Evaluating the Clinical Outcomes of Three Medication Regimens for Treating a Sample of Iraqi Persistent Asthmatic Patients

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Abstract

Asthma is a complex disease defined by chronic airway inflammation and airflow limitation causing variable respiratory symptoms which include shortness of breath, wheezing, chest tightness and cough. Asthma guidelines recommend adding a second long acting bronchodilator to medium doses of inhaled corticosteroids rather using high doses of inhaled corticosteroid alone to control moderate to severe persistent asthma. The aim of this study was to evaluate the clinical outcomes of three medication regimens indicated for treating a sample of Iraqi patients suffering from persistent asthma.

This study was interventional randomized clinical study conducted on a sample of adult Iraqi asthmatic patients in Baghdad City. The study composed of three visits distributed over eight weeks; baseline visit followed by first follow up and second follow up visits after four and eight weeks respectively. The study enrolled **78** adult patients with moderate to severe persistent asthma as diagnosed by specialist physician according to patient history and baseline pulmonary function test and allocated them randomly to three groups (each group included **26** patients) to receive equivalent medium doses of budesonide inhaler in addition to either formoterol inhaler, oral modified release aminophylline tablets or tiotropium inhaler (first, second and third group respectively). Sixty four patients completed this study. The mean ages of patients were above 35 years with slightly more male predominance.

The study groups developed significant increase of peak expiratory flow rate and forced vital capacity values at the first follow up visit compared to baseline values (p<0.001). Thereafter, the first and third groups achieved significant higher values at the second follow up visit compared to first follow up visit (p<0.001), while second group produced no change. All the groups developed significant improvement of Mini asthma quality of life questionnaire scores and percentage of symptom free days at first follow up visit and continued further significant improvement at the second follow up visit (p<0.001). Generally, between groups comparison according to extent of change of study parameters revealed that third group produced the greatest improvement over the entire study period followed by the first group, whereas the second group was associated with the least extent of improvement.

This study concluded that all groups caused significant improvement in study parameters compared to baseline values and also concluded that the third group which consisted of budesonide and tiotropium inhalers was associated with the highest extent of improvement followed by first group, while the second group was the least.

Key words: Persistent asthma, Tiotropium inhaler, Pulmonary function test, Mini asthma quality of life questionnaire.

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تقييم المخرجات السريرية لثلاثة انظمة دوائية في علاج عينة من مرضى الربو المزمن العراقيين

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الخلاصة

الربو مرض معقد يعرف بالتهاب مزمن يصيب المجاري التنفسية وتقييد مزمن في تدفق الهواء مما يسبب اعراض تنفسية متفاوتة تشمل صعوبة التنفس و صفير اثناء الزفير وضيق الصدر وسعال. توصي القواعد الارشادية باضافة دواء ثان مديد الفعالية موسع للقصبات الى جرع متوسطة من الكورتيكوستيرويدات المستنشقة بدلا عن استعمال الكورتيكوستيرويدات منفردة بجرع عالية في علاج الربو متوسط الى شديد الدرجة. الهدف من هذه الدراسة هو لتقييم المخرجات السريرية لثلاثة انظمة دوائية مختلفة في علاج عينة من مرضى عراقيين مصابين بالربو المزمن.

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الدراسة الحالية هي دراسة تداخلية سريرية عشوائية اجريت على عينة من مرضى الربو العراقيين في مدينة بغداد وتكونت من ثلاث زيارات موزعة على ثمانية اسابيع: الزيارة الاساسية و زيارة المتابعة الاولى و زيارة المتابعة الثانية بعد اربعة و ثمانية اسابيع من الزيارة الاساسية على التوالي. سجلت الدراسة ٧٨ مريضا بالغا مصابا بالربو المزمن متوسط الى شديد الدرجة حسب تشخيص الطبيب الاختصاصي المبني على تاريخ المريض و فحص وظائف الرئة الاساسية. تم تقسيم المرضى عشوائيا الى ثلاثة مجاميع علاجية بواقع ٢٦ مريضا في كل مجموعة ليتم علاجهم بجرع متوسطة متكافئة من بخاخ البودسونايد بالاضافة الى بخاخ فورموترول أو أقراص الامينوفيللين الفموية ذات التحرير المديد للدواء أو بخاخ تايوتروبيام (المجموعة الاولى و الثانية والثالثة بالتتابع). أكمل اربع و ستون مريضا الدراسة من مجموع ٧٨ مريضا. تجاوز معدل المرضى ٣٥ عاما مع غلبة قليلة للمرضى الذكور.

انتجت مجموعات الدراسة زيادة معنوية في القيم المقاسة لكل من سرعة جريان الزفير القصوى و السعة الحيوية القسرية خلال زيارة المتابعة الاولى بالمقارنة مع الزيارة الاساسية. بعد ذلك حققت المجموعتان الاولى والثالثة قيما أكبر معنويا في زيارة المتابعة الثانية بالمقارنة مع زيارة المتابعة الاولى بينما لم تنتج المجموعة الثانية اي تغيير. انتجت المجاميع الثلاثة تحسنا معنويا في الاستبيان المختصر لتاثير الربو على جودة الحياة و النسبة المئوية لايام الاسبوع الخالية من اعراض الربو في زيارة المتابعة الاولى واستمر التحسن المعنوي المسجل في زيارة المتبعة الثانية. اجمالا, بينت المقارنة بين المجاميع على اساس مقدار التغير في معالم هذه الدراسة ان المجموعة الثالثة انتجت الدرجة الاكبر في مقدار التحسن خلال فترة الدراسة الكلية متبوعة بالمجموعة الاولى بينما كانت المجموعة الثانية صاحبة الدرجة الاقل في مقدار التحسن

استنتجت الدراسة ان جميع المجموعات سببت تحسنا معنويا في معالم الدراسة مقارنة مع قيمها الاساسية قبل الدراسة كما واستنتجت ان المجموعة الثالثة المكونة من بخاخي التايوتروبيام و البودسونايد سببت المقدار الاكبر من هذا التحسن متبوعة بالمجموعة الاولى في حين ان المجموعة الثانية كانت الاقل مقدارا

الكلمات المفتاحية: الربو المزمن, بخاخ التايوتروبيام, فحص وظائف الرئة, الاستبيان المختصر لتاثير الربو على جودة الحياة

Introduction

"Asthma is a complex disease defined by chronic airway inflammation causing the characteristic history of respiratory symptoms which include shortness of breath (SOB), wheezing, chest tightness and cough that vary in intensity and frequency together with variable expiratory airflow limitation" [1]. The variable nature of airflow obstruction is the principle cause of variable asthma symptoms which resolve spontaneously or in response to certain asthma medications forming the reversible pattern of asthma [2]. Asthma is an important cause of health resources utilization, lessened activities and impaired quality of life (QoL) of the asthmatic patients [3].

The major mechanism responsible for the fluctuating pattern of chronic or persistent asthma is the chronic inflammation leading to functional and structural abnormalities of respiratory airways [4]. The parasympathetic neurotransmitter, acetylcholine (ACh), is a key pathophysiologic factory involved in precipitating multiple changes in asthmatic air passages; it stimulates airway smooth muscle spasm, mucus hpersecretion in addition to airway remodeling through its effects on many types of muscarinic (M) receptors which are M1, M2 and M3 receptors [5].

The most important goal of persistent asthma treatment is to achieve the maximum possible extent of asthma control by decreasing the frequency and severity of asthma symptoms [6], enhance patients' QoL [7] status and improve the pulmonary function test (PFT) parameters which represent objective measure of airway obstruction [8].

Inhaled corticosteroids (ICS.s) are the most effective and are considered the first line anti-inflammatory drug for controlling moderate or severe persistent asthma when co-administered with one or more controller medication; the dose requirement of ICS increases as severity worsens [9].

Because risk of ICS induced systemic side effects increases when their doses increase beyond the daily dose of 800 µg of budesonide or its equivalent, guidelines of asthma therapy advocate adding a second long acting bronchodilator to lower doses of ICS to control moderate to severe persistent asthma instead of high doses of ICS monotherapy [10].

Long acting β-2 agonists (LABA.s) are inhaled bronchodilators indicated for long term control of persistent asthma when used in combination with ICS since they have a long duration of action of 12-24 hours. The most commonly prescribed LABAs are salmeterol and formoterol [11]. Unfortunately, it was noted that patients may experience reduced response to LABAs as well as reliever short acting β-2 agonist (SABA) up on long term regular administration of LABAs which was attributed to tachyphylaxis [12].

Oral methyl xanthine bronchodilators [theophylline and its derivative aminophylline] represent a well-known class of bronchodilators which was used for long time in the management of persistent asthma [13], but their use declined due to narrow therapeutic index which can be overcome by prescribing relatively lower doses of theophylline in the range of 400-600 mg/day [14].

The inhaled long acting muscarinic antagonist (LAMA), tiotropium, is approved recently for the control of persistent asthma based on findings of many studies that demonstrated its clinical efficacy [15] and excellent safety profile [16]. Tiotropium should co prescribed with ICS to avoid the possible increase mortality associated with LAMA monotherapy [17].

This study aimed to assess the clinical efficacies of three medication regimens which consist of a corticosteroid inhaler with a controller bronchodilating medication for treatment of a sample of Iraqi patients suffering from moderate to severe persistent asthma .

Patients and Methods

Patients

This study was interventional open label randomized eight weeks clinical study conducted from September -2018 till June 2019 on adult Iraqi

asthmatic patients in two centers in Baghdad City; the first center was Dowaly Private Hospital (Respiratory Clinic) and the second center was AL-Zahra Center of Asthma and Allergy. The study enrolled **78** adult patients and allocated them randomly to three groups (each group included **26** patients) to receive one of the following treatment regimens:

First group: Budesonide 160 µg / formoterol 9 µg **(Bud/For)** combined in one dry power inhaler (DPI) as two puffs every 12 hours

Second group: Budesonide 200 µg DPI + modified release aminophylline 225 mg tablet **(Bud/Ami)**: Budesonide was administered as two puffs every 12 hours and aminophylline tablets were administered as one tablet every 12 hours after meals.

Third group: Budesonide 200 µg DPI + tiotropium 18 µg DPI **(Bud/Tio)**: Budesonide was administered as two puffs every 12 hours and tiotropium was administered as single capsule inhaled via the DPI at evening

Inclusion criteria

1- Adult male and female patients between 18 – 70 years old with symptomatic moderate – severe persistent asthma as diagnosed by the specialist physician

2- History of asthma symptoms or diagnosis of asthma for at least 6 months. In both situations, the status of asthma symptoms and severity should continue for at least one month prior to baseline visit

3- Use of inhaled or nebulized salbutamol for quick relief of asthma attacks for at least 4 weeks before baseline visit

4- Nonsmoker or ex-smoker of less than 10 pack years that stopped smoking at least one year before enrollment visit

Exclusion criteria

1- Pregnant and breast feeding women

2- Current significant respiratory or cardiac diseases

3- Regular administration of asthma controlling medications within 4 weeks of the baseline visit

4- Respiratory tract infections or asthma exacerbation which was treated by systemic steroids within four weeks of the enrollment visit

Methods

This study composed of three visits; the baseline visit which was set for recruiting patients and recording their baseline data, while the remaining visits after four and eight weeks respectively were set for assessing the patients' responses to the study medication regimens (first and second follow up visits). Patients performed PFT maneuver and recorded their QoL level and percentage of symptom free days (SFDs) at each visit. The PFT procedure was performed using spirometers under the supervision of well-trained technician. The procedure was performed three times and the best results of the PFT parameters were recorded. The QoL status was estimated using the Mini asthma quality of life questionnaire (MiniAQLQ) which is a simple tool used to measure the impact of asthma and its treatment on patient QoL during the past two weeks [18]. This questionnaire consists of fifteen elements; each element can be measured from 1-7 numbering scale where one reflects worst impairment, while seven reflects no impairment. A change of 0.5 point from the mean score represents the minimal clinically important difference (MCID) [19]. The English format of MiniAQLQ was used in this study and patients took about 4-6 minutes to complete it by the support of researcher.

The percentage of SFDs was calculated roughly according to the evaluation of the patients themselves during the last seven days preceding each visit. To calculate percentage of SFD; number of days with no symptoms were divided by seven and then multiplied by 100 %.

Statistical analysis

Continuous variables were presented using their means ± standard deviation (SD), whereas discrete variables were presented using their numbers and percentages. For the analysis of discrete variables, Chi square test or Fisher-Freeman-Halton exact test was applied.

Trend (or repeated measure) ANOVA was applied to test the differences of means within each individual group using the measured values in the three visits, while one way ANOVA was used to analyze the differences among the groups using the means of values at baseline visit and then used the means of changes (increment or decrement) of values produced during the first and second four weeks of study. Thereafter, if the overall comparison revealed significant differences, post Hoc Tukey test was applied to analyze the significance difference between each pair of means.

If data did not follow normal distribution, Kruskal Wallis test was performed instead of one way ANOVA, whereas Friedman ANOVA was used instead of trend ANOVA. Statistical Package for the Social Sciences (SPSS) version 23.0.0 (Chicago, IL), GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, and 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

Sixty-four patients completed this study; twenty-one patients in each of first and second group, while twenty-two patients completed the study in the third group. Fourteen patients discontinued prematurely the medication regimens due to different reasons and their data were excluded.

The socio-demographic data of the recruited patients were well - balanced between the studied groups as shown in table 1; the mean ages of patients were older than 40 years in the first group, whereas they

were 35 - 40 years in the remaining two groups. The first and second groups included slightly more male patients, while the third group included equal numbers of both genders. All patients were overweight and their BMI values were in the range of 25-30 kg/m². Marital status showed predominance of married patients in the groups.

About two thirds of patients were urban residents and the remaining third were rural. Nearly 70% of patients never smoked and the majority of them were unemployed. Educational status revealed higher proportion of secondary level followed by college, primary and illiterate levels respectively.

Table 1. Comparison of Socio-demographic data between the study groups.

Group	First group (Bud/For)	Second group (Bud/Ami)	Third group (Bud/Tio)	p-value
Number of patients	21	21	22	-
Age (y), mean ± SD	41.6±15.2	35.4±10.4	36.3±10.9	0.218[a]
Gender, n (%)				0.893[b]
Female	9 (42.9%)	10 (47.6%)	11 (50.0%)	
Male	12 (57.1%)	11 (52.4%)	11 (50.0%)	
BMI (kg/m²), mean ± SD	27.0±3.6	27.7±3.1	28.5±2.7	0.305[a]
Marital status, n (%)				0.904[b]
Married	13 (61.9%)	14 (66.7%)	15 (68.2%)	
Unmarried	8 (38.1%)	7 (33.3%)	7 (31.8%)	
Residency, n (%)				0.691[b]
Urban	15 (71.4%)	14 (66.7%)	13 (59.1%)	
Rural	6 (28.6%)	7 (33.3%)	9 (40.9%)	
Smoking, n (%)				0.619[b]
Non-smoker	17 (81.0%)	16 (76.2%)	15 (68.2%)	
Ex-smoker	4 (19.0%)	5 (23.8%)	7 (31.8%)	
Occupation, n (%)				0.782[c]
Student	3 (14.3%)	3 (14.3%)	3 (13.6%)	
Unemployed	12 (57.1%)	12 (57.1%)	12 (54.5%)	
Employed	4 (19.0%)	6 (28.6%)	4 (18.2%)	
Retired	2 (9.5%)	0 (0.0%)	3 (13.6%)	
Education level, n (%)				0.782[c]
Illiterate	4 (19.0%)	1 (4.8%)	2 (9.1%)	
Primary	5 (23.8%)	4 (19.0%)	5 (22.7%)	
Secondary	7 (33.3%)	9 (42.9%)	9 (40.9%)	
College	5 (23.8%)	7 (33.3%)	6 (27.3%)	

Bud/For: Budesonide/Formoterol
Bud/Ami: Budesonide/Aminophylline
Bud/Tio: Budesonide/Tiotropium
y: years
SD: standard deviation
n: number
BMI: body mass index with unit of kilogram per square meter
a: One way ANOVA
b: Chi square test
c :Fisher-Freeman-Halton exact test

Asthma history and baseline symptom characteristics of recruited patients were shown in table 2; patients randomized to first, second and third groups were diagnosed to have asthma before 9.8, 9 and 6.7 years respectively, while the duration of disease deterioration before the baseline visit was 3.3, 3.1 and 3.3 months respectively.

Shortness of breath and wheezing were the most commonly encountered symptoms at time of presentation (each symptom was developed by 61 patients). The other less commonly presented symptom was chest tightness and the least one was coughing.

Table 2. Comparison of baseline asthma characteristics between the study groups.

Group	First group (Bud/For)	Second group (Bud/Ami)	Third group (Bud/Tio)	p-value
Number of patients	21	21	22	-
Duration of asthma (y), mean ± SD	9.8±5.1	9.0±4.3	6.7±3.5	0.064[a]
duration of asthma deterioration (month), mean ± SD	3.3±1.5	3.1±1.4	3.3±1.5	0.842[a]
Asthma symptoms				
SOB, n (%)	20 (95.2)	20 (95.2)	21 (100.0)	0.542[b]
Cough, n (%)	17 (81.0)	17 (81.0)	16 (72.7)	0.806[b]
Wheezing, n (%)	21 (100.0)	21 (100.0)	19 (86.4)	0.096[b]
Chest tightness	17 (81.0)	19 (90.5)	18 (81.8)	0.755[b]
Bud/For: Budesonide/Formoterol Bud/Ami: Budesonide/Aminophylline Bud/Tio: Budesonide/Tiotropium y: years SOB: shortness of breath n: number a: One way ANOVA b: Fisher-Freeman-Halton exact test				

The effect of study regimens on patients' peak expiratory flow rate (PEFR), a PFT parameter, was illustrated in table 3. All groups developed significant increase of PEFR values at the first follow up visit compared to the baseline visit ($p<0.001$). Thereafter, the measured values of first and second groups at the second follow up visit were significantly higher than their counterpart first follow up values ($p<0.001$), unlike the second group which produced no change between the first and second follow up visits ($p=1.0$).

Table 3. Effect of study regimens on PEFR

Group	First group (Bud/For)	Second group (Bud/Ami)	Third group (Bud/Tio)	p-value
Number of patients	21	21	22	-
PEFR (L/sec)				
Baseline	2.7±0.7	3.1±1.1	3.3±0.9	0.111 [a]
First follow up (after 4 weeks)	3.1±0.8 *	3.6±1.4 *	4.0±1.0 *	0.041 [a]
Second follow up (after 8 weeks)	3.5±0.9 *, ¥	3.6±1.2 *	4.3±1.08 *, ¥	0.073 [a]
p-value	<0.001[b]	<0.001[b]	< 0.001[b]	
Bud/For: Budesonide/Formoterol Bud/Ami: Budesonide/Aminophylline Bud/Tio: Budesonide/Tiotropium PEFR: Peak expiratory flow rate L/sec: Liters/seconds 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 the three groups according to the extent of change of PEFR revealed no significant difference among the groups during the first four weeks of treatment (p=0.093), although numerically third group produced the highest change as shown in figure 1.
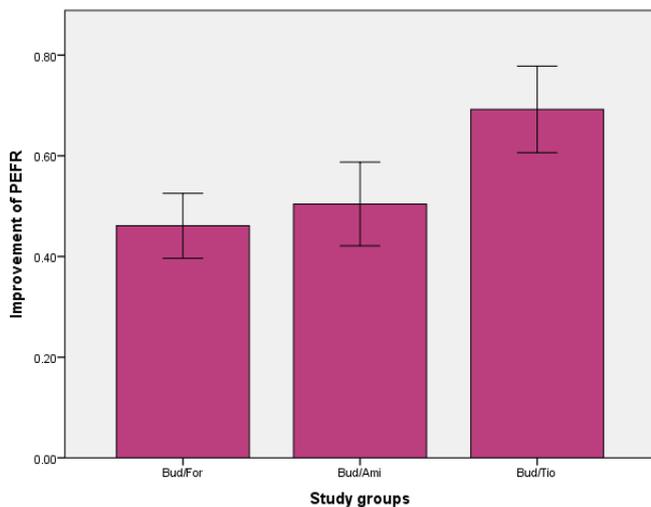

Figure 1. Comparison of groups according to extent of PEFR change during the first four weeks of study.

Bud / For (First group): Budesonide/Formoterol
Bud /Ami (Second group):Budesonide / Aminophylline
Bud / Tio (Third group): Budesonide /Tiotropium .

Both first and third groups maintained significant higher increments of PEFR than the second group during the second four weeks of study (p=0.002, p=0.003 respectively). Meanwhile, there was no significant difference between the first and second groups (p=0.97) as demonstrated in figure 2.
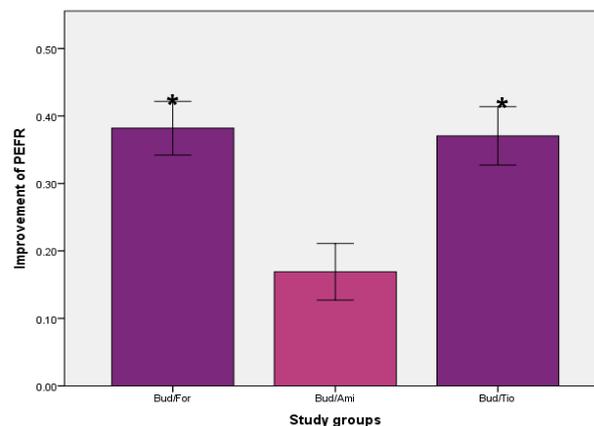
Figure 2. Comparison of groups according to extent of PEFR change during the second four weeks of study.
*: significant difference compared to second group (Bud/Ami group)
Bud/For (First group): Budesonide/Formoterol
Bud/Ami (Second group): Budesonide/ Aminophylline
Bud / Tio (Third group): Budesonide / Tiotropium .

The impact of medication regimens on the patients' forced vital capacity (FVC), another PFT parameter, was demonstrated in table 4. The FVC values measured in the first follow up visit were significantly increased in comparison with pretreatment values in all groups (p<0.001). The FVC continued to increase further in first and third groups and attained new significant higher values in the second follow up visit compared to the first follow up visit (p<0.001), while the second group demonstrated similar values in the first and second follow up visits (p=0.201).

Table 4. Effect of study regimens on FVC.

Group	First group (Bud/For)	Second group (Bud/Ami)	Third group (Bud/Tio)	p-value
Number of patients	21	21	22	-
FVC (Liters)				
Baseline	2.3±0.4	2.9±0.7	3.2±0.9	<0.001 [a]
First follow up (after 4 weeks)	2.5±0.4 *	3.1±0.7 *	3.6±0.9 *	<0.001 [a]
Second follow up (after 8 weeks)	2.7±0.4 *, ¥	3.1±0.7 *	3.7±0.8 *, ¥	<0.001 [a]
p-value	<0.001 [b]	<0.001 [b]	<0.001 [b]	
Bud/For: Budesonide/Formoterol Bud/Ami: Budesonide/Aminophylline Bud/Tio: Budesonide/Tiotropium FVC: Forced vital capacity a: One way ANOVA b: Trend ANOVA (repeated measure ANOVA) *: significant difference compared to baseline values ¥: significant difference compared to first follow up values				

Conducting comparisons between the groups revealed that extent of FVC improvement over the first four weeks of study was significantly better in the third group compared to first and second groups (p=0.026, 0.004 respectively) and revealed no significant difference between the first and second groups (p=0.79) as shown in figure 3.
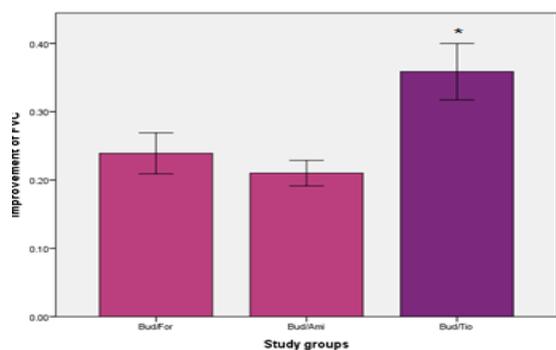

Figure 3 Comparison of groups according to extent of FVC change during the first four weeks of study
*: significant difference compared to first and second groups
Bud/For (First group): Budesonide/Formoterol
Bud/Ami (Second group): Budesonide / Aminophylline Bud / Tio (Third group): Budesonide/Tiotropium.

Both first and third groups created significant higher increment in FVC values compared to the second group during the interval between fourth and eighth week of study (p=0.001), while there was no significant difference between these two groups (p=0.99) as illustrated in figure 4.
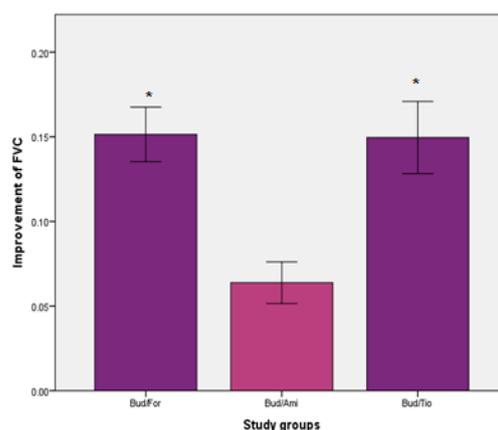

Figure 4.Comparison of groups according to extent of FVC change during the second four weeks of study
*: significant difference compared to second group
Bud/For (First group): Budesonide/Formoterol
Bud/Ami (Second group): Budesonide /Aminophylline . Bud/Tio (Third group): Budesonide/Tiotropium .

The effect of study medication regimens on the percentage of SFDs was explained in table 5. The percentages of SFDs were significantly increased in the first follow up visit compared to baseline visit and continued the significant increment in the second follow up visit compared to the first follow up visit within all groups of study (p≤0.001). Between groups comparison based on the degree of SDFs increment during the first four weeks of study revealed no significant differences among the three groups (p=0.365) as shown in figure 5.

Table 5. Effect of study regimens on percentages of SFDs

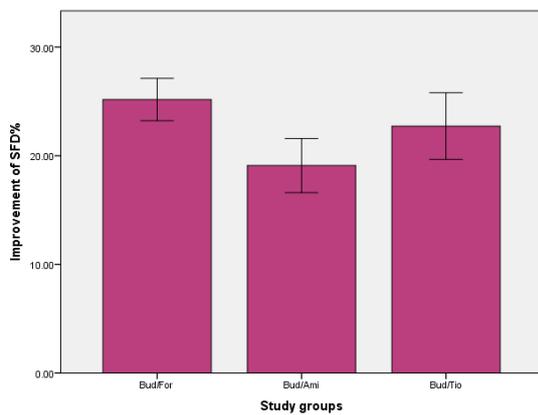| Group	First group (Bud/For)	Second group (Bud/Ami)	Third group (Bud/Tio)	p-value
Number of patients	21	21	22	-
SFD%				
Baseline	7.5±10.7	3.4±7.7	3.9±6.5	0.335[c]
First follow up (after 4 weeks)	32.7±13.7 *	22.5±16.1 *	26.6±17.2 *	0.365 [c]
Second follow up (after 8 weeks)	48.97±13.96 *, ¥	36.1±14.0 *, ¥	50.0±22.8 *, ¥	0.013 [c]
p-value	<0.001[d]	≤0.001[d]	<0.001[d]	
Bud/For: Budesonide/Formoterol Bud/Ami: Budesonide/Aminophylline Bud/Tio: Budesonide/Tiotropium SFD%: Percentage of symptom free days c: Kruskal Wallis H test d: Friedman ANOVA *: significant difference compared to baseline values ¥: significant difference compared to first follow up values				

Figure 5. Comparison of groups according to extent of change in percentages of SFDs during the first four weeks of study
Bud/For (First group): Budesonide/Formoterol
Bud / Ami (Second group): Budesonide / Aminophylline
Bud/Tio (Third group): Budesonide/Tiotropium

Significant difference was noted among the groups during the 4th – 8th weeks of study; the third group produced significantly the best increment in the percentage of SFDs compared to the remaining groups (p=0.01 each). Although the first group developed numerically larger extent of SFDs increment, there was non- significant difference observed between first and second groups (p=0.75) as shown in figure 6.
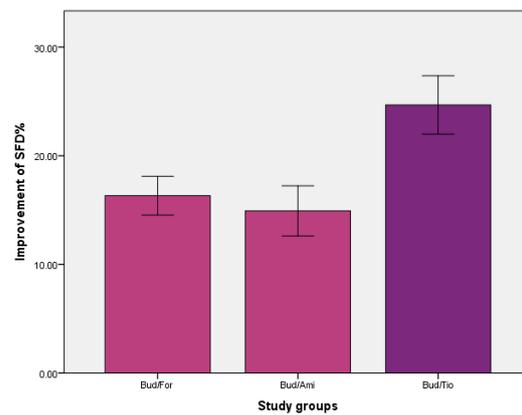
Figure 6. Comparison of groups according to extent of change in percentages of SFDs during the first four weeks of study
*: significant difference compared to first and second groups
Bud/For (First group): Budesonide/Formoterol
Bud/Ami (Second group): Budesonide/Aminophylline
Bud/Tio (Third group): Budesonide/Tiotropium

The impact of medication regimens on the patients' MiniAQLQ scores was demonstrated in table 6. All study groups showed significant improvement at the first follow up visit compared to pretreatment levels and continued their significant improvement in the second follow up visit compared to the first follow up scores (p<0.001) .

Comparing groups regarding extent of improvement of MiniAQLQ scores over the first four week of administering study regimens showed no significant differences among the studied groups (p=0.645) as explained in figure 7.

Table 6. Effect of study regimens on patients' MiniAQLQ scores

Group	First group (Bud/For)	Second group (Bud/Ami)	Third group (Bud/Tio)	p-value
Number of patients	21	21	22	-
MiniAQLQ scores				
Baseline	3.2±0.4	3.2±0.5	3.6±0.6	0.044 [a]
First follow up (after 4 weeks)	4.3±0.4 *	4.3±0.5 *	4.7±0.4 *	0.645 [a]
Second follow up (after 8 weeks0	4.9±0.5 *, ¥	4.6±0.6 *, ¥	5.6±0.34 *, ¥	<0.001 [a]
p-value	<0.001[b]	<0.001[b]	<0.001[b]	

Bud/For: Budesonide/Formoterol
Bud/Ami: Budesonide/Aminophylline
Bud/Tio: Budesonide/Tiotropium
MiniAQLQ: Mini asthma quality of life questionnaire
a: One way ANOVA
b: Trend ANOVA (repeated measure ANOVA)
*: significant difference compared to baseline values
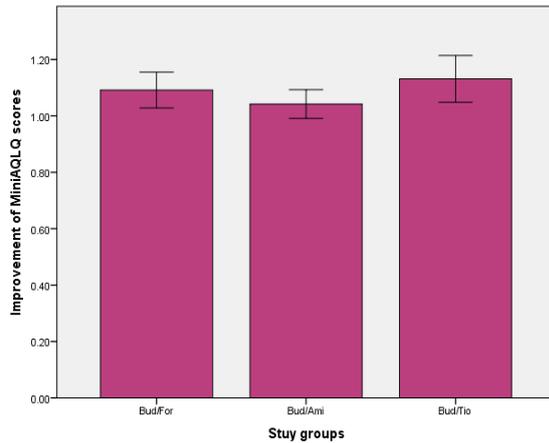¥: significant difference compared to first follow up values

Figure 7. Comparison of groups according to extent of change in the MiniAQLQ scores during the first four weeks of study

Bud/For (First group): Budesonide/Formoterol
Bud/Ami (Second group): Budesonide/Aminophylline
Bud/Tio (Third group): Budesonide/Tiotropium

The second four weeks revealed that the third group produced significantly higher improvement in MiniAQLQ scores compared to first and second groups (p=0.004, p<0.001 respectively). Also, the first group was associated significantly with larger extent of improvement compared to the second group (p<0.001) as shown
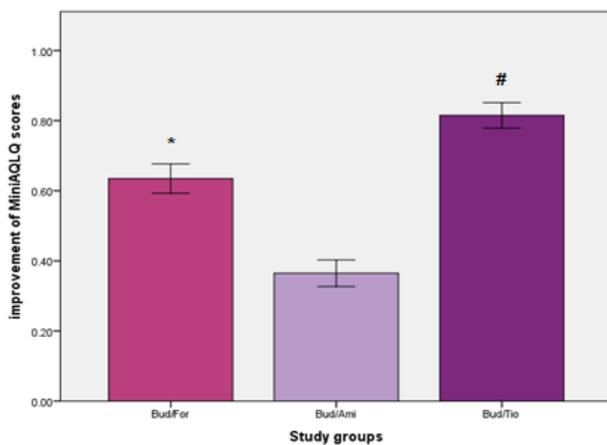

Figure 8. Comparison of groups according to extent of change in the MiniAQLQ scores during the second four weeks of study

*: significant difference compared to second group
#: significant differences compared to first and second groups
Bud/For (First group): Budesonide/Formoterol
Bud/Ami (Second group): Budesonide/Aminophylline
Bud / Tio (Third group): Budesonide/Tiotropium

Discussion

To the authors' knowledge, there were no comparative studies conducted to evaluate the efficacies of asthma controller medications in Iraqi patients, so this study was the first study that aimed to compare between different controller medication regimens in such patients and the results of this study may be explained by comparison with other studies conducted in different societies.

The baseline socio-demographic data and clinical characteristics of asthma were well balanced across the groups of this study. Moreover, the doses of inhaled budesonide in the groups were chosen to be in the clinically equivalent range of 640-800 µg/day [20]. Therefore, the two components of each regimen may be responsible for the changes within each group, but any difference in the clinical outcomes among the groups after administering the medication regimens can be attributed to the second controller medication which was different among these groups.

The PEFR is the maximum rate obtained during forceful expiratory phase after deep maximum inspiration. It is considered as a primary outcome for evaluating efficacies of different asthma controllers. This spirometric parameter is primarily concerned with evaluating airflow in large and medium sized airways [21]. A previous study aimed to compare efficacies of tiotropium/ICS and salmeterol/ICS regimens according to many outcomes including PEFR found that these two regimens caused significant improvements of PEFR after 8 weeks of treatment compared to their pretreatment values with non-significant difference between them (1.93±0.88 vs. 1.91±0.68 respectively) and concluded that these two regimens were comparable in treating persistent asthma [22]. Another randomized clinical study conducted by Wang *et al*., to compare between efficacies of LABA combined with ICS and those of oral long acting theophylline combined with ICS in patients with moderate to severe persistent asthma demonstrated that both groups produced significant elevation of PEFR values after eight weeks of treatment compared to pretreatment values (from 3.43±1.62 to 4.37± 2.00 L/Sec in ICS/LABA group and 3.96 ±1.38 to 4.68 ±1.7 L/Sec in ICS/theophylline group) and also demonstrated no significant difference between the two groups regarding their extents of PEFR changes (p=0.6) although ICS/LABA regimen was associated with larger numerical increment [23]

The FVC is considered essential PFT parameter for describing asthma severity and assessing disease response to the controller medications especially bronchodilators[24]. It was recommended that FVC should be considered in evaluation process because some patients with severe asthma responded to bronchodilators with significant elevation of FVC instead of other PFT parameters [25]. It was shown that both LABA and tiotropium caused significant increment in FVC compared to their pretreatment levels when added to an ICS. Also, it was observed that FVC improvement produced by the LABA was not significantly different from that produced by tiotropium, although numerically LABA was associated with higher values than tiotropium (0.121 versus 0.95 liter respectively)[26]. In agreement with the current study, Adachi *et al.* noted that combination of salmeterol and fluticasone produced progressive significant increment of FVC over four and then eight weeks compared to the pretreatment values, while the slow release theophylline preparation caused less increment of FVC at the 4th week followed by decrement to values approaching those of baseline visit at the 8th week [27].

Symptom free days are considered important indicators of successful asthma treatment for patients as well as their physicians [28]. A previous study was performed to assess the outcomes of adding LABA or tiotropium for 16 weeks in asthmatic patients poorly controlled on ICS alone showed that both medications caused improvement of common baseline SFD value of 1.4 days per week to post treatment values of 2.4 and 2.2 days per week in the ICS/LABA and ICS/tiotropium respectively with non-significant differences between the two groups [29]. Assessing the pre- and post-randomization outcomes of administering either sustained release oral theophylline/ICS or salmeterol/ICS regimens for eight weeks in patients with moderate persistent asthma revealed that all patients were presented with daily symptoms for one week before enrollment (percentage of patients with SFD=0.0). The percentage of patients who felt symptom free during the last week of study showed significant increment in response to study medications compared to baseline values and the response the ICS/salmeterol was significantly better than that to ICS/theophylline (percentage of patients with SFD was 18.2 versus 9.5 respectively) [27].

Mini asthma quality of life questionnaire is a shortened and simplified mode of the original asthma quality of life questionnaire (AQLQ). These two formulas can be considered comparable to each other and the MCID was 0.5 for both [18]. A previous study aimed to investigate the clinical outcomes of LABA versus tiotropium when added to ICS for 16 weeks in persistent asthmatic patients found that the changes of MiniAQLQ scores after 16 weeks of receiving treatment in both groups neither met the MCID nor significantly differed from baseline values [differences from baseline were 0.28 (p=0.064), 0.131 (p=0.068) for LABA and tiotropium groups respectively] [29]. Concordant with the current study, Wang *et al.* noted that both oral theophylline/ICS and LABA/ICS regimens started to cause significant improvement of AQLQ scores after 4 weeks of receiving treatment compared to baseline values (4.36±0.45 compared to 3.94±0.67 p<0.05, 4.26±0.133 compared to 3.82±0.98 p<0.05 respectively), while the MCID was recorded at the 12th week of study (0.53 versus 0.54 respectively). The important observation was that extent of improvement of AQLQ scores from baseline was not different between the two groups [23].

Conclusions

This study concluded that using inhaled formoterol, inhaled tiotropium or modified release oral aminophylline tablets in addition to equivalent doses of inhaled budesonide in a sample of Iraqi persistent asthmatic patients produced significant control of asthma status and significant improvement in pulmonary function test measures and quality of life levels compared to pretreatment values. Also, the study concluded that medication regimens of formoterol or tiotropium inhalers with inhaled budesonide were associated with significant better extents of improvement in all study parameters compared to oral aminophylline/inhaled budesonide regimen and that inhaled tiotropium/inhaled budesonide regimen caused higher values of improvement in most of study parameters compared to inhaled formoterol/inhaled budesonide regimen.

Acknowledgments

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