CORRELATION BETWEEN SYMPTOM SCORE, WHEEZE, REVERSIBILITY OF PULMONARY FUNCTION TESTS AND TREATMENT RESPONSE IN ASTHMA

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ABSTRACT

Asthma management is a major concern because some asthmatic patients either do not respond or else hardly respond to treatment. Therefore in the present study, an attempt has been made to determine the predictors of treatment response in asthmatic patients.

Thirty six asthmatic adults including 13 male and 23 female were studied during a 3 month treatment period. Asthma symptom score (SS) and wheezing were recorded before and after treatment. Pulmonary function tests (PFTs) including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), maximal expiratory measured at the beginning and the end of the study. The increase in PFT values 10 min after 200 µg inhaled salbutamol (in percentage) was considered as reversibility in airway constriction.

There were significant improvements in SS ($p<0.001$) and PFT variables ($p<0.05$ to $p<0.001$) except of MEF_{25} due to 3 months treatment. However, the reversibility of airway constriction improved after treatment but these improvements were not statistically significant except that of PEF (p<0.05). There were significant correlations between both baseline symptom score and wheeze with an improvement seen in these two parameters (p<0.05 to p(0.001). There were also significant correlations between reversibility in FEV_1 with improvement in FEV_1 and MEF_{25} aftet treatment and between reversibility in PEF and improvement in FEV_1 at end of the study ($p<0.05$ to $p<0.001$).

The results of these study showed that a well conducted therapeutic program could lead to improvement in symptoms, wheeze, and PFT values. In addition symptom score, wheeze, and reversibility in FEV1 and PEF could be good indicators of response to treatment in asthma.

Keywords: Asthma, Pulmonary function tests, Reversibility, symptom score. Treatment response.

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INTRODUCTION

Asthma is known as a chronic disease, and epidemiological studies indicate that it is on an increase throughout the world,[1] although the reason for this increase is not yet clear.[2] Asthma affects over 10% of children and 5-10% of adults in many European countries, and imposes a large burden on the health services of these countries.[1] In Iran asthma affects 4.19% of children[3] and 2.8% of adults.[4] The management of asthma could be achieved by appropriate drug administration, avoidance of exacerbating factors and patient education. There is an overwhelming evidence that asthma is due to a special type of inflammation of the airway.

There is a general consensus on how to treat moderate and severe asthma, but there is a debate as to how mild asthma should be treated and at what stage anti-inflammatory therapy should be introduced.[5] It is difficult to see much improvement, even with inhaled steroids, when peak expiratory flow and forced expiratory volume in one second are used as indicators of improvement, as these are often normal or near normal.[6] Low use of beta2-agonist like quality-of-life measurements, measurement of bronchial reactivity, or some measurement of airway inflammation are needed to determine treatment of asthma. It is difficult to define the severity of asthma in the clinic specially to confirm whether a patients has mild asthma or not. Asthma symptoms are often underestimated, leading to inadequate therapy.[3] The goals of asthma treatment have been significantly altered in the new guidelines. A large amount of attention is being paid to the area of patient satisfaction, which in turn places great emphasis on quality of life goals, and the notion of partnership between the patient and the provider rather the provider telling the patient what to do.[7]

Therefore, in the present study, the relationship between treatment response and indices of asthma severity was examined to determine indicator(s) of treatment response in this disease.

METHODS AND MATERIALS

Thirty six asthmatic patients were recruited from the Asthma Clinic, Ghaem Medical Centre, Mashhad University of Medical Sciences. All patients had the

Table I: The criteria for asthma severity score

Symptom	Frequency	Score
Night wheezing	None	0
	Sleeping well with a little wheezing	1
	Waking once at nigh	2
	Waking most of the night	3
Night cough	None	0
	Sleeping well with a little cough	1
	Waking once at night	2
	Waking most of the night	3
Exercise cough and wheezing	Non existent during heavy exercise	0
	Existing only during heavy exercise	1
	Existing during climbing stairs	2
	Existing during ordianry activity	3
Morning cough, tightness, and wheezing	None	0
	Existing during exertion	1
	Mild symptoms without exertion	2
	Waking in the morning due to symptoms	3
Day time cough, tightness, and wheezing	None	0
	Once a day	1
	Two or more times a day	2
	Affecting day time activity	3
		16

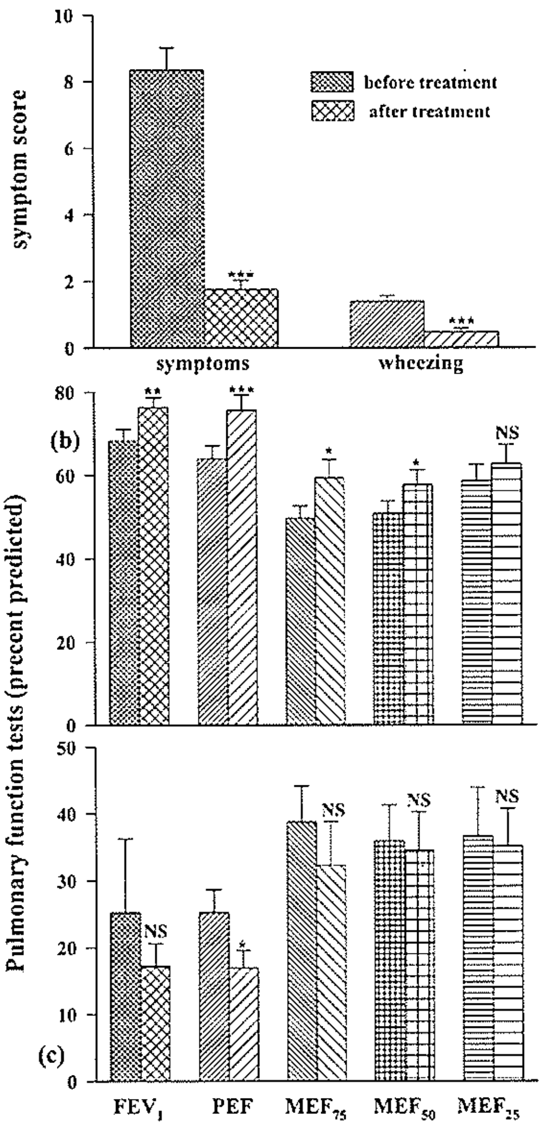

Fig. 1. Comparison of symptom score and wheeze (a) pulmonary function tests (b), and increase in PFT values due to inhalation of 200 μg salbutamol of studied asthmatic patients (c) before (fine filled bars) and after three months treatment (coarse filled bars). FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expriatory flow; MEF_{75}, MEF_{50}, and MEF_{25}: maximal expiratory flow at 75%, 50%, and 25% of the FVC, respectively. All values of PFTs were quoted as percentage predicted. Statistical difference in different parameter between starting and the end of treatment: NS; non significant difference, *: $p<0.05$, **: $p<0.002$, ***, $p<0.001$.

following criteria: 1) previously diagnosed asthma by a physician and having two or more of the following symptoms: recurrent wheeze, recurrent cough or tightness at rest; wheeze, cough or tightness during night or early morning; wheeze or cough during exercise, 2) having FEV1 and PEF less than 80% of the predicted values, 3) no history or symptoms of cardiovascular or other respiratory diseases that required treatment (excluding the common cold). The studied patients had moderate to severe asthma according to Gina guiudelines.[6] The protocol was approved by the Ethics Committee of our institution, and each subject gave an informed consent. The study was carried out during spring and summer 2002.

Protocol

Medical examination was performed and asthma symptoms were taken in all patients in the beginning and at the end of the study. Asthma symptom score was counted according to Table I.[8] The degree of wheezing was considered between 0-3 as follows: no wheezing= 0, hardly heard wheezing= 1, moderate wheezing= 2, and loud wheezing= 3. Pulmonary function tests were also measured in the beginning and at the end of the study using a spirometer with a pneumotachograph sensor (Model ST90, Fukuda, Sangyo Co., Ltd. Japan) before and 10 min after 200 μg inhaled salbutamol. Prior to pulmonary function testing, the required manoeuvre was demonstrated by the operator, and subjects were encouraged and supervised throughout test performance. Pulmonary function testing was performed using the acceptability standards outlined by the American Thoracic Society (ATS) with subjects in a standing position and wearing nose clips.[9] All tests were carried out between 1000 and 1700 hours. Lung function tests were performed three times in each subject with an acceptable technique. The highest level for forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), maximal expiratory flow at 75%, 50%, and 25% of the FVC (MEF75, MEF50, and MEF25 respectively) was taken independent from the three curves.

The increase in PFT values 10 min after 200 μg inhaled salbutamol (in percentage) was considered as reversibility in airway constriction as follows:

$$\frac{\text{PFT values after inhaled salbutamol} - \text{baseline PFTs}}{\text{Baseline PFTs}} . 100$$

Improvement in SS, wheeze and PFT values at the end of the study was considered as treatment response.

Treatment duration and administered drugs

Each patient was treated for a period of three months

Table II: Characteristics of studied asthmatic patients.

Variables	Male		Female		Total	
	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD
Number	13		23		36	
Height (cm)	137-188	163.08+3.6	142-165	154.3+1.22	137-188	157.47+1.64
Age (year)	10-73	42.31+6.15	13-68	36.49+13.06	10-73	39.06+2.78

Table III: Family history of asthma and history of allergy in studied patients.

History	Male		Female		Total	
	Number	Precent	Number	Precent	Number	Precent
Family history	7	53.84	13	56.52	20	55.55
Allergy	8	61.53	15	65.21	23	63.88

Table IV: Different types of drugs in treatment regimen of asthmatic patients and percentage of patients using each type of drug.

Type of Drugs	Male		Female		Total	
	n	%	n	%	n	%
Inhaler β_2-agonist	8	61.54	13	56.52	21	58.33
Oral methyl xanthine	13	100	22	95.96	35	97.22
Inhaler corticosteroid	13	100	23	100	36	100
Oral corticosteroid	9	64.23	14	60.87	23	63.84
Sodium cromoglycate	1	7.64	0	0	1	2.78
Anti-histamine	2	15.38	3	13.04	5	13.84

Table V: Pulmonary function tests (PFTs) of asthmatic subjects prior (baseline) and their increments 10 min after inhalation of 200 μg salbutamol at the beginning and the end of the study.

PFTs	Baseline		Increment after salbutamol inhalation	
	Beginning	End	Beginning	End
FEV_1(1)	68.25+2.83	76.28+2.47**	25.24+11.01	17.19+3.40 NS
PEF(1/s)	63.95+3.13	75.68+3.66 ***	25.23+3.5	16.92+2.64 *
MEF_{75}(1/s)	49.64+2.98	59.32+4.37 *	38.79+5.36	32.29+6.56 NS
MEF_{50}(1/s)	50.83+2.75	57.70+3.58 *	35.79+5.36	34.56+5.73 NS
MEF_{25}(1/s)	58.64+3.98	62.73+4.59 NS	36.61+7.25	35.14+5.61 NS

EFV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow; MEF_{75}, MEF_{50}, and MEF_{25}: maximal expiratory flow at 75%, 50%, and 25% of the FVC, respectively. All values of PFTs were quoted as percentage predicted. Statistical difference in different parameters between the start and the end of treatment: NS; non significant difference, *; $p<0.05$, **;$p<0.002$, ***; $p<0.001$.

Table VI: Correlation between treatment response (improvement in different parameters due to 3 months treatment= I) with symptom score (SS), wheeze, and increase of different PFT values due to inhalation of 200 μg salbutamol (reversibility of airway constriction= R).

	SS	Wheeze	FEV_1 R	PEF R	MEF_{75} R	MEF_{50} R	MEF_{25} R
SS I	r= 0.823***	r= 0.440 **	NS	NS	NS	NS	NS
Wheeze I	r= 0.320 *	r= 0.823 ***	NS	NS	NS	NS	NS
FEV_1 I	NS	NS	r= 0.694 ***	r= 0.372*	NS	NS	NS
PEF I	NS	NS	NS	NS	NS	NS	NS
MEF_{75} I	NS	NS	NS	NS	NS	NS	NS
MEF_{50} I	NS	NS	NS	NS	NS	NS	NS
MEF_{25} I	NS	NS	R= 0.323*	NS	NS	NS	NS

For abbreviations see Table 5. Significance Correlations: NS; non significance, *; $p<0.05$, **; $p<0.01$, ***; $p<0.001$.

and was visited and controlled almost three times during treatment duration. The treatment regimen of all studied patients included inhaled corticosteroid, mostly beclomethasone dipropionate (400-1400 μg dependeing upon the severity of the disease) and in some cases fluticasone dipropionate (500 μg). Sixty four precent of patients had oral corticosteroid in their treatment regimen mostly consumed at the start of the study or during exacerbation. Ninety seven precent of patients received methyl xanthine and 58% inhaled salbutamol. None of the patients had oral β-agonist drugs in their treatment regimen. At the beginning of the study a few patients were under an acceptable theraputic regimen for asthma and used inhaled corticosteroids.

Data analysis

The data of asthma symptom score, degree of wheeze, PFT values, and reversibility of PFTs due to inhalation of 200 μg salbutamol were expressed as measn±SEM and those of height and age as mean±SD. All data were compared between the beginning and the end of the study using paired "r" test. The improvement in symptom score, degree of wheeze and PFT values were related to baseline values of symptom score, degree of wheeze, and reversibility of PFTs using the least square regression. Significance was accepted at $p<0.05$.

RESULTS

Symptoms and wheezing

Symptom score was significantly improved due to 3 months treatment (8.35+0.67 vs 1.76+0.27, $p<0.001$). Wheezing was also significantly reduced at the end of the study period (1.39+0.17 vs 0.47+0.11, $p<0.001$), (Fig 1a).

Pulmonary function tests

All PFT variables were abnormally low in studied asthmatic patients at the beginning of the study (49.64+2.98% to 68.25+2.83%). PFT variables were significantly improved due to 3 months treatment (57.70+3.58 to 76.28+2.47, $p<0.05$ to $p<0.001$) except MEF_{25} (Table 5, Fig. 1b).

There was a considerable reversibility in airway constriction in asthmatic patients at the beginning of the study. All PFT vairables were increased due to inhalation of 200 μg salbutamol (25.23±11.01 to 38.79±5.36). Increase in PFT variables due to inhalation of 200 μg salbutamol were reduced at the end of the study (16.92+2.64 to 35.14±5.61) but these reductions were not statistically significant except for PEF ($p<0.05$), (Table 5, Fig. 1c).

Correlation between treatment response with baseline symptom score, wheeze and reversibility of airway constriction

There were significant correlations between both baseline symptom score and wheeze with an improvement of these two parameter ($p<0.05$ to $p<0.001$). There were also significant correlations between reversibility in FEV_1 with improvement in FEV_1 and MEF_{25} after treatment. The relationship between reversibility in PEF and improvement in FEV_1 at end of the study was also statistically significant ($p<0.05$ to $p<0.001$). However, correlation between baseline symptom score, wheeze and reversibility in other PFT values and criteria of treatment response in asthma were not statistically significant (Table 6).

DISCUSSION

The result of the present study showed improvement in symptom score, wheezing and PFT values. According to recent guidelineg for asthma management,[6] the main aims of asthma management include, control of symptoms, maintaining pulmonary function tests as close to normal level as possible and maintainance of normal activity levels.[6] Although in the present study, asthmatic patients were treated for a short preiod of time, there were significant improvements in PFT values. The increase in PFT values due to inhalation of salbutamol (air way reversibility) was slightly reduced at the end of study. The reduction of airway reversibility is probably due to improvement in PFT values. The main pathological feature of asthma is airway inflammation. Therefore treatment of asthma should focus on reduction of airway inflammation. The treatment regimen of all asthmatic patients in this study included beclomethasone or fluticasone inhaler during the entire period of the study. Although the dose of corticosteroid in treatment regimen of studied patients varied at the beginning of the study, during the last two months of the study all patients had received 400-800 μg beclomethasone or 500 μg fluticasone (in only 5 case). Regarding the age of the patients, 8 patients had age under 30 years and one patient over 65. The age of the rest of patients was between 32 and 65 years (44.72±8.94). Comparison of data among this age group was very similar to that of total patients.

However the main concern in asthma managment is adjusting drug therapy with treatment response. It is apparent that no single measure of disease control can encompass all of the clinical problems in asthma.[10] The principals of response to asthma therapy are forced expiratory volume in one second (FEV_1), morning peak expiratory flow rate (PEFR), symptom score (day and night), $beta_2$-agonist use, and number of exacerbations. In many ways these measurements give different informations about the patient's physiology in an objective way, whereas symptom give more information about how the disease is affecting the patient.[11] FEV_1 and PEFR may not be the ideal measurements in mild asthma.[12] The FEV_1 and PEFR values are comparable with those seen in other studies. However, the percentage changes from baseline are higher for symptoms and $beta_2$-agonist use than for long function measurements, suggesting that these measurements are more sensitive indices of differential therapeutic effects. These data suggest that future studies should use clinical effect as one of the outcome measures.

Because the response to treatment in different asthmatic subjects is variable, stabilizing a treatment plan is not easy. Therefore, in the present study the correlation between symptom score (SS), wheezing, and reversibility of airway constriction was examined. The significant correlation between baseline SS and wheeze with improvement in these two parameters at the end of the study indicated that SS and wheeze could be indicators of treatment response.

Positive correlation between reversibility of the FEV_1 and MEF_{25}, and positive correlation between reversibility of PEF with improvement in FEV_1 at the end of the treatment period showed that reversibility of FEV_1 and PEF could also serve as indicators of treatment response in asthma. The objective criteria such as reversibility of FEV_1, PEF, and degree of wheeze are of particular improtance in predicting treatment response in this disease. However, the lack of significant correlation between indicators of asthma severity with all of criteria of treatment response indicate that no SS and wheezing neither reversibility of PFTs could be a strong indicator or treatment response in asthma.

There are several studies regarding self management of asthma. Most of these studies demonstrate that different criteria of asthma severity specially values of PEF could be used as indicators of self management of this disease. For example it has been shown that the regular measurement of PEF can lead to reduction of using drugs specially bronchodilators and corticosteroids in asthmatic patients,(13,14) reduction of asthma symptoms, increase in PFT values,[15] and prediction paitents,[13,14] reduction of asthma symptoms, increase in PFT values,[15] and prediction of asthma attack.[16] It has also been shown that regular PEF measurement is a good indicator for determining the treatment regimen (drugs) in asthmatic patients.[13] Our previous study[17] also showed that regular measurement and morning evening variability in PEF is a valuabel means in self management of asthma. All the above studies support the results of the present study to some extent and emphasize that regular PEF measurement could be a good indicator for treatment response in asthma.

The present study is a further effort regarding the examination of indicators of treatment response in asthma. However the treatment response varies in patients with similar severity of asthma. The dose of a drug sufficient to normalize PFTs or prevent asthma exacerbations varies among different asthmatic patients.[18] It is known that those patients with a marked diurnal variability in lung function are at greater risk of exacerbations of asthma, hospital admission and asthma related death.[19] Thus, in deciding the correct level of treatment, a clinician needs to known the degree of spontaneous variability and the degree of improvement of asthma exacerbation, the symptoms, and the amount of $beta_2$-agonist use. Therefore this issue should be examined in further studies. For example morning evening variability in PEF may be a good indicator in this regard. Measuring Airway hyperresponsiveness (AHR) is perhaps the best indicator for treatment response in asthmatic patients but it is an expensive test and it is not available in all clinics. However the correlation between treatment response and AHR in asthmatic subjects should be examined in further studies. In addition, studying more patients with wider severity of disease could be helpful in this regard.

In conclusion the results of this study showed that a well conducted therapeutic program can lead to improvement of both symptom, wheeze, and PFT values. In addition symptom score, wheeze, and reversibility in FEV_1 and PFF could be good indicators of response to treatment in asthma.

REFERENCES

1. Ven A Lewis S, Cooper M, Hill J. Increasing prevalence of wheeze and asthma in Nottingham primary school children 1988-95. Eur Respir J 11: 1324-1328, 1998.
2. Barnes PJ, Jonsson B, Klim J. The cost of asthma. Eur Respir Rev 9: 636-642, 1996.
3. Boskabady MH, Karimian M, Prevalence of asthma among guidance school students (aged 11-16 years) in the city of Mashhad (north east of Iran). Arch Iran Med 3: 165-169, 2000.
4. boskabady MH, Kolahdoz GH, Prevalence of asthma symptom among adult population in the city of Mashhad (north east of Iran). Respirology 11: 267-272, 2002.
5. Barnes P. Introductory remarks. Eur Respir Rev 7: 309, 1997.
6. Shefer AL: Global Initiative for asthma. Global strategy for asthma management and prevention. WOH, INHLB Workshop Report, Publication no. 95-3659, National Institute of Health, Bethesda, 1995.
7. Buist S. Development of evidence based guidelines for inhaled therapeutic interventions in asthma. Eur Respir Rev 8: 322-323, 1998.
8. Makino S, Clinical significance of bronchial sensitivity to acetylcholine and histamine in bronchial asthma. J Allergy 38: 127-142, 1966.
9. American Thoracic Society. Standardization of spirometry: 1994 Update. Official Statement of American Thoracic Society. Am J Respir Crit Car Med 152: 1107-1136, 1995.
10. Barnes N, Evaluating asthma and its treatment: clinical markers and indications of efficacy. Eur Respir Rev 6: 31-37, 1996.
11. Laitinen LA: Comparative clinical data in mild asthma populations. Eur Respir Rev 7: 313-315, 1997.
12. Kuo HP, Yu TR, Yu CT: Hypodense eosinophil number relates to clinical severity, airway hyperresponsiveness and response to inhaled corticosteroids in asthmatic subjects. Eur Respir Rev 7: 1452-1459, 1994.
13. Janson-Bjerklie S and Shnell S: Effect of peak flow information on patterns of self-care in adult asthma. Heart and Lung 17: 543-549, 1988.
14. Charlton I, Charlton G, Broomfiled J, Mullee MA: Evaluation of peak flow and symptoms on self management plans for control of asthma in general practice. Br Med J 301: 1355-1359, 1990.
15. Beasley R, Cushley M, Holgate ST: A self management plan in the treatment of adult asthma. Thorax 44: 200-204, 1989.
16. Pinzone HA, Carlson BW, Kotses H, Creer TL: Prediction of asthma episodes in children using peak expiratory flow rates, medication compliance and exercise data. Annals of Allergy 67: 481-486, 1991.
17. Boskabady MH, Hossaini M: Effect of patient education and regular PEF measurement on self management of asthma. Ir J Allergy Asthma Immunol 1: 159-1659, 2000.
18. Toogood JH, Lefave Haines DSM, et al: A graded dose assessment of the efficacy of beclomethasone dipropionate aerosol for severe chronic asthma. J Allergy Clin Immunol 5: 298-308, 1977.
19. Hetzel MR, Clark TJH, Branthwaite MA, Asthma: analysis of sudden death and ventilatory arrests in hospital. Br Med J 1: 808-811, 1977.