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Best Drugs for Avoiding Paradoxical Bronchospasm During Spirometry

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ABSTRACT

Background: *Asthma could be diagnosed by its characteristic presentation. Spirometry can help the diagnosis by revealing post-bronchodilator response. Classically, salbutamol (albuterol) is used for evaluating post-bronchodilator response. This drug causes paradoxical bronchospasm in less than 10% of asthmatic patients. This study aimed to evaluate the frequency of paradoxical bronchospasm with salbutamol during spirometry and compare it with other drugs that did not reveal paradoxical bronchospasm such as levalbuterol and ipratropium.*

Materials and Methods: *One hundred-Ninety two asthmatic subjects were entered in this clinical trial. All patients showed clinical manifestations of asthma and revealed obstructive pattern during spirometry. They were randomly assigned into three groups of drugs included: salbutamol, levalbuterol and ipratropium. Two puffs of these drugs were administered via a spacer and patients waited for fifteen minutes for the maximal effect to take place. Then spirometry was obtained again and post-bronchodilator FEV1 and its alterations were compared among the three groups.*

Results: *The mean± SD age of patients was 49.40±17.4 years; the mean age, demographic data, clinical findings and spirometry results showed no significant difference among groups. FEV1 percent of predicted was 58.6± 19.5 which proved that most subjects were suffering from severe asthma. Improvement of FEV1 by salbutamol (22.2±3%) and levalbuterol (16±18%) was significantly more compared with ipratropium (9.4±11%) (t=2.5, P=0.01 and t=2.2, P=0.01, respectively). Paradoxical bronchospasm (more than 12% decrease in FEV1) was seen in two (3%), one (1.5%) and four (6%) subjects of salbutamol, ipratropium and levalbuterol groups, respectively. Regarding clinical improvement, levalbuterol resulted in the higher frequency of clinical improvement compared to salbutamol and ipratropium.*

Conclusion: *With the dosage recommended for reversibility testing during spirometry, salbutamol showed comparable bronchodilator response and paradoxical bronchospasm frequency compared to levalbuterol and ipratropium.* ***(Tanaffos 2009; 8(3): 58-64)***

Key words: *Asthma, Paradoxical bronchospasm, Salbutamol, Albuterol, Levalbuterol, Ipratropium*

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INTRODUCTION

Asthma can be diagnosed by its typical presentation such as frequent episodes of cough, wheezing and chest tightness especially at night which is reversible spontaneously or by medication (1). Spirometry can be useful since it shows obstructive pattern that typically improves more than 12% in FEV1 or FVC (2). This finding can aid to confirm diagnosis in typical subjects mentioned above or help in diagnosing subjects without a typical history. To evaluate reversibility, usually 400 µg salbutamol (albuterol) should be used when given by metered dose inhaler using a spacer. Tests should be rechecked after a 15-minute delay (3).

Salbutamol contains two isomers, R and S in a half and half ratio (4). R isomer is responsible for the bronchodilatory effect of salbutamol but S isomers cause bronchospasm (called paradoxical bronchospasm) in up to 8% of asthmatic subjects via increasing Ca influx to bronchial smooth muscles (5) and increasing airway hyper-responsiveness (6). In this regard, using salbutamol may cause misleading in diagnosis due to decrement in FEV1 during spirometry. Other short acting bronchodilators such as levalbuterol that exclusively contains R isomer of salbutamol devoid bronchial reactivity of Salbutamol and cause more potent bronchial dilation than salbutamol (7). Hypothetically by using this drug or ipratropium bromide that are not used for evaluation of bronchodilator test, paradoxical bronchospasm could be prevented during spirometry and better interpretation of pulmonary function test may be obtained. On the other hand, usually minimum dosage of salbutamol is used during spirometry and the S component of this drug does not seem to be enough to produce paradoxical bronchospasm. Nevertheless, it was not clearly defined that whether this effect is able to affect the result of bronchodilator test. The aim of this study was to compare the frequency of paradoxical bronchospasm in salbutamol, levalbuterol and ipratropium groups and to determine the effect of this phenomenon on diagnosis of asthma by using spirometry.

MATERIALS AND METHODS

Subjects

One hundred-ninety two asthmatic subjects (mean ±SD age: 49.40±17.4 years; range 10- 86 yrs) were enrolled in this prospective clinical trial. For diagnosis of asthma, following criteria were used:
1- history of cough, dyspnea, wheezing and air way hyper-responsiveness, 2- exacerbation of symptoms at night and some seasons, 3- spirometry showing obstructive pattern. 4- all patients were new cases or subjects that withheld their drugs for a long time.

The exclusion criteria were evidence of other eosinophilic lung diseases, abnormal chest x- ray, history of smoking, corticosteroid usage (systemic or inhaled) and recent infection.

Technique and protocol

Spirometry: Standard spirometry was performed on all subjects before sample collection (Superspiro, Microedical Inc. England) according to American Thoracic Society standards (8) by well-trained and experienced personnel. Main variables measured consist of forced vital capacity (FVC), forced expiratory volume in one second (FEV1), forced expiratory flow in 25 to 75% of vital capacity (FEF_{25-75}) and FEV1/FVC.

Random assignment: The whole group was randomly divided into three equal number groups by drawing lots from a box containing three numbers by a person that was not aware of the study and subjects. Then the numbers were translated to the appropriate drugs consisted of salbutamol (ventalex, Sina Daru Inc.), levalbuterol (xoponex, Sepracor Inc.) and Ipratopium bromide (atrovent, Bohringer Ingelheim Inc.) by another person. The appearances of drugs were similar and only could be differentiated by a number.

Technique: Two puffs of drugs mentioned above

(salbutamol 200 µg per puff, levalbuterol 45 µg per puff, ipratropium 20 µg per puff) were used as metered dose inhaler via a spacer and patients were asked to take a deep and slow breath from the spacer (3). After the administration of drugs, patients waited for fifteen minutes to take a better response from the most retard drug (ipratropium). Spirometry and FVC were checked again after this period and post-bronchodilator changes. FEV1 was used in this study for determination of post bronchodilator changes. It is approved that this parameter showed lower variability than resistance of airways (RAW, SGAW and IOS parameters such as R5, R20) and also it revealed higher improvement than FVC and MMEF (9). After the test, patients were asked about the clinical effect and subjective improvement or deterioration of symptoms and the information were entered in a questionnaire.

Ethical consideration: The experiments were approved by the Ethical Committee of Islamic Azad University of Mashhad and each subject gave an informed consent.

Statistical analysis

Sample size was calculated according to 5% alpha error, 80% power and frequency of paradoxical bronchospasm obtained from a pilot study. The mean age and spirometric data were quoted as arithmetic mean and standard deviation. The mean spirometric values were compared among different under study groups. Post bronchodilator FEV1 and response to bronchodilator in each group were compared with each other using unpaired "t" test. Frequency of paradoxical bronchospasm was compared among the under study groups by using chi-square test. Significance was accepted at $p<0.05$.

RESULTS

General data

One hundred-Ninety two asthmatic subjects with a mean ± SD age of 49.40±17.4 years were entered in this study. The mean age and sex distribution in different groups were not significantly different. Frequency of clinical findings and aggravating factors in the 3 groups are shown in Table 1. Comparison of these demographic and clinical parameters revealed no significant difference (except for sputum and exacerbation with exercise that were significantly lower in the salbutamol group).

Table 1. Comparison of demographic data and clinical findings and aggravating factors among asthmatic subjects tested with three different bronchodilators

	Salbutamol (N=64)	Ipratropium (N=64)	Levalbuterol (N=64)
Male/ Female	41/23	35/28	34/30
Age (yrs)	49±17.9	48±17.9	50±17
Occupational pollution	7 (10.9%)	9 (14.3%)	10 (15.6%)
Cough	55 (90%)	60 (93%)	60 (94%)
Dyspnea	58 (95%)	60 (95%)	63 (98%)
Wheezing	58 (97%)	62 (97%)	61 (95%)
Sputum*	36 (59%)	50 (78%)	53 (82%)
AHR	36 (87%)	45 (92%)	54 (84%)
Night symptoms	31 (74%)	45 (90%)	48 (75%)
Exacerbation during exercise*	37 (90%)	48 (96%)	64 (100%)
Family history of asthma	26 (44%)	31 (48%)	31 (48%)
Allergy history	28 (47%)	34 (54%)	27 (42%)
GERD	31 (52%)	41 (65%)	40 (62%)

*= P<0.05
AHR=Airway hyper-responsiveness
GERD: Gastroesophageal Reflux Disease

Spirometry results

Spirometry data in all subjects showed low levels of FVC (2.23 ± 0.87 L), FEV1 (1.47 ± 0.66 L) and FEV1/FVC (66.3± 10.4 %) which were in favour of obstructive pattern. FEV1 percent of predicted was 58.6±19.5 which proved that most subjects were suffering from severe asthma. Comparison of

baseline spirometry data among different groups of drugs tested showed no significant difference except FVC in salbutamol group. Post bronchodilator FEV1 and its percent of predicted in different groups were not significantly different. Improvement of FEV1 by salbutamol and levalbuterol was significantly more than that of ipratropium group (t=2.5, p=0.01 and t=2.2, p=0.01, respectively) (Table 2). Comparison of salbutamol and levalbuterol groups showed no significant difference. Paradoxical bronchospasm (more than 12% decrease in FEV1) was seen in two, one and four subjects of salbutamol, ipratropium and levalbuterol groups respectively.

Post bronchodilator results:

Physiologic assessment after using bronchodilators showed the highest mean FEV1 with salburamol followed by Levalbuterol (Table 3). On the contrary, Levalbuterol showed the greatest decrease in FEV1 in subjects with paradoxical bronchospasm (according to mean decrease of FEV1 and frequency of subjects) (Figure 1). After excluding the subjects with no change in their clinical findings, comparison of clinical improvement showed that Levalbuterol resulted in the highest frequency of clinical improvement compared to Salbutamol and Ipratropium (X^2= 9.13, P=0.002, X^2= 5.64, P=0.01 respectively).

Table 2. Comparison of baseline and post-bronchodilator spirometry results among asthmatic subjects tested with three different bronchodilators

	Salbutamol (N=64)		Ipratropium (N=64)		Levalbuterol (N=64)	
	Mean	% Pred	Mean	% Pred	Mean	% Pred
VC (L)	2±0.85	63±17	2.2±0.93	67±16	2.2±0.82	64±18
FVC (L)	1.98±0.83*	69±19*	2.3±0.9	77±18	2.2±0.86	72±20
FEV1 (L)	1.37±0.62	57±19	1.53±0.69	61±20	1.5±0.66	56±19
FEV1/FVC (%)	48.5±10		65.4±11		67±1.6	65±10
FEF25-75 (L/S)	1.04±0.6	31±16	1.1±0.69	33±18	1.15±0.66	31±13
MEF50% (L/S)	1.16±0.63	29±15	1.3±0.88	31±18	1.2±0.72	29±14
Post BD FEV1 (L)	1.6±0.73	67±19	1.6±0.76	67±21	1.7±0.76	65±21

Table 3. Comparison of physiologic and clinical response after using bronchodilator in asthmatic subjects tested with three different bronchodilators

		Salbutamol (N=64)	Ipratropium (N=64)	Levalbuterol (N=64)
Physiologic response	Post BD change in FEV1 (%)	+22.2±3*	+9.4±11	+16±18†
	≥12% decrease in FEV1	2 (3%)	1 (1.5%)	4 (6%)
	Mean decrease in FEV1	-7.5±5.6	-4.5±3.5*	-12.3±12
Clinical response	Get better	28 (44%)	38 (60%)	49 (76%)
	Get worse	8 (12%)	7 (11%)	1 (1.5%)
	No change	27 (42%)	19 (30%)	14 (22%)

* = Significant difference between Salbutamol and Ipratropium groups

†= Significant difference between Levalbuterol and Ipratropium groups

%Pred= Percent of predicted

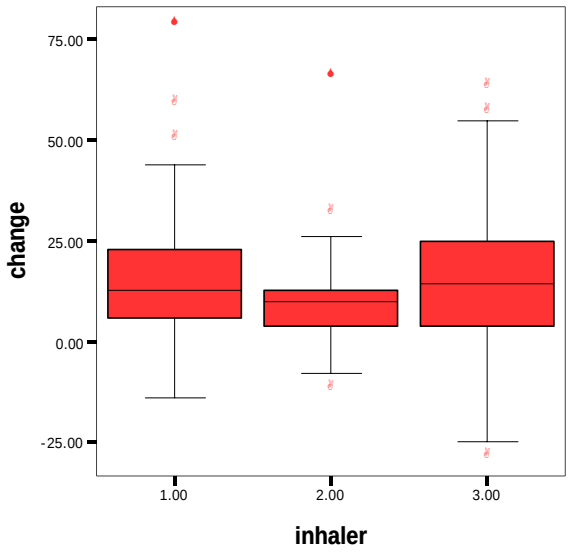

Figure 1. Comparison of mean FEV1 changes after using bronchodilator between salbutamol (1), ipratropium (2) and levalbuterol (3)

DISCUSSION

In this double-blinded clinical trial, the acute effects of three different short acting bronchodilator inhalers were compared on moderate to severe asthma. FEV1 was the parameter used for evaluation of post bronchodilator improvement because it showed lower variability than resistance of airways and changes more significantly than FVC and MMEF (9). According to previous reports on levalbuterol and ipratropium, before the study we expected that these drugs induce higher degree of bronchodilation and lesser frequency of paradoxical bronchospasm.

Overall, results of this study showed that the degree of elevation or decline in mean FEV1 (as a marker of bronchodilation or bronchospasm) was not significantly different in three drugs. The apparent clinical effect of these drugs was not so obvious as spirometry results. In all groups a large fraction of subjects reported no significant change in their symptoms. Worsening of symptoms by levalbuterol was only reported in one subject and this difference was not statistically significant between groups.

Clinical effects of these drugs were compared for longer in-hospital management (10), but comparable studies of one dosage of these drugs in the literature are scanty. Pharmacologically, salbutamol had been assumed to induce higher degree of bronchospasm than levalbuterol and ipratropium. Experience of paradoxical bronchospasm in routine clinical practice for the first time is usually so surprising and frightening that most clinicians search for a safer drug to substitute with salbutamol. In epidemiological studies, paradoxical bronchospasm induced by Salbutamol was not so frequent.

Nicklas reported paradoxical bronchospasm by salbutamol in 126 subjects during a 14-year period in the United States (1974- 1988) (11), and in a new recent large study salbutamol in the form of MDI inhaler and Respimat soft mist inhaler did not induce bronchospasm in 631 asthmatic and 1538 COPD patients (12).

In another study by Smeenk et al. the complications of salbutamol were not significant (13). Actually, the recommended dosage of salbutamol during spirometry is not high enough to deliver large amount of S isomer and induce paradoxical bronchospasm. In this regard, this study revealed that paradoxical bronchospasm with salbutamol was not more frequent than other substitute drugs.

Theoretically, levalbuterol is a drug that devoids bronchospastic effect of S isomer. However, it induced paradoxical bronchospasm in this study. Surprisingly this drug showed the highest decrement of mean FEV1 among the three drugs tested. We should remember that paradoxical bronchospasm was also reported for levalbuterol in other studies (14) in addition to the present study. Therefore, the etiology of paradoxical bronchospasm cannot be solely described by R- S isomer hypothesis.

Morley et al. (15) proposed five different

mechanisms for paradoxical bronchospasm. He concluded that among these mechanisms, increased inflammatory burden and induction of airway hyper-reactivity, alone or in combination are the most plausible reason for induction of paradoxical bronchospasm. Other confounding factors that may decrease the post bronchodilator FEV1 such as fatigue due to repeating the FVC manoeuvre and sputum production should be considered. In this study by choosing an appropriate sample size, we tried to decrease these confounding factors.

Ipratropium was used as a bronchodilator. In comparison to beta-2 agonists, it exerts lesser degree of improvement in FEV1 and lower side effects (16). In this study, ipartrpium revealed the least mean FEV1 increment, but unexpectedly this drug showed a greater improvement reported by the patient in comparison to salbutamol. Due to low sensitivity, clinical improvement is not an approved criterion for evaluation of reversibility for the time being. Therefore, ipratropium is a safe drug but it may increase false negative results during post bronchodilator testing.

Salbutamol is the most well known drug that is widely used for treatment of exacerbation of asthma. On the other hand, predisposition to paradoxical bronchospasm should be assessed under supervision of a physician. Experiencing paradoxical bronchospasm warns the physicians and the patients to avoid using salbutamol in situations that high dose of drug is used (such as asthma emergency). During spirometry and post-bronchodilator reversibility testing, attention to changes in FEV1 during spirometry is the best opportunity for confirming the presence of paradoxical bronchospasm. For this reason and equivalent frequency of paradoxical bronchospasm with other drugs (ipratropium and levalbuterol), we recommend using salbutamol during bronchodilator testing.

Reversibility change is not exclusively determined in asthma, it is also used in COPD (17). We believe that in COPD, salbutamol-induced paradoxical bronchospasm should be lower than that of asthmatic subjects, but it should be investigated in further studies.

In conclusion, we believe that salbutamol is still a valuable drug for bronchodilator testing and it does not need to be replaced by a newer drug except in subjects with an approved history of complication with salbutamol.

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