ORIGINAL ARTICLE

Is it necessary to treat mild asthmatic patients with the full dose treatment?

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Background: Routine protocol of asthma treatment has been focused on symptom suppression but severity of inflammation and spirometry findings may be neglected. We investigated the efficacy of full dose treatment protocol on patients with mild asthma symptoms with normal spirometry. **Materials and Methods:** A before-after clinical trial study was conducted on patients with asthma symptoms (dyspnea, cough, and wheezing), while they had a near to normal pulmonary function test. Full dose treatment protocol (prednisolone 1 mg/kg for 5 days then fluticasone spray 250 mg four puffs daily plus salmeterol spray 25 μg four puffs daily), which was routinely used for severe asthma, was administrated and patients were followed up for 2 months. **Results:** Sixty-eight patients (mean age (±SD) = 43.77 ± 10.70 years, female/male ratio; 47/53%) finally finished the study. At the baseline, mean forced expiratory volume in first second (FEV1) and forced vital capacity (FVC) were 91 ± 12% and 87 ± 11% of the predicted value, respectively. Two months after treatment, the mean FEV1 and FVC were 105 ± 14% and 97 ± 10%, respectively, which both improved compared with the baseline, significantly ($P < 0.001$). Frequencies of cough and dyspnea were significantly decreased ($P = 0.041$ and 0.034, respectively). **Conclusion:** Our result declared that full dose treatment can improve spirometry amounts and frequency of symptoms in patients with near to normal spirometry and obvious asthmatic symptoms. Routine treatment protocol of mild asthma recommends sole short-acting b_2 receptor agonist, but it seems that pulmonary function and volume can be increased with more aggressive treatment.

Key words: Asthma, clinical findings, full dose treatment, mild asthma, signs and symptoms, spirometry, treatment

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INTRODUCTION

Asthma is a chronic inflammatory disease which affected about 5% of population. Asthma is a chronic lower airways inflammatory disorder that results from genetic factors and environmental exposure to allergens and irritants characterized by episodic and reversible airways obstruction and airway hyperresponsiveness.[1] With effective treatment and avoiding allergens and irritants, the majority of patients have a controlled disease.[2] The treatment protocol for asthma is designed to control symptoms and airways inflammation; airways hyperresponsiveness and airway remodeling were usually forgotten.[3,4]

Recent findings indicated that airway remodeling can occur in patients with mild intermittent asthma. It was shown that the remodeling process will be permanent unless treated with inhaled steroid.[5] According to current asthma management guidelines, inhaled corticosteroid (ICS) should be used for severe symptoms and lung function.[6]

On the other hand, severity of symptoms/lung function and inflammation is not consonant.[7] The importance of early prescription of inhaled steroids even in mild asthma has been documented in several studies, but it is not clear whether the treatment should be started in symptomatic patients with near to normal asthma.[8] There are evidences which confirmed a mismatch between severity of symptoms, clinical findings, and severity of inflammation. Symptoms are sometimes inconsistent with paraclinical especially spirometery findings.

In our knowledge, until now no comparison has been published to assess the efficacy of the full-dose anti-asthma treatment in subjects with mild to moderate asthma and normal pulmonary function test (PFT) volumes. Thus, in this study we aimed to determine the effects of the prescription of full dose anti-asthma treatment on PFT in mild to moderate asthmatic patients with normal baseline PFT.

MATERIALS AND METHODS

Participants

This study was conducted on patients who referred to Baqiyatallah University of Medical Sciences, Tehran,

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Iran, between 2010 and 2011. The sampling method was simple randomized as a probability sampling method. All patients were in step 1 of severity of asthma and had a clear history of relevant symptoms for asthma. Mild asthma was defined as the Global Initiative for Asthma (GINA) criteria[9-11] including asthma symptom (dyspnea, cough, and wheezing in auscultation) and also having near to normal PFT (forced expiratory volume in first second (FEV1), forced vital capacity (FVC), FEV1/FVC, and mean expiratory flow (MEF) ³80% predicted normal). Study actually started when patients were selected and asked them to start a certain type of therapy for their disease. They had not used corticosteroids, theophylline, antihistamines, cromolyn sodium, or nedocromil sodium. Cases with a history of heart failure, lung cancer, abnormal spirometry findings, abnormal chest radiography findings, abnormal lung examination findings, and/or evidence of acute respiratory tract infection were excluded. The patients with the following conditions were included; FEV1 without bronchodilator in the normal range, participants with the normal range of FEV1 percent-predicted values more than 80%, mean forced expiratory flow during the middle half of the FVC (FEF 25-75%) percent-predicted value of >80%, and FVC percent-predicted value >80% without using bronchodilators. Finally, 68 cases met our inclusion and exclusion criteria.

Medications

Eligible participants received the full-dose therapy containing 50 mg/day prednisolone (tab prednisolone fourt, Aburihan Co., Tehran, Iran) for 5 days followed by ICS (spray fluticasone, Glasgow, Scotland, 250 µg, two puff/12 h) and long-acting beta agonist (spray salmeterol, Aburihan, Tehran, Iran, 25 µg, 2 puff/12 h) for 2 months. Asthma symptoms and spirometry were evaluated before and after the 8-week period. Study protocol was described for each patient and they signed the informed consent before including the study. This study protocol was approved by ethical and scientific committee of Faculty of Medicine, Baqiyatallah University of Medical Science, Tehran, Iran (registry code: 753).

Spirometry

Spirometric indexes were measured with a Vmax 20 Spirometer (Chest, Italy). The best of three maneuvers was selected and expressed as a percentage of the predicted value and as an absolute value. Spirometry was carried out by one technician who had enough experience in this field.

Data analysis

Quantitative data were expressed by mean ± standard deviation (SD). *P*-values less than 0.05 were considered statistically significant. Statistical Package for Social Sciences (SPSS) software (version 16th, SPSS Inc., Chicago, USA) was used for statistical analysis. Independent *t*-test and Mann-Whitney U test were used for examining a quantitative variable in two groups. Also, paired samples *t*-test and Wilcoxon test were used for a quantitative variable before and after treatment. Also we used were McNemar's test and repeated measurement analysis of variance (ANOVA) for analyzing variables during the study. Variables with a significant level of <0.2 in univariate analysis might be entered into multivariate analysis.

RESULTS

All included cases completed the treatment course and returned for the follow-up examination after 2 months. The mean ± standard deviation (SD) of age was 43.78 ± 10.74 years and 36 (52.9%) patients were male. Mean duration of disease was 19.71 ± 15.74 months, 46 patients (67.6%) had no history of asthma among their family, and 42 patients (61.8%) had symptoms of rhinitis allergic. Demographic and baseline characteristics are shown in Table 1.

During the study, frequency of abnormal lung sounds decreased: wheeze from 57.4% to 15.7%, cough from 61.8% to 24.6%, and dyspnea from 82.4% to 14.1% following the treatment ($P < 0.001$ in all three items) [Table 2]. After controlling the confounding factors (such as weight, gender, etc.) in multivariate analysis, it was shown that age ($P = 0.024$, EXP[b]: 1.069, CI [95%]: 1.009-1.133) and family history of asthma ($P = 0.010$, EXP[b]: 6.285, CI [95%]: 1.563-25.273) were only factors which can effect on the change of wheezing frequency during the study.

Table 1: Baseline characteristics

Variable		Frequency	Percent (%)
Education	Collegiate	18	26.5
	Under diploma	50	73.5
Occupation	Employee	19	27.9
	Housekeeper	26	38.2
	Self-employed	22	32.4
	Student	1	1.5
	FHx of asthma	22	32.4
	Symptoms of RA	42	61.8

FHx = Family history; RA = Rhinitis allergic

Table 2: Changes in frequency of clinical symptoms during study

Item		Before	After	*P*-value
Lung sound	Wheeze	47 (69.1%)	5 (7.4%)	<0.001
	Clear	21 (30.9)	63 (92.6%)	
Cough	Positive	52 (76.5%)	7 (10.3%)	<0.001
	Negative	16 (23.5%)	61 (89.7%)	
Dyspnea	Positive	58 (85.3%)	5 (7.4%)	<0.001
	Negative	10 (14.7%)	63 (92.6%)	

FEV1 values increased from 90.94 ± 10.66 to 106.34 ± 13.28 and FVC increased from 86.32 ± 8.93 to 100.04 ± 9.71 after 2 months ($P < 0.001$). Also, MEF increased from 95.20 ± 27.65 to 104.95 ± 22.84 ($P = 0.010$) and FEV1/FVC increased from 84.39 ± 7.98 to 85.52 ± 8.09, respectively ($P = 0.266$, power: 19.7%) [Table 3].

There were no significant differences in changes of spirometry parameter in terms of duration of disease, symptoms of rhinitis, and asthma family history during the treatment ($P > 0.05$). Using multivariate analysis showed that age can associate with changes of FEV1 ($P = 0.024$, adjusted r: 2.136) and MEF ($P = 0.045$, adjusted r: 2.052), while primary symptoms associated with FEV1/FVC changes ($P = 0.029$, adjusted r: 2.240), baseline wheezing associated with MEF changes ($P = 0.001$, adjusted r: 3.665), and finally gender associated with FEV1/FVC changes ($P = 0.012$, adjusted r: 2.608) [Table 4].

DISCUSSION

Our study finding showed that full-dose anti-asthma treatment in patients with normal or near to normal spirometry can significantly improve the FEV1, FVC, and FEV1/FVC and clinical symptoms. Also, we found that age and gender are two factors that can associate with changes of spirometric parameters. Also, among clinical symptoms, only primary wheezing in baseline physical examination could predict spirometric parameters.

Table 3: Changes in spirometry findings during study

	Before	After	Differences	*P*-value
FVC	86.32±8.93	100.04±9.71	13.71±10.74	<0.001
FEV1	90.94±10.66	106.34±13.28	15.40±14.46	<0.001
FEV1/FVC	84.39±7.98	85.52±8.09	-1.013±8.33	<0.001
MEF	95.20±7.65	104.95±22.84	-9.74±30.29	<0.001

FEV_1 = Forced expiratory volume in first second; FVC = Forced vital capacity; MEF = Mean expiratory flow

There are several studies on the efficacy and necessity of inhaled corticosteroids on asthma, but few study focused on efficacy of oral corticosteroid in addition to the inhaled form on mild asthma. In patients with mild asthma, regular use of inhaled corticosteroids improves symptoms and lung function. It also reduces using β2-agonist and most importantly reduces the exacerbation rate. Boushey *et al*.[12] treated asthmatic patients with two methods: (1) budesonide 800 μg twice daily for 10 days and (2) prednisone 0.5 mg/kg for 5 days and then regular budesonide, 200 μg/day. They found that morning peak expiratory flow (PEF) showed no significant difference between two groups in addition to symptom free days, sputum eosinophil level, exhaled nitric oxide values, improvement in bronchial hyperresponsiveness, and improvement in asthma control score.

Most importantly, three larger and longer studies showed that regular inhaled steroids are beneficial in mild asthma. The START study investigated 5000 patients over a 3-year period and showed a marked reduction in exacerbation rate with small improvement in lung function.[13] Moreover, the OPTIMA study showed reduced exacerbation rate and improvement in lung function in patients who received regular inhaled steroids.[14] A recently published study by Reddel *et al*. showed the beneficial effects of regular inhaled steroid therapy in asthmatic patients.[15]

A study by Covar *et al*.[16] demonstrated that significant numbers of children with mild intermittent asthma had reduction in post-bronchodilator FEV1 values despite treatment with budesonide or nedocromil. These researchers believed that this reduction in lung function begins early in the course of asthma and does not proceed uniformly over time. Another study reported significant reduction in the prevalence of airway remodeling in patients who were treated with long-term inhaled steroids. Also, higher

Table 4: Correlation between improvements of clinical symptoms in terms of spirometry changes and factors which confound spirometry changes

Variables		FEV1	FVC	FEV1/FVC	MEF
Lung sound	Improved	18.59±16.20	14.00±11.21	1.97±6.40	19.21±20.59
	Not improved	12.90±12.58	12.48±10.23	1.36±5.74	6.59±23.33
	P-value	0.180	0.604	0.018	0.054
Cough	Improved	14.38±17.21	14.04±10.96	1.73±5.49	14.45±20.61
	Not improved	16.55±12.42	12.57±10.61	1.04±6.66	11.48±24.56
	P-value	0.431	0.596	0.094	0.773
Dyspnea	Improved	14.04±12.34	12.73±11.07	0.65±5.95	14.60±21.86
	Not improved	16.99±16.54	13.84±10.22	0.64±7.00	9.93±25.02
	P-value	0.487	0.434	0.353	0.442
Effective variable*		Age (P=0.024, r: 2.136)	–	Gender (P=0.012, r: –2.608), primary wheezing (P=0.029, r: 2.240)	Age (P=0.045, r: 2.052) Primary wheezing (P=0.001, r: 3.665)

*Effective variable which was significantly effective on spirometry changes in multivariate analysis. C = Constant; FEV1 = Forced expiratory volume in first second; FVC = Forced vital capacity; MEF = Mean expiratory flow

incidence of airway remodeling was reported at the end of the study in children with mild intermittent asthma that did not receive inhaled steroids.[17] A study by van der Molen *et al* reported the changes in symptoms and PEF rate (PEFR) and bronchial hyperresponsiveness rate after using a low dose (200 μg/day) and a high dose (800 μg/day) of inhaled corticosteroid.[18] Haahtela *et al*.[19] found that early treatment with inhaled budesonide with a dose of 1200 mg day via a metered-dose inhaler results in long-lasting control of mild asthma. Results from another study revealed that even good clinical response to the low dose of inhaled corticosteroid is not sufficient to suppress asthmatic inflammation.[8] Also, Reddel *et al*. concluded that outcomes in poorly controlled asthma improved with starting inhaled corticosteroid higher than cases that were treated based on international guidelines.[20]

Asthma is an ongoing disease and patients show a significant decrease in lung volume when its symptoms reveal. An increase in PFT indices at higher percentages following treatment represents greater pulmonary dysfunction and a more lung volume reduction compared with the same increased value in lower percentages. Therefore, we can hypothesize that an ongoing process may contribute with silent underlying airway destruction, before a definitive PFT abnormality could occur.

It seems that the best PFT and the best amount of lung volume is more than which was previously thought. It appears that when a physician visits an asthmatic patient who presents mild symptoms, it is necessary to respond to these two questions before designing a treatment plan; first, what is the best amount of lung volume which is declined and the patient presents symptoms? And second, dose the patient need more lung volumes for exercising and also can the full dose treatment increases them?

Moreover, we think that if patients with mild asthma treats with full-dose protocol (short course of oral corticosteroid and then inhaled form in addition to short or long acting b_2 agonist), they can achieve their optimal lung volumes which are restricted before revealing the symptoms. Therefore, results of our study suggest a revision in guideline of mild asthma treatment and it seems that a course of full-dose treatment can be helpful before more deterioration in the FEV1/FVC ratio although more studies are needed in this area to suggest a change in the guidelines.

In addition to the PFT changes, previous studies confirmed the efficacy of corticosteroid on prevention of airway remodeling in mild asthma[21] although there are several differences between our study and them. Also, it was shown that a short course of oral corticosteroid (e.g., 5 day) can effectively improve symptoms of patients with acute asthma exacerbation in adults[22] and the short course of oral corticosteroid has only approved for the treatment of acute attack, but not for long-term treatment or the initial phase of treatment. Chhabra in a trial study has used oral corticosteroid, prednisolone, compared to sustained-release theophylline for the management of nocturnal mild asthma and concluded that short course of oral prednisolone was more effective than sustained-release theophylline.[23]

On the other hand, we found that age could predict changes of PFT and clinical symptoms during the study, but duration of disease was not so that this finding is not reported in previous studies. Also, we found that wheezing could predict the PFT and symptoms changes. Previous reports confirmed that there is a weak relationship between PFT changes and symptom improvement in asthmatic patient during treatment.[24,25]

Unfortunately, we have some limitation in this study which concluded our result. One of our study's limitations is lack of control group. Also, pathologic and laboratory studies were not performed that if it had been done it could be helpful for final conclusion. Also, the PEF variability and asthma control levels were not evaluated. These measurements would allow us to evaluate the patient better and enable us to make better decisions for treatment in our patients. Moreover, the spirometry is one of segmentation tools for asthma classification and more advanced tools should be used to examine this hypothesis.

In conclusion, this study was conducted in patients with mild clinical features of asthma and near to normal spirometry, the majority of who were not under a regular treatment. We observed significant and clinically important increase in PFT indexes in our patients that may be correlated with the role of full-dose therapy on process of disease progression. Further study is needed to declare the role of short course of oral corticosteroid on symptoms and PFT of mild asthmatic patients.

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