Assessing the Response of a Sample of Iraqi Asthmatic Patients to Different Medication Regimens

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Abstract

Asthma is a chronic inflammatory disease of respiratory airways characterized by distinctive history of respiratory symptoms due to variable airflow obstruction which reverses either spontaneously or in response to certain medications. Acetylcholine is a parasympathetic neurotransmitter which plays fundamental roles in the development of persistent asthma. Treatment guidelines recommend using medium doses of inhaled corticosteroids in addition to another controller bronchodilator instead of using high doses inhaled steroid alone for treatment of moderate to severe persistent asthma. The inhaled long acting muscarinic antagonist, tiotropium, was approved recently to control unresponsive asthma to inhaled corticosteroid with or without a long acting β-2 agonist. The aim of this study was to assess and compare the responses of a sample of Iraqi asthmatic patients to three different medication regimens.

Key words: *Persistent asthma, Medication regimens, Tiotropium*

Introduction

Asthma is a disease characterized by chronic inflammation of respiratory airways causing the distinctive history of variable respiratory symptoms which include wheezing, shortness of breath (SOB), cough and chest tightness due to variable airflow obstruction which reverses either spontaneously or in response to certain medications [(1)].

Acetylcholine (ACh) is a parasympathetic neurotransmitter and plays principle roles in the development of chronic or persistent asthma via multiple types of muscarinic receptors resulting in enhancement of inflammatory mechanism, mucus hypersecretion, bronchial lumen narrowing and remodeling of respiratory airways [(2)].

Two important terms are used in the assessment of asthma; the first being severity which is concerned with describing disease process and is used primarily when initiating treatment, whereas the term control is a dynamic tool concerned with describing the response of patients to therapy depending on the efficacies of the prescribed therapeutic agents [(3)].

The level of asthma control during the previous four weeks can be assessed by asthma control test (ACT) questionnaire which involves five questions with answering score ranges from one which means worst control to five which means best control [(4)]. A change of three points in the total score of ACT is considered minimal clinically important difference (MCID) [(5)]. Pulmonary function test (PFT) maneuver is a valuable non invasive procedure for measuring airway caliber of both large and small airways [(6)].

Inhaled corticosteroids (ICS.s) are the cornerstone anti-inflammatory medication indicated alone or in combination with other controllers for controlling all severities of persistent asthma. Treatment guidelines recommend using medium doses of ICS in addition to another controller bronchodilator instead of using high doses of ICS monotherapy for long term control of moderate to severe persistent asthma [(7)]; long acting β-2 agonists (LABAs), formoterol and salmeterol, are the first line bronchodilator indicated for this purpose, but reduced responsiveness due to tachyphylaxis limits their prolonged use [(8)].

The recent addition to the list of maintenance treatment of persistent asthma is the inhaled long acting muscarinic antagonist (LAMA), tiotropium, which was approved to control unresponsive asthma to ICS with or without a LABA [9]. The aim of this study was to assess and compare the responses of a sample of Iraqi asthmatic patients who reside in Baghdad, Capital of Iraq, to three different medication regimens.

Patients and Methods

Patients

This study was designed as a prospective interventional open label randomized clinical study to evaluate the clinical efficacies of three medication regimens assigned for Iraqi patients with persistent asthma. The study was conducted in 2 sites located in Baghdad, Capital of Iraq, fromSeptember-2018 till June-2019. These sites were the respiratory clinic of Dowaly Private Hospital and AL-Zahra Center of Asthma and Allergy.

The inclusion criteria were: age between 18 and 70 years, current status of poorly controlled or uncontrolled moderate - severe persistent asthma according to diagnosis of the specialist physician, baseline forced expiratory volume in one second (FEV1) of 40-80 % of predicted values and patient being nonsmoker or previous smoker of less than 10 pack years who stopped before at least a year.

Meanwhile, patients should devoid of the following exclusion criteria: pregnancy or lactation for female patients, concurrent serious respiratory or cardiac disease, use of any maintenance asthma controllers within 4 weeks of enrollment visit and respiratory tract infection or use of systemic corticosteroids within the previous 4 weeks of the baseline visit.

Patients were allocated randomly to one of three groups according to the type of treatment regimen being studied:

First group: Combination of budesonide 160 µg and formoterol 9 µg **(Bud/For)** per inhalation of dry powder inhaler (DPI): dose was two inhalations every 12 hours

Second group: composed of budesonide 200 µg per inhalation of DPI and oral modified release aminophylline 225 mg tablets **(Bud/Ami)**: dose of budesonide was two inhalations every 12 hours, while dose of aminophylline tablets was a single tablet every 12 hours after meals.

Third group: composed of budesonide 200 µg per inhalation of DPI and tiotropium capsule containing 18 µg of dry powder intended for oral inhalation **(Bud/Tio)**: dose of budesonide was two inhalations every 12 hours, while that of tiotropium was a single capsule inhaled at evening

All patients were allowed to continue their use of salbutamol metered dose inhaler (MDI) when needed for reliving the acute attacks of asthma symptoms.

Method

The duration of current study was 8 weeks and involved 3 visits: baseline or enrollment visit, first follow up visit 4 weeks after the baseline one and second follow up visit after additional 4 weeks.

Pulmonary function test procedure was performed and ACT values were recorded in each visit. Patients were instructed to perform PFT under the supervision of a well-trained technician for three times and the device recorded the best result automatically.

Statistical Analysis

Discrete variables were presented using their numbers and percentages, whereas continuous variables were presented using their means ± standard deviation (SD). Discrete variables were analyzed using Chi square test or Fisher-Freeman-Halton exact test.

Trend ANOVA was applied to analyze the differences of means within each studied group over three visits (baseline, first follow up and second follow up visits) using the means of values measured in each visit, while One way ANOVA was used to test the differences among the groups using the means of values in the baseline visit and then means of changes of values (increment or decrement) produced during the first and second four weeks of study.. Thereafter, if the general comparison showed significant differences, post Hoc Tukey test was applied to test the significance difference between each pair of means.

Statistical Package for Social Sciences (SPSS) version 23.0.0 (Chicago, IL), GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, software package was applied to conduct the statistical analysis. The level of difference

was chosen to be significant when p value was less than 0.05

Results

This study recruited 78 patients. Fourteen patients terminated the treatment regimens prematurely due to different causes with subsequent exclusion of their data, while those who completed it were 64 patients; 21 patients in the first and second group and 22 patients in the third group. Socio-demographic data of patients were matched across the studied group; patients were older than 40 years in the first group. The first and second groups showed slight male predominance. Patients in all groups were overweight and their BMI values were between 25 and 30 kg/m^2. Nearly two thirds of patients were urban and one third was rural. About 70% of patients were nonsmokers and the majority of them were unemployed. Educational status showed higher ratio of secondary level.

The FEV1 values were increased after initiating study in all groups; medication regimens caused significant increases of measured FEV1 values in first follow up visit compared to baseline one. Both first and third groups developed further significant increase of FEV1 values measured in the second follow up visit in comparison with first follow up values (p<0.001), unlike the second group which showed a non-significant decrease of FEV1 values in second follow up visit compared to first follow up one (p=1.0) as presented in table-1

Table-1: Effects of medication regimens on FEV1

Group	**First group (Bud/For)**	**Second group (Bud/Ami)**	**Third group (Bud/Tio)**	**p-value**
Number of patients	21	21	22	-
FEV1 (Liters)				
Baseline	1.6±0.3	2.0±0.5	2.1±0.6	<0.01a
First follow up (After 4 weeks)	1.9±0.3 *	2.4±0.6 *	2.6±0.6 *	<0.001a
Second follow up (After 8 weeks)	2.2±0.3 *,¥	2.3±0.4 *	2.9±0.7 *, ¥	<0.001a
p-value	<0.001b	<0.001b	<0.001b	

FEV1: Forced expiratory volume in one second
a: One way ANOVA

b: Trend ANOVA (repeated measure ANOVA)
*: significant difference compared to baseline values
¥: significant difference compared to first follow up values

Between groups analysis according to extent of FEV1 improvement revealed that third group developed significantly the largest improvement compared to other two groups during the first four weeks of study (p<0.001), while no significant difference was noted between first and second groups (p=0.71), as shown in figure-1

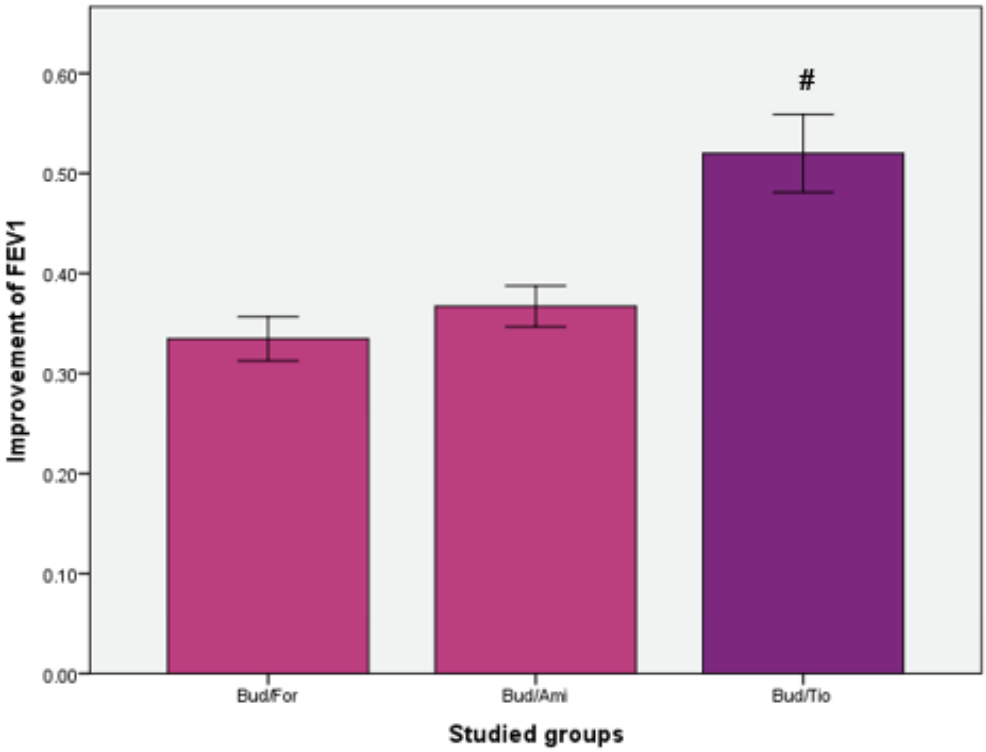

Figure-1: Extent of FEV1 improvement during the first four weeks of study

#: significant difference compared to other groups

The magnitude of FEV1 improvement during the second four weeks of study produced in first and third groups was significantly better than that produced in second group ($p<0.001$), while it was not significantly different between first and third groups ($p=0.93$) as shown in figure-2.

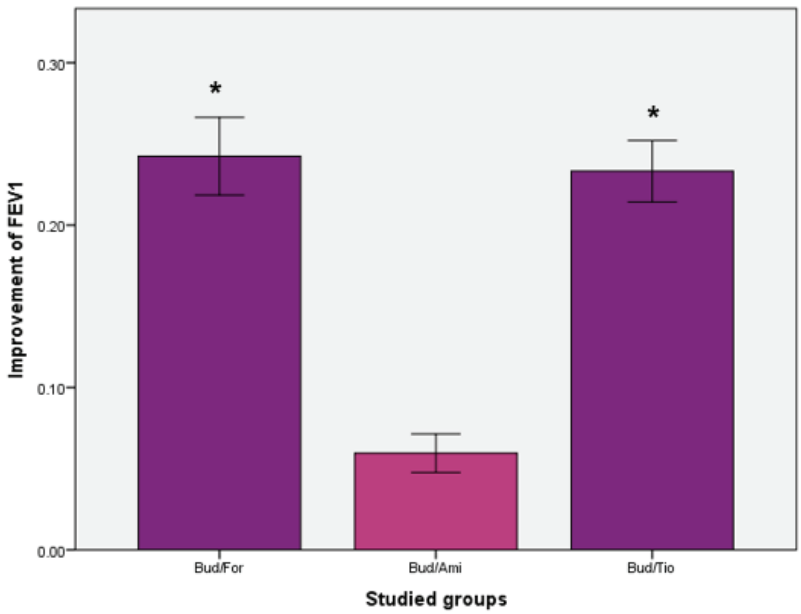

Figure-2: Extent of FEV1 improvement during the second four weeks of study

*: significant difference compared to second group

In all groups, treatment regimens caused significant improvement of ACT scores after 4 weeks of administration compared to pretreatment values (p<0.001). Studied groups continued the improvement and developed significant higher scores of ACT in the second follow up visit in comparison with first follow up scores (p<0.001) as illustrated in table-2.

Table-2: Effects of medication regimens on ACT scores

Group	**First group (Bud/For)**	**Second group (Bud/Ami)**	**Third group (Bud/Tio)**	**p-value**
Number of patients	21	21	22	-
ACT scores				
Baseline	11.5±2.0	11.1±2.2	10.8±1.5	0.433 a
First follow up (after 4 weeks)	17.0±1.3 *	16.6±2.0 *	17.4±1.1 *	0.011 a
Second follow up (after 8 weeks)	21.0±1.4 *, ¥	18.5±2.5 *, ¥	21.3±1.9 *, ¥	<0.001 a
p-value	<0.001b	<0.001b	<0.001b	

ACT: Asthma control test
a: One way ANOVA
b: Trend ANOVA (repeated measure ANOVA)
*: significant difference compared to baseline values
¥: significant difference compared to first follow up values

Comparison between studied groups based on extent of ACT scores increment during the first four weeks of study demonstrated that third group produced the largest significant increment compared to other two groups (p=0.024), while the first and second groups developed nearly equal extents of increment (p=1.0) as presented in figure-3

During the second four weeks of study, the first and third groups produced larger significant extent of ACT scores increment compared to second group (p<0.001) with non-significant difference between them (p=0.99) as shown in figure-4

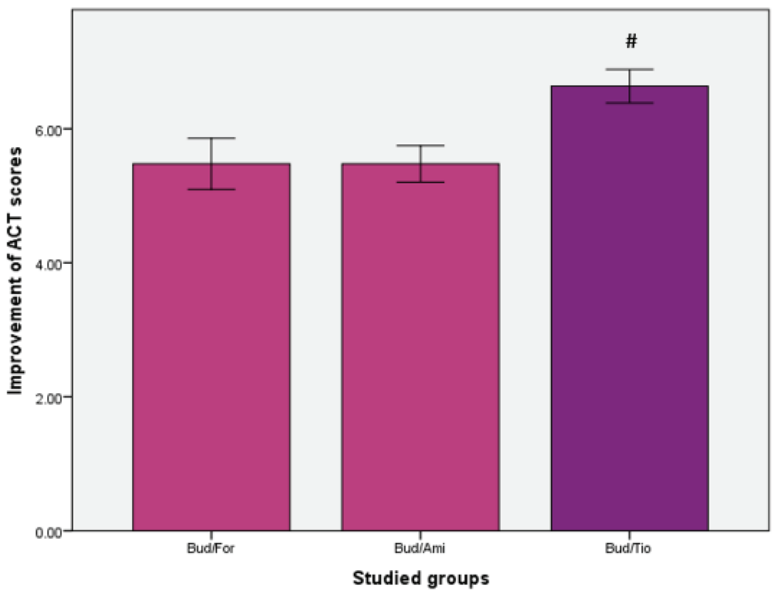

Figure-3: Extent of improvement of ACT scores during the first four weeks of study

#: significant difference compared to other groups

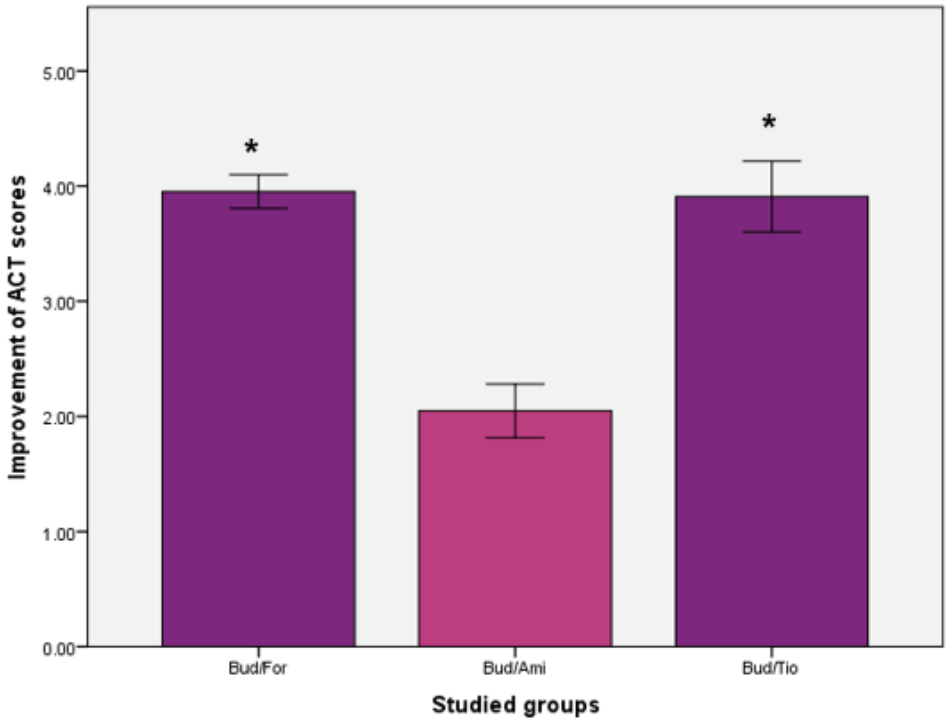

Figure-4: Extent of improvement of ACT scores during the second four weeks of study

*: significant difference compared to second group

Discussion

The doses of budesonide inhaler used in studied groups of the present study were chosen to be equivalent in the medium range of 640-800 µg per day [10]. Therefore, the differences in clinical efficacies among the studied groups may be attributed to the second controlling medication which was combined with inhaled budesonide in each group, while the clinical efficacies within each group after initiating medication regimens in comparison with pretreatment status may be attributed to both components of studied regimens.

The FEV1 is a very important parameter for assessing the response of respiratory airways to bronchodilator medications indicated for long term maintenance of asthma [11] and it is obvious that the principle mechanism of action of the second medication combined with budesonide in each group of this study was bronchodilation

Zhang *et al*, noted that after 8 weeks of adding either tiotropium or LABA to asthmatic patients inadequately controlled on corticosteroid inhaler alone produced significant increment of FEV1 compared to pretreatment values. They also noted that despite the non-significant difference between these two controllers, tiotropium produced higher FEV1 increment (0.73±0.31) than LABA (0.68±0.26) [12]. This finding highlights the primary role of parasympathetic transmission in affecting asthma through its effects especially on airway patency despite the abundance of β-2 receptors in respiratory airways.

The results of the current study were consistent with those observed by Adachi *et al*, who conducted a double blind randomized study to assess the clinical outcomes of two treatment regimens; the first was ICS/salmeterol combination and the second was ICS plus prolonged release oral theophylline for 8 weeks in adult Japanese patients having persistent asthma. The ICS/salmeterol group showed continuous progressive increment of FEV1 at 4 and 8 weeks, while the ICS/theophylline group showed initial improvement of FEV1 during the first 4 weeks followed by decrement to baseline values during

the second 4 weeks. At the 8th week, the FEV1 change of the salmeterol group was significantly higher than the FEV1 change of theophylline group [13]. This finding supports the fact that locally administered medications by inhalation route produced more powerful effects on airways diameter than systemically administered ones.

In agreement with this study, Zhang *et al*, found that after 8 weeks of allocation to the studied treatment combinations, the ICS/tiotropium significantly improved the ACT scores from 14.4±2.41 (uncontrolled status) at baseline visit to 23.3±2.92 (controlled status). Similarly, ICS/salmeterol regimen significantly increased the pretreatment ACT scores of 12.6±2.2 (also uncontrolled) to reach 22.1±2.46 (controlled status). The magnitude of ACT improvement was not significantly different between these two medication regimens [12].

Wang *et al*, assessed the clinical outcomes of oral theophylline (400 mg daily) administered with fluticasone aerosol (500 µg daily) versus combined salmeterol and fluticasone (100/500 µg daily) in patients with moderate to severe persistent asthma for 12 weeks. Before treatment, the ACT scores were 17.09±3.837 and 16.24±3.936 in the theophylline/ICS and LABA/ICS respectively. Both medication regimens produced significant improvement of ACT scores after weeks of regular administration compared to baseline scores (20.39±3.43, 19.81±4.37 in the theophylline/ICS and LABA/ICS respectively). The changes in ACT scores brought about by these two regimens were not significantly different between them [14].

Limitations of study

1- The design of study did not involve blinding or enrollment of placebo group

2- The study recruited small sample size and was conducted at only two center in Baghdad

3- Duration of study was relatively short which did not allow for assessing the effects of treatment regimens on rate of asthma exacerbation as well as long term safety profile

Conclusions and recommendation

1. All studied group caused significant improvements in FEV1 and ACT scores in comparison with baseline values.

2. Patients who received inhaled tiotropium/ICS were associated with the best significant improvement of study parameters followed by those treated with inhaled formoterol/ICS and finally the group allocated to oral long acting aminophylline tablets/ICS developed the least extents of improvement

Acknowledgement: Great thanks and appreciation to the specialist physician, Ibtisam S. Hassan Zwaylif, for her great and valuable role in clinical evaluation of patients.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: Self-funding

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