved? The Gaining Control Optimal Asthma control study. Am J Respir Crit Care Med 2004 Oct; 170: 836-44.
10. OByrne PM, Bisgaard H, Godard PP. Budesonide/Formoterol combination

therapy as both Maintenance and Reliever Medications in Asthma. Am J Respir Crit Care Med 2005 Jan; 171: 129-36.
11. Dahl R, Chuchalin A, Lindberg A, et al. EXCEL – regular maintenance therapy with salmeterol / fluticasone propionate combination (SFC) reduces exacerbations more effectively than with formoterol / budesonide combination (FBC). Eur Respir J 2004 Aug; 24: 309.
12. Kuna P. Effect of Budesonide/Formoterol Maintenance and Reliever Therapy on Asthma Exacerbations. Int J Clin Pract 2007 May; 1: 1-12.
13. Marie Boltz. Best practices in Nursing care to adults [online]. 2012 [cited 2013 Feb 22]; Available from: URL:http://www.consultgerirn.org/
14. Johns MW. A new method for measuring day time sleepiness: the Epworth Sleep Scale. Sleep 1991 Oct; 14 (6): 540-45.
15. Jarjour NN, Lacouture PG, Busse WW. Theophylline inhibits the late asthmatic response to nighttime antigen challenge in patients with mild atopic asthma. Ann Allerg Asthma Immunol 1998 Jan; 81: 231-6.
16. Wcislo J, Plisko R, Glogowski C, Gierczynski J. A comparative analysis of the efficacy of combination of salmeterol and fluticasone in single inhaler for the treatment of asthma versus placebo and versus formoterol and budesonide in separate inhalers. Annu Meet Int Soc Technol Assess Health Care Meet 2003, 19: Abst 21