Comparing the Asthma Control and Anti-inflammatory Effects of Different Fixed Combinations of Inhaled Corticosteroids Plus Long-acting Beta 2 Agonist; A Randomized Clinical Trial

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Abstract

BACKGROUND: Asthma is the most common chronic inflammatory disease of the pulmonary system. The prevalence of asthma is growing enormously worldwide posing a significant health and economic burden. Asthma treatment guidelines recommend a combination of inhaled corticosteroid (ICS) and long-acting beta 2 agonist (LABA). However, there is little guidance for clinicians on selecting a specific ICS/LABA combination.

AIM: The aim of the study is to compare the effectiveness of three fixed dose ICS/LABA combination therapies, i.e. fluticasone/salmeterol, fluticasone/formoterol, and budesonide/formoterol for the management of moderate-to-severe asthma.

DESIGN: This was a prospective interventional, three-armed, parallel group, open label, and randomized clinical trial.

METHODS: Adult asthmatic patients of both genders (n = 135) were randomly allocated to the three ICS/LABA treatment groups: fluticasone/salmeterol-treated group (n = 45), fluticasone/formoterol-treated group (n = 45) and budesonide/formoterol-treated group (n = 45). All groups were treated for 3 months. The main outcome parameters included lung function (forced expiratory volume in 1 s [FEV1], FEV1%, FEV1/forced vital capacity [FVC]), asthma control test (ACT).

RESULTS: After 3 months of treatment, fluticasone/formoterol significantly increased FEV1 compared to fluticasone/salmeterol (p < 0.01) and FEV1% compared to budesonide/formoterol (p < 0.01). Both fluticasone-containing combinations significantly increased FEV1/FVC (p < 0.001), decreased serum hs-CRP (p < 0.01, p < 0.001), and improved ACT (p < 0.05, p < 0.01) compared to budesonide. Fluticasone/formoterol significantly reduced ECP in comparison to fluticasone/salmeterol (p < 0.05).

CONCLUSION: Our study showed a superiority for fluticasone-containing combinations over budesonide for the treatment of moderate to severe asthma. Within the former combinations, fluticasone/formoterol was better than fluticasone/salmeterol.

Introduction

Asthma is a chronic heterogeneous disease characterized by chronic airway hyperresponsiveness and inflammation [1]. If uncontrolled, asthma can severely limit the patient’s regular daily activity [2]. The key long-term goals for asthma management include achieving proper symptom control, maintaining normal lung function, and minimizing flare-ups and mortality [3].

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory medications for long-term asthma management that reduce airway inflammation and hyperresponsiveness, asthma-related mortality, and improve quality of life [4], [5]. However, patients show variable responsiveness to ICS and some individuals may require higher ICS doses to gain full benefit from the treatment. Long-term treatment with high doses of ICS is associated with systemic side effects and therefore, combining normal-dose ICS with another class of controller is preferable to increasing the ICS dose [6].

Current guidelines recommend the use of ICS, for example., fluticasone and budesonide, in combination with long-acting beta 2 agonist (LABA), for example., formoterol and salmeterol, for patients with moderate-to-severe asthma [7]. The use of ICS/LABA combinations has resulted in extraordinary improvements in asthma outcomes compared with increasing the dose of ICS [8]. Several fixed-dose ICS/LABA combinations are available; however, there is little guidance for clinicians on selecting a specific ICS/LABA combination [9].

Here, we designed a randomized clinical study to compare the effect of three available fixed-dose...
ICS/LABA combinations, i.e. fluticasone/salmeterol, fluticasone/formoterol, and budesonide/formoterol on the management of patients with moderate to severe asthma. The main outcome parameters that were investigated include lung function, systemic and airway inflammation, and asthma control.

Materials and Methods

Sample size

Assuming that the percent of enhancement in FEV1 following first dose of fluticasone/salmeterol versus budesonide/formoterol was (58% vs. 31%) so the sample size is 135, using open epi, Confidence interval 95%, power of the test is 80%

Study subjects and ethical approval

Patients with moderate-to-severe asthma aged ≥18 years were recruited in this prospective, interventional study conducted at Zagazig University Hospital, a large tertiary hospital in Egypt. The study has been approved by the Institutional Research Board of Zagazig Faculty of Medicine under the code: 5246/18-12-2019. Written informed consent was obtained from each patient.

Inclusion criteria

Asthma history that bronchodilator reversibility testing reported (about 12% enhancement in FEV1 and about 200 ml enhancement after four puffs, 90 μg each, of salbutamol).

Exclusion criteria

Individuals younger than 18 years, patients with respiratory tract infection within the last 3 months before admission and hepatic, kidney, cardiovascular diseases, diabetes mellitus, cancer, systemic inflammatory disorders, and any patients with signs and symptoms of recent exacerbation of asthma during the period of study were excluded.

Study design

The study was a randomized, open-label, parallel-group, monocentre. After an initial screening visit, patients were randomized to one of three treatment groups according to the global Initiative for asthma guidelines (i.e. low dose for step 3, medium-dose for step 4 or high dose for step 5): Group A, fluticasone/salmeterol (n = 45), group B, fluticasone/formoterol (n = 45) and Group C, budesonide/formoterol (n = 45). The study flow diagram is shown in (Figure 1).

All patients underwent a thorough evaluation of symptoms, clinical examination, and review including full blood count (including eosinophilic circulating [CE] count), chest X-ray (posteroanterior view), serum total immunoglobulin E (IgE) (at baseline), lung function test (at baseline and after 3 months), serum high sensitivity C-reactive protein (hs-CRP) (at baseline and after 3 months), serum eosinophilic cationic protein (ECP) (at baseline and after 3 months), and asthma control test (ACT) (at baseline and every 4 weeks for 3 months).

Lung function test

Spirometric lung function test was performed using Sensor Medicus 2450 computerized pulmonary function apparatus with reversibility tests after salbutamol inhalation (4 × 100 mcg) provided by metered-dose inhaler using a spacer system. It would test forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). The best value of three maneuvers was calculated as a percent of the presumed value and as absolute value.

Blood collection

Peripheral venous blood samples were collected from all patients after overnight fasting. The blood samples were centrifuged at 1300 g for 10 min at 4°C, and the serum samples were kept frozen at −70°C until analysis.

Serum hs-CRP

Serum hs-CRP levels were measured using the Human hs-CRP ELISA Kit (Shanghai Sunred Biological Technology Co., Ltd.; Cat no. 201-12-1806).

Serum ECP

Serum ECP levels will be measured using Human ECP ELISA Kit. (Shanghai Sunred Biological Technology Co., Ltd.; Cat no. 201-12-1392).

Serum total IgE

Serum total IgE levels were measured by ImmunoSpec IgE Quantitative Enzyme Immunoassay (ImmunoSpec Corporation, Ref no. E29-006). Measurement of Serum total IgE levels was used as a diagnostic tool to differ between atopic and non-atopic asthmatic patients so it was measured at baseline only.
Figure 1: The study flow diagram

**ACT**

The ACT is a standardized self-administered questionnaire that contains five questions relevant to the last 4 weeks: episodes of breathless, nocturnal waking, regular activity restrictions, need for rescue therapy, and patients self-rating of asthma management [10]. Each question contains five modalities of answer with a score ranging from 1 to 5 by increasing asthma control level, so the global arithmetic score ranges from 5 (poorest asthma control) to 25 (optimal asthma control). Scores from 20 to 25 are classified as well-controlled asthma; 16 to 19 as not well-controlled; and 5 to 15 as very poorly managed asthma.

**Statistical analysis**

All data are expressed as the mean ± SD for numeric variables and as the number (percentage) for categorical variables. Comparisons were determined by paired t-test, one-way ANOVA, or repeated measures two-way ANOVA for continuous variables as appropriate followed by Tukey’s or Sidak’s multiple comparisons tests (post-hoc tests). Comparisons of categorical variables were assessed by a $\chi^2$ (Chi-square) or McNemar-Bowker test as appropriate. A $p < 0.05$ was considered to indicate statistical significance after multiple testing corrections. Data were analysed using Graph Pad Prism version 8.2 and SPSS version 26.
Results

Demographic data of all asthmatic patients at baseline and Patient characteristics

About 160 asthmatic patients were recruited from the outpatient department at Zagazig University Hospitals. Twenty-five patients were excluded as they did not meet the inclusion criteria. The remaining 135 patients were randomly allocated to the treatment groups. During the study, 15 patients were excluded due to exacerbation (n = 10) and loss of follow-up (n = 5). Therefore, the final number of patients included in the analysis was 120 (40 in group A, 42 in B, and 38 in C). Demographic data, smoking history, comorbidities, lung function, and other biomarkers at baseline are summarized in (Table 1). Patients' characteristics, i.e. age, gender, comorbidities, smoking history, and duration of asthma were similar between the three groups (Table 2).

| Table 1: Demography and baseline characteristic |
|-----------------------------------------------|
| **Mean ± SD or n (%)**                        |
| Age (years) | 36 ± 11 |
| Male, n (%)  | 67 (56%) |
| Female, n (%) | 53 (44%) |
| Atopic asthmatic patients, n (%) | 42 (35%) |
| Non atopic asthmatic patients, n (%) | 78 (65%) |
| Smokers, n (%) | 45 (38%) |
| Non-smokers, n (%) | 45 (38%) |
| Duration of asthma (years) | 13.5 ± 13.7 |
| Comorbidities, n (%) | 77 (64%) |
| Hypertension, n (%) | 9 (12%) |
| Obesity, n (%) | 13 (17%) |
| GERD, n (%) | 10 (13%) |
| Allergic comorbidities, n (%) | 45 (55%) |
| FEV1 | 2.4 ± 0.5 |
| ACT | 16.4 |
| hsCRP (mg/l) | 2.8 ± 1.0 |
| ECP (mg/l) | 22.8 ± 6.9 |

Values are represented as mean ± SD or n (%). ACT: Asthma control test; ECP: Eosinophilic cationic protein; FEV1: Forced expiratory volume; GERD: Gastro esophageal reflux disease; hsCRP: high sensitivity C-reactive protein.

Table 2: Patients’ characteristics in the different treatment groups

| Group A (n = 40) | Group B (n = 42) | Group C (n = 38) | p-value |
|------------------|------------------|------------------|---------|
| Age (years)      | 37 ± 11          | 37 ± 12          | 34 ± 10 | 0.66 |
| Male, n (%)      | 17 (43%)         | 28 (66%)         | 22 (58%) | 0.08 |
| Female, n (%)    | 23 (57%)         | 14 (34%)         | 16 (42%) | 0.08 |
| Asthma onset (years) | 24 (60%)         | 28 (86%)         | 23 (60%) | 0.79 |
| Hypertension, n (%) | 4 (10%)          | 1 (3%)           | 1 (3%) | 0.39 |
| Allergic rhinitis, n (%) | 6 (15%)          | 3 (7%)           | 6 (16%) | 0.43 |
| Atopic dermatitis, n (%) | 5 (13%)          | 3 (7%)           | 3 (8%) | 0.66 |
| Allergic conjunctivitis, n (%) | 3 (8%)           | 3 (8%)           | 3 (8%) | 0.99 |
| Allergic contact dermatitis, n (%) | 3 (8%)           | 4 (10%)          | 3 (8%) | 0.94 |
| GERD, n (%)      | 5 (13%)          | 5 (12%)          | 3 (8%) | 0.78 |
| Smokers, n (%)   | 12 (30%)         | 12 (29%)         | 12 (32%) | 0.96 |
| Duration of asthma (years) | 11 ± 10          | 14 ± 15          | 15 ± 15 | 0.43 |

Values are represented as mean ± SD or n (%). Comparisons of categorical variables were assessed by a χ2 (Chi-square), Comparisons of continuous variables were determined by one-way ANOVA followed by Tukey’s multiple comparison tests (post-hoc tests). Duration of asthma in years. GERD: Gastroesophageal reflux disease

Serum total IgE measured at baseline

Total IgE is a surrogate marker of eosinophilic inflammation in patients with allergic asthma. ImmunoSpec IgE quantitative test was used to differentiate between atopic and non-atopic asthmatic patients. Indeed, there was no significant statistical difference between the three groups in total serum IgE values (Figure 2).

![Figure 2: Serum total IgE in asthmatic patients at baseline](https://oamjms.eu/index.php/mjms/index)

Lung function test at baseline and after treatment for 3 months

Spirometry lung function test showed a significant increase in FEV1, FEV1%, and FEV1/FVC ratio in all groups after treatment compared to baseline (p < 0.001). The increase in FEV1 and FEV1% by fluticasone/formoterol (group B) was significantly higher than fluticasone/salmeterol (group A) (Figure 3a) and budesonide/formoterol (group C) (Figure 3b), respectively. The increases in FEV1/FVC ratio in fluticasone/formoterol and fluticasone/salmeterol groups were significantly higher than budesonide/formoterol group (Figure 3c).

Inflammatory biomarkers at baseline and after treatment

To compare systemic inflammation status between the treatment groups, serum hs-CRP levels were measured in all patients at baseline and after treatment for 3 months. All patients of the 3 groups had high serum hs-CRP levels at baseline which were significantly decreased after treatment for 3 months (p < 0.001). However, the decreases in serum hs-CRP levels in group A and group B were significantly different from group C after 3 months of treatment (Figure 4a).

To compare eosinophils activation/airway inflammation between the treatment groups, serum ECP levels were measured in all patients at baseline and after treatment for 3 months. All patients of the 3 groups had high serum ECP levels at baseline which were significantly decreased after treatment for 3 months (p < 0.001). However, the decreases
in serum ECP levels in Group A and Group B were significantly different from Group C after 3 months of treatment. Interestingly, serum ECP levels were significantly reduced in Group B compared to Group A (Figure 4b).

**ACT**

To determine and compare the effects of treatments on the control of asthma, ACT was performed at baseline and every month for 3 months after treatment. At baseline, all patients of the three groups had low ACT scores that were significantly improved at all the subsequent time points (p < 0.001). After 3 months of treatment, ACT score was significantly higher in Group A and Group B compared to Group C (Figure 5).

Further analysis of ACT score showed that there were 40%, 69%, and 37% well-controlled cases in groups A, B, and C, respectively, after 3 months of treatment. In Group A, there was significant change in asthma control from partially controlled to well-controlled. In Group B, there was significant change in asthma control from poorly controlled to partially controlled and from partially controlled to well-controlled. Similarly, in Group C, there was significant change in asthma control from poorly controlled to partially controlled and from partially controlled to well-controlled (Table 3).

**Asthma severity**

In this study, patients with moderate and severe asthma were recruited and randomly assigned

| Table 3: The change in asthma control (ACT) |
|-------------------------------------------|
| Group | ACT | Baseline | After 3 months | p-value | Post-hoc | p-value |
|-------|-----|----------|----------------|---------|----------|---------|
| A     | Poorly controlled | 6 (15%) | 5 (12.5%) | 0.0041 | Poorly  Partially | ns |
|       | Partially controlled | 28 (70%) | 19 (47.5%) |     |          |         |
|       | Well controlled | 6 (15%) | 16 (40%) |     | Partially  Well | 0.002 |
| B     | Poorly controlled | 12 (28.5%) | 0 (0%) | 0.000005 | Poorly  Partially | 0.004 |
|       | Partially controlled | 23 (54.8%) | 13 (31%) |     | Poorly  Well | ns |
|       | Well controlled | 7 (16.7%) | 29 (69%) |     | Partially  Well | 0.000002 |
| C     | Poorly controlled | 14 (36.8%) | 6 (15.8%) | 0.0004 | Poorly  Partially | 0.016 |
|       | Partially controlled | 21 (55.3%) | 18 (47.4%) |     | Poorly  Well | ns |
|       | Well controlled | 3 (7.9%) | 14 (36.8%) |     | Partially  Well | 0.002 |

Ns: Non-significant. McNemar-Bowker test followed by (post-hoc tests).
to the different treatment groups. At baseline, there was no significant difference in asthma severity between the 3 groups. After 3 months of treatment, there was significant improvement in all groups compared to baseline, however, group B had significant improvement compared to group A and group C. Number and percentage of patients with mild, moderate and severe asthma at baseline and after treatment are represented in (Figure 6).

Discussion

In this study, we compared the efficacy of three common ICS/LABA combinations i.e. fluticasone/salmeterol, fluticasone/formoterol and budesonide/formoterol, in controlling asthmatic patients after 3 months of treatment. All ICS/LABA tested improved lung function, asthma control, and reduced systemic and airway inflammations. Fluticasone-containing combinations, in particular fluticasone/formoterol, were more effective than budesonide-containing combination.

Previous studies showed that ICS/LABA combinations used in our study have greatly improved lung functions in asthmatics compared to placebo after 12-week treatment [11]. Fluticasone/formoterol has been shown to be effective as fluticasone/salmeterol, yet has a more rapid onset of action, reflecting the faster bronchodilator effects of formoterol compared with those of salmeterol [12]. In contrast to our findings that fluticasone-containing combinations are superior to budesonide-containing combination, others showed that budesonide/formoterol is more effective than fluticasone/salmeterol in treatment of moderate to severe asthma [13]. This conflict might be indicative of the different treatment responsiveness in different populations.

Inflammatory markers as hs-CRP and ECP are increased in asthmatics compared to healthy individuals [14], [15], [16]. hs-CRP is an indicator of chronic, low grade inflammation in many conditions including asthma [17]. High serum ECP level may be a predictor for asthma exacerbation and treatment effect, thus it may be a useful control parameter in asthma [18]. ICS including fluticasone and budesonide have been shown to be effective in reducing serum levels of hs-CRP [19] and ECP [20] asthma. In line with our findings, previously serum hs-CRP and ECP were reduced in asthmatic patients who were followed up after 2 months of therapy [16]. To our knowledge, our study is the first to compare the effectiveness of different ICS/LABA combinations on serum levels of hs-CRP and ECP and thus further studies are needed.

The ACT is a numerical score, developed by asthma experts, to assess the control of asthma. It is a useful measure to help determine the level of treatment required [21]. In a study that contained 5789 asthmatic patients from Poland, treated in clinically appropriate doses using one of three ICS/LABA inhalers fluticasone/salmeterol, beclomethasone/formoterol or budesonide/formoterol the investigators reported that control increased from 22.6% to 66.4% after 6 months of follow up. While our study showed an overall increase of asthma control from 13.3% to 49.2% [22]. This difference between our study and this study could be attributed to different study population as we studied less controlled subjects and they followed their subjects for more prolonged period (6 months vs. 3 months in our study). Another, large real-life study that included 1563 asthmatic patients receiving fluticasone/formoterol treatment and were observed over 1 year, showed a

![Figure 6: Asthma severity in asthmatic patients at baseline and after treatment for 3 months. Data are represented as n (%)](https://oamjms.eu/index.php/mjms/index)
comparable increase in the number of patients with asthma control from 30.9% at baseline to 62.4% at the end of the study versus 16.7% to 69% in our fluticasone/formoterol group. Moreover, the percentage of patients whose disease was ‘somewhat controlled’ (total score 16–19) decreased slightly from baseline to end of study (25.9–21.0%) versus (54.8–31%) in our study; the percentage of patients whose disease was poorly controlled (total score <15) decreased substantially (43.1–16.7%) versus (28.5–0%) in our study [23].

The current work has some limitations. First, relatively low number of study population. Second, being a mono center study. Third, the absence of a control arm to compare the effect of the studied medications to placebo or other treatments. Fourth, data on prior medications was not reported for our included patients. Finally, as randomized trial, our study needs to be complemented with real-life observational studies.

Conclusion

The effectiveness of three fixed-dose ICS/LABA combinations i.e. fluticasone/salmeterol, fluticasone/formoterol and budesonide/formoterol for the management of moderate to severe asthma was studied. Overall, based on the findings of the current study, all ICS/LABA combinations tested were effective in improving lung functions, reducing inflammations and controlling asthma. Fluticasone-containing combinations have the upper hand in asthma related inflammation and control. However, fluticasone/formoterol was better than fluticasone/salmeterol and budesonide/formoterol. Therefore, fluticasone/formoterol is suggested as a first-line ICS/LABA combination therapy to be used in patients with moderate to severe asthma.

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