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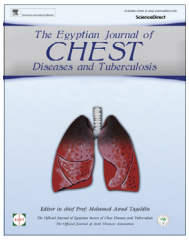

ORIGINAL ARTICLE

The effect of adding long acting beta 2 agonists to inhaled corticosteroids versus increasing dose of inhaled corticosteroids in improving asthma control

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Asthma control

Abstract To asthmatic patients with moderate to severe persistent asthma, two main treatment options are recommended: The combination of a long-acting inhaled β_2-agonist with inhaled corticosteroids or the use of a higher dose of inhaled corticosteroids. The aim of this study was to evaluate which drug option is more favorable.

Patients and methods: This study included 60 asthmatic patients uncontrolled on low doses of ICSs. They were randomized into two groups. Group (1): 30 patients received twice daily inhaled formetrol and budesonide in a dose of 12 mcg and 400 mcg, respectively. Group (2): 30 patients received two fold the previous dose of budesonide 800 mcg/BID alone. A comparative study was carried out at Outpatient Chest Clinic of Fayoum Hospital University for a period of 24 weeks using the spirometric data of patients of the two groups before and after treatment.

Results: Results showed that the combination therapy of inhaled formetrol and budesonide is modestly more effective in the reduction of symptoms and in improving the lung functions than with a higher dose of budesonide alone.

Conclusion: Adding formetrol in a dose of 12 μg plus budesonide in a dose 400 μg b.i.d. is more favorable in treatment of asthma than a higher dose of budesonide (800 μg b.i.d).

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Introduction

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in early morning. These episodes are usually associated with wide spread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment [5].

A number of factors that influence a person's risk of developing asthma have been identified. These can be divided into host factors (primarily genetic) and environmental factors [3]. Measurements of lung function (spirometry) provide an assessment of the severity of airflow limitation, its reversibility, and its variability provide confirmation of the diagnosis of asthma [1].

The aim of asthma treatment is to achieve and maintain clinical control for prolonged periods [2].

Medications to treat asthma can be classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their ant-inflammatory effects.

Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms [5].

To reach clinical control, add on therapy of inhaled LABA to ICS is preferred over increasing the dose of inhaled glucocorticosteroids. Long-acting inhaled β_2-agonist, including formetrol should not be used as monotherapy in asthma as these medications do not appear to influence airway inflammation in asthma. The addition of the long-acting inhaled β_2-agonist to the daily regimen of inhaled glucocorticosteroids improves symptom scores, decreases nocturnal asthma symptoms, improves lung function, decreases the use of rapid-acting inhaled β_2-agonist [10] and achieves clinical control of asthma in more patients, more rapidly, and at a lower dose of ICS than ICS alone [2].

The study was conducted on asthmatic patients among those attending the outpatient chest clinic in Fayoum Hospital University during the period from January 2010 till December 2012.

The study included 60 patients with moderate to severe persistent asthma, uncontrolled on low doses of ICSs (budesonide or beclomethasone dry powder inhaler, 400 mcg/day).

All of these patients were >18 years old.

Exclusion criteria

Patients using systemic corticosteroids, those having respiratory infections affecting asthma control within the previous 4 weeks, patients with severe cardio-pulmonary disease or other concomitant disease and *smoking patients* were excluded. The patients included were randomized into two groups:

- *Group 1*: 30 patients received twice daily inhaled formetrol and budesonide in the form of dry powder inhaler (aerolizer) in a dose of 12 mcg and 400 mcg,
- *Group 2*: 30 patients received two fold the previous dose of budesonide which is the maximum in the form of dry powder inhaler (aerolizer) in a dose of 800 mcg/BID.

Treatment with systemic anti-histaminic or other anti asthma products will not be permitted.

These individuals were subjected to the following:

1. Full history taking with proper analysis of the complaint and full history of atopic state.
2. Full clinical examination: general and local.
3. Chest X-ray.
4. Routine laboratory investigation.
5. Pulmonary function tests: The patients were instructed to stop medications 24 h before performing the test to avoid faulty results. The spirometric parameters estimated by using the Compact Vitalograph were:
   a. Forced vital capacity (FVC).
   b. Forced expiratory volume in the first second (FEV_1).
   c. $FEV_1/FVC_{\ ratio}$.
   d. Peak expiratory flow rate (PEFR). The test was repeated 3 times and the highest result was recorded.
6. Reversibility testing using repeated neubilization by 5 mg salbutamol and 500 mcg of ipratropium.

Any patient $<12\%$ improvement in FEV_1 was considered COPD patient and excluded.

The patients were started on predetermined therapy for a period of 6 months during which they were weekly supervised in the out-patient Chest Clinic at Fayoum Hospital University. At these visits, the patient's questions were discussed, and any problems with asthma and its treatment are reviewed. Checking of the inhaler device technique with correction and re-checking if it is inadequate were done until the period of treatment ended.

At the end of the test pulmonary function tests (spirometry) were repeated by comparing their results with those of the tests previously done before the therapy.

Adherence to therapy was assessed by reviewing patient's questionnaire which was done at the clinic before initiating the treatment and by the end of the predetermined period of treatment.

At the end of the period of the study all the data were collected, tabulated and statistically analyzed.

Statistical analysis

Statistical analysis for the obtained data was carried out to determine the effect of adding inhaled formetrol to inhaled budesonide compared to a higher dose of inhaled budesonide in improving asthma control using descriptive analysis of the results, Cross tabulation test, Student's *t*-test, Fisher's exact test, and Paired samples *t*-test. Statistical package for social science (SPSS) software version 17 was used.

Results

This study was conducted on asthmatic patients among those attending the outpatient chest clinic in Fayoum Hospital University. Their ages ranged from 20 to 60 years (with moderate to severe asthma).

Table 1 shows comparison between mean (SD) of FVC, FEV_1, FEV_1 ratio, and PEFR before and after therapy of the two groups shows that; mean (SD) of FVC of group 1

and group 2 before treatment is 72.6 (3.6) and 73.1 (5.1), respectively, with *p*-value equal to 0.662 which indicates no significant difference in FVC before treatment, and mean (SD) of FVC after treatment of group1& group 2 is 80.0 (2.3) and 75.6 (4.2), respectively, with *p*-value equal to 0.001 which indicates highly significant differences in FVC after treatment as shown in Fig. 1, mean (SD) of FEV_1 of group 1 & group 2 before treatment is 55.8 (3.1) and 58.4 (6.8), respectively, with *p*-value equal to 0.062 which indicates no significant difference in FEV_1 before treatment, mean (SD) of FEV_1 of group 1 and group 2 after treatment is 65.7 (4.8) and 62.0 (4.5), respectively, with *p*-value equal to 0.003 which indicates highly significant differences in FEV_1 after treatment as shown in Fig. 2, mean (SD) of FEV_1/FVC ratio of group 1 and group 2 before treatment is 65.7 (3.1) and 67.6 (5.9) respectively with *p*-value equal to 0.110 which indicates no significant difference in FEV_1 ratio before treatment, and mean (SD) of FEV_1 ratio after treatment is 72.4 (4.5), and 68.7 (5.8), respectively with *p*-value equal to 0.005 which indicates highly significant differences in FEV_1 ratio after treatment as shown in Fig. 3, mean (SD) of PEFR before treatment of group 1 & group 2 is 53.2 (5.5), and 50.1 (6.8), respectively, with *p*-value equal 0.060 which indicates no significant difference in PEFR between both groups before treatment, and mean of PEFR after treatment of group 1 and group 2 is 57.5 ± 5.6 and 54.4 ± 6.5, respectively, with *p*-value equal to 0.045 which indicates significant differences between both groups in PEFR after treatment as shown in Fig. 4.

Discussion

The aim of our study was to compare the effect of adding (LABA) formetrol to (ICS) budesonide versus increasing the dose of budesonide alone in improving asthma control. Descriptive statistical analysis shows a significantly greater improvement in lung function that was achieved by patients treated with formetrol/budesonide regimen than among those who received higher-dose budesonide regimen.

A 2011 Cochrane reviews examine the effect of adding a LABA to ICS in various scenarios in adults with asthma. The addition of LABA to ICS as first line treatment in patients who had persistent asthma and were steroid-naïve compared to ICS alone resulted in improvements in FEV_1, symptoms and reduced rescue beta2-agonist use compared to ICS in our study with similar rates of adverse events while continuing the same dose of ICS [4].

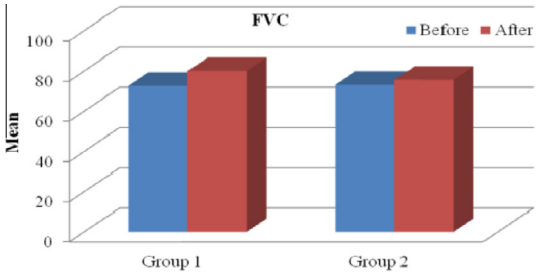

Figure 1 FVC of both groups.

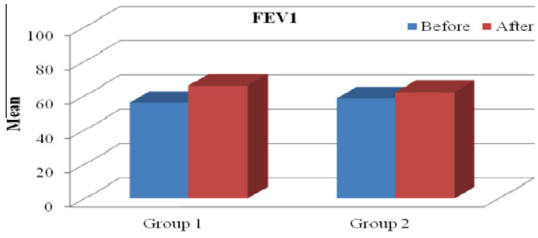

Figure 2 FEV_1 of both groups.

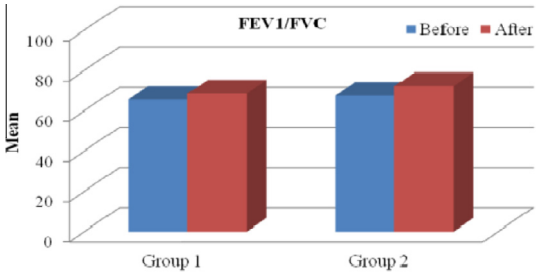

Figure 3 FEV_1/FVC ratio of both groups.

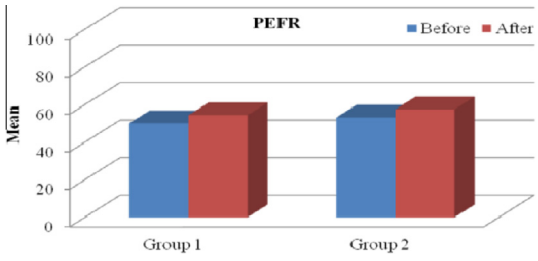

Figure 4 PEFR of both groups.

Table 1 Comparison between group 1 and group 2 at before and after treatment according to FVC, FEV_1, FEV_1/FVC and PEFR.

	TTT	Group 1 Mean ± SD	Group 2 Mean ± SD	*p*-Value	Sig.
FVC	Before	72.6 ± 3.6	73.1 ± 5.1	0.662	NS
	After	80.0 ± 2.3	75.6 ± 4.2	0.001	HS
FEV_1	Before	55.8 ± 3.1	58.4 ± 6.8	0.062	NS
	After	65.7 ± 4.8	62.0 ± 4.5	0.003	HS
FEV_1/FVC	Before	65.7 ± 3.1	67.6 ± 5.9	0.110	NS
	After	68.7 ± 5.3	72.4 ± 4.5	0.005	HS
PEFR	Before	50.1 ± 6.8	53.2 ± 5.5	0.060	NS
	After	54.4 ± 6.5	57.5 ± 5.6	0.045	S

The STEAM study by Rabe et al. [8] has shown similar results to those of our study. They observed that patients who received budesonide/formetrol as maintenance and reliever showing significant improvement in lung functions in terms of both PEFR and FEV_1 $p < 0.001$. Patients who required fewer as-needed inhalations each day (treatment difference: −0.34), had more symptom-free days $p = 0.0043$ and more asthma control days $p = 0.0012$ than those on a higher dose of budesonide. The STEAM study was a 6-month, randomized, double blind, parallel-group study done in patients with mild to-moderate asthma (mean baseline forced expiratory volume over 1 min [FEV_1] 75% expected) [8].

The STEP study by Scicchitano et al. [9] compared the budesonide/formetrol maintenance and reliever regimen with a higher-dose budesonide regimen in patients with moderate to severe asthma (mean baseline FEV_1 70% predicted). It was a 12 month study and recruited 1890 patients the majority of whom (83%) were classed as having severe asthma and showed similar results to those of our study. A significantly greater improvement in lung function was achieved by patients treated with formetrol/budesonide regimen than among those who received a higher-dose budesonide regimen (FEV_1 mean treatment difference 0.101, $p < 0.001$) and also resulted in more symptom-free and asthma control days $p < 0.001$. Moreover, 45% fewer severe exacerbations per patient required medical intervention with the budesonide/formetrol regimen ($p < 0.001$) versus higher-dose budesonide [9].

Greening and colleagues who carried out the first double-blind study of 6-month duration in 426 patients with uncontrolled asthma [6] despite a low dose ICS (200 μg b.i.d.) found little improvement in symptoms and morning peak expiratory flow rate (PEF) when the dose is increased to 500 μg b.i.d. but much greater improvements were observed if salmetrol (50 μg b.i.d.) was added to the same dose of beclomethasone. These findings were confirmed in the Landmark FACET study. This study showed in 852 patients with moderately severe asthma that the addition of formetrol (12 μg b.i.d.) to budesonide (100 μg b.i.d.) more effectively controls symptoms and lung functions than a fourfold increase in the dose of budesonide (i.e. 400 μg b.i.d.), as shown in our study and this benefit persisted during the 12 months of study [7]. Moreover the addition of formetrol (12 μg b.i.d.) significantly reduced the number of mild and severe attacks when added to both a low (100 μg b.i.d.) and a high (400 μg b.i.d.) dose of budesonide.

Conclusion

In conclusion, there is a modest advantage in adding long-acting β_2 agonist to inhaled corticosteroids, compared with increasing the dose of inhaled corticosteroids in the reduction of symptoms as well as improvement in lung function tests in patients with sub-optimal control on low dose ICS monotherapy.

Conflict of interest

None.

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