Original Article

Comparing clinical efficacy of Symbicort versus Pulmicort in reducing asthma symptom and improving its control

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Abstract

Background: Recently, higher efficacy of the combination of long-acting beta2-adrenoceptor agonist and inhaled corticosteroids on controlling asthma symptoms has been hypothesized. This study aimed to examine the clinical effects of the combination of Budesonide with formoterol (Symbicort) and Budesonide (Pulmicort) alone in persistent asthma.

Materials and Methods: In a randomized double-blinded clinical trial, 76 patients with definite diagnosis of moderate-to-severe asthma were randomized to receive Pulmicort 180 mcg/inhalation two puffs twice daily, or receive Symbicort 80/4.5 mg/inhalation two puffs twice daily, or receive Symbicort 160/4.5 mg/inhalation two puffs twice daily for 3 months. All participants were initially evaluated by spirometry for assessing respiratory parameters and also the level of asthma control was assessed by Asthma Control Test (ACT).

Results: More significant improvement in spirometry parameters, including forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, as well as in peak expiratory flow (PEF) in both groups of Symbicort with the regimens 80/4.5 mg/inhalation or 160/4.5 mg/inhalation 2 puffs twice daily compared with Pulmicort group, ACT score was significantly improved in Symbicort group with the regimens 160/4.5 mg/inhalation compared with both Symbicort groups with lower dosage and Pulmicort group . Response to treatment in PEF parameter and also in ACT level was significantly more in those who received Symbicort with the regimens 160/4.5 mg/inhalation compared with other two interventional groups adjusted for gender and age.

Conclusion: Symbicort with the regimens 160/4.5 mg/inhalation has higher efficacy in reducing asthma symptom and improving its control compared with low doses of this drug and with Pulmicort.

Key Words: Asthma symptom, symbicort, pulmicort

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INTRODUCTION

Improved understanding of the molecular mechanisms of antiasthmatic drugs led to developing new therapeutic schedules that can provide greater treatment efficacy with a reduced risk of systemic side effects. This understanding has resulted in novel combinations of conventional with novel drugs to minimize side effects

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and restore corticosteroids sensitivity in asthmatic patients.[1] Several years, inhaled corticosteroids have been widely applied as reliever therapy to control symptoms of asthma and there are enough molecular-based evidences on potential effects of these medications. Besides, although the use of a short-acting beta(2)-adrenoceptor agonist as first-line treatment in patients with asthma is effective treatment protocol, its use alone in persistent asthma states cannot adequately control asthma symptoms.[2] Recently, higher efficacy of the combination of these two types of drugs has been hypothesized.[3] This option seems to be well tolerated and offers greater reductions in asthma exacerbations providing improved efficacy with a lower overall drug load in comparison with fixed-dose of each of these drugs.[4] This approach can also result in lower rate of hospitalization in uncontrolled asthma.[5] In this regard, for patients with poor asthma control, one of these two main options can be considered: Either an increase in dose of inhaled corticosteroids or the addition of a long-acting beta2-agonist that the latter regimen may be preferable. Thus, the combination of Budesonide (reducing and preventing respiratory tract inflammation) with formoterol (dilating the respiratory tract) as Symbicort drug has been recently preferred to the use of Budesonide (Pulmicort) alone. Here, the clinical effect of these two types of medication in persistent asthma states was examined.

MATERIALS AND METHODS

In a randomized double-blinded clinical trial, 76 patients with definite diagnosis of moderate to severe asthma based on the increase of FEV1 at least 15% after inhalation of two puffs of salbutamol according to the American Thoracic Society definition referred to Al-Zahra Hospital between 2012 and 2013 were enrolled.[6] Inclusion criteria comprised (1) 18-65 years of age, and (2) developing moderate asthma (symptoms begin with light exercise, the number of asthma attacks 1-2 times a week, and FEV1 60%-80%) or severe asthma (severe limitations in performing activities, the number of asthma attacks more than 2 times a week, and FEV1 < 60%). The exclusion criteria included inability to perform spirometry testing; underlying disease aggravating asthma such as corpulmonale, diabetes, or chronic obstructive pulmonary disease; current smoking; history of respiratory infection within 30 days before study; using a rectal or oral or parenteral glucocorticoid within 30 days before trial, previous treatment with budesonide/formoterol for both maintenance and reliever therapy, instability at study entry, or pregnancy. Isfahan University of Medical Sciences Ethical Committee approved the study. Written informed consent was obtained from each patient.

All the participants were initially evaluated by spirometry for assessing respiratory parameters of forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), forced vital capacity (FVC), and FEV1/FVC ratio and also the level of asthma control was assessed by Asthma Control Test (ACT). All eligible patients were allocated a randomization code assigned from a computer-generated randomization schedule and were randomized to receive Pulmicort 180 mcg/ inhalation two puffs twice daily (group P180, n = 27)(Figure 1), or receive Symbicort 80/4.5 mg/inhalation two puffs twice daily (group S80, n = 25), or receive Symbicort 160/4.5 mg/inhalation two puffs twice daily (group S160, n = 24). Treatment protocols were carried out for 3 months to check the response to treatment and within this period, each patient was visited by a specialist once a month. At the end of the treatment period, all patients were also assessed by spirometry to determine response to treatment as well as by ACT test to determine the level of asthma control.

The results are reported as mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the one-way analysis of variance test for the continuous variables and the Chi-square test (or the Fisher's exact test if required) for the categorical variables. The change in respiratory parameters after interventional regimens compared with before was assessed using the paired t test. Predictors exhibiting a statistically significant relationship with response to treatment in the two groups in the univariate analyses were fed into a multivariate logistic regression analysis to investigate their independence as predictors. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. This study was done with the power of 90%. A P value $\leq$ 0.05 was considered statistically significant. All the statistical analyses

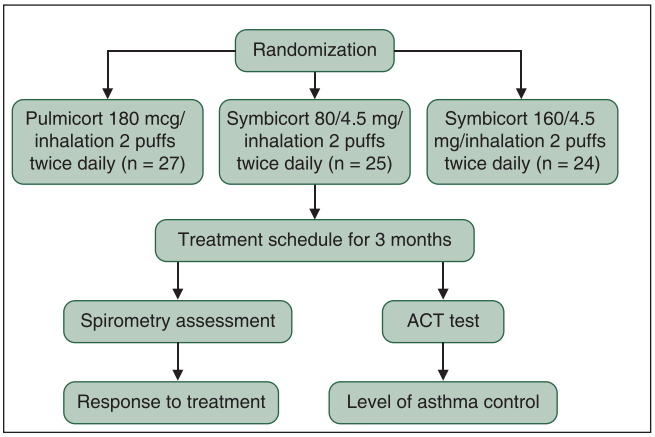

Figure 1: Study CONSORT flowchart

were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

The baseline demographics were comparable between treatment groups so that the average of patients in group P180 was 40.26 ± 10.61 years, in group S80 was 45.00 ± 12.40 years, and in group S160 was 46.00 ± 12.36 years (P = 0.179) with the male frequency of 55.6%, 52.0%, and 50.0%, respectively (P = 0.129). Also, spirometry parameters at baseline were also similar across the three groups [Table 1]. Also, these parameters were all significantly improved in three study groups compared with baseline measurements. However, our study revealed more significant improvement in spirometry parameters, including FEV1, FVC, FEV1/FVC ratio, as well as in PEF in both groups receiving Symbicort with the regimens 80/4.5 mg/inhalation or 160/4.5 mg/inhalation two puffs twice daily compared with group receiving Pulmicort; however, improvement in these parameters were statistically similar between the two groups receiving Symbicort with the different dosages [Table 1]. Regarding the level of asthma control assessed by ACT, this score was significantly improved in those receiving Symbicort with the regimens 160/4.5 mg/inhalation compared with both groups receiving Symbicort with lower dosage and group receiving Pulmicort, but changes in ACT level was not discrepant between group S80 and group P180. According to the multivariable linear regression analyses [Table 2], response to treatment in PEF parameter and also in ACT level was significantly more in those who received Symbicort with the regimens 160/4.5 mg/inhalation compared with other two interventional groups adjusted for gender and age.

DISCUSSION

In the present trial, we aimed to examine the hypothesis that adding regular treatment with the long-acting inhaled beta2-agonist formoterol to therapy with the inhaled glucocorticoid budesonide would improve symptoms of asthma and its severity level as indicated by the rates of severe and mild exacerbations. For this purpose, we compared three highly effective asthma treatment strategies including Pulmicort, as well as low-dose and high-dose Symbicort. In all study scheduling, symptoms, lung function, and level of asthma control all improved. There were significantly greater, and clinically important, reductions in asthma severity and its manifestations with high-dose Symbicort versus low-dose of this drug or Pulmicort. However, higher efficacy of high-dose Symbicort seems to be dependent on the dose of budesonide, but independent of the dose of formoterol. A recent meta-analysis of randomized controlled trials using a fixed effects model showed that the risk of severe exacerbations was significantly reduced: 41% versus higher-dose budesonide alone, 43% versus equivalent dose budesonide/formoterol as maintenance twice daily; 24% versus higher-dose salmeterol/fluticasone twice daily; and 26% versus higher-dose budesonide/formoterol twice daily.[7] Several clinical studies have shown that the effects of inhaled corticosteroids can be enhanced by long-acting beta(2)-adrenoceptor such as formoterol, in mild, moderate, and severe asthma.[8,9] In several in vitro systems, there is increasing evidence that

Table 1: Respiratory parameters before and after interventional regimens

Index	Group P180 (n = 27)	Group S80 (n = 25)	Group S160 (n = 24)	P value
FEV1 (before)	56.96±8.51	60.00±7.25	57.04±8.19	0.314[a]
FEV1 (after)	68.07±8.19	77.76±7.86	75.67±8.68	<0.001
P value	<0.001[b]	<0.001	<0.001	
FVC (before)	86.33±9.74	89.88±7.03	86.29±9.15	0.254
FVC (after)	89.59±8.09	94.40±6.41	92.67±7.59	0.036
P value	<0.001	<0.001	<0.001	
FEV1/FVC (before)	75.07±3.27	81.44±4.41	81.00±3.56	0.339
FEV1/FVC (after)	86.33±9.74	89.88±7.03	86.29±9.15	<0.001
P value	<0.001	<0.001	<0.001	
PEF (before)	50.14±9.33	54.56±10.89	54.21±11.01	0.241
PEF (after)	63.52±9.56	77.76±10.96	73.75±10.32	<0.001
P value	<0.001	<0.001	< 0.001	
ACT (before)	13.22±2.22	14.20±2.25	13.75±2.54	0.326
ACT (after)	18.59±1.89	20.24±1.74	20.17±2.04	0.003
P value	<0.001	<0.001	<0.001	

FEV1: Forced expiratory volume is the volume that has been exhaled at the end of the first second of forced expiration; FVC: Forced vital capacity; PEF: Peak expiratory flow; ACT: Asthma control test. [a]Between-group comparing was performed using the one-way analysis of variance test. [b]Intergroup analysis (before and after intervention) was done using the paired t test

Table 2: Multivariable linear regression analysis to assess response to treatment

Item	Beta	SD	*P* value
PEF improvement			
Treatment group	3.102	0.425	<0.001
Gender	0.621	0.692	0.373
Age	−0.015	0.029	0.606
Item	Beta	SD	*P* value
ACT improvement			
Treatment group	0.489	0.211	0.023
Gender	0.177	0.344	0.609
Age	0.005	0.014	0.737

PEF: Peak expiratory flow; ACT: Asthma control test

formoterol or salmeterol enhanced glucocorticoid effects.[10,11] The exact mechanisms for increased exacerbation control with Symbicort therapy have yet to be fully determined. One important factor is the early increase in anti-inflammatory treatment provided by as-needed inhalations of Symbicort during periods of deteriorating symptoms. It has been shown that high dose of budesonide and budesonide/formoterol combination significantly reduced IL-8 mRNA expression.[12] Also, use of high-dose budesonide has been shown to reduce eosinophilic inflammation within a 6-h period. Additional nongenomic effects of as-needed budesonide have been reported, including rapid airway vasoconstriction leading to a reduction in airway edema.[13-15] According to this fact that acute exacerbations of asthma are associated with an influx of eosinophils, neutrophils, or both,[16,17] these effects of high-dose budesonide can explain the beneficial effects of high dose of budesonide on asthma control. Besides budesonide, formoterol has been shown to inhibit the influx of inflammatory cells and reduce acute airway inflammation.[18] Formoterol is a potent functional antagonist of airway smooth muscle stimulants and inhibits plasma extravasation.[19-22] Although higher dose of Symbicort was shown to be effective to control asthma, but it should be noted that higher doses of the combinations of this drug may lead to a greater increase in the potential of side effects and thus proper doses of this drug should be considered with minimizing these probable side effects. Conclusion: According to our observations, Symbicort with the dose of 160/4.5 mg/inhalation two puffs twice daily is significantly more effective than this drug with lower doses or Pulmicort at reducing severe exacerbations and asthma symptoms.

CONCLUSIONS

Symbicort with the regimens 160/4.5 mg/inhalation has higher efficacy in reducing asthma symptom and improving its control compared with low doses of this drug and with Pulmicort.

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