Comparing the clinical efficacy and safety of high doses of beclomethasone inhaler with medium doses of beclomethasone inhaler combined with oral aminophylline or montelukast tablets in persistent asthmatic Iraqi patients.

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الخلاصة

الربو عبارة عن حالة التهاب مزمن يصيب المجاري التنفسية تلعب فيه دورا عدة أنواع من الخلايا وعناصر خلوية. توصي الارشادات العلاجية باضافة دواء ثان الى جرع متوسطة من بخاخات الكورتيكوستيرويدات بدلا من استخدام جرع عالية من هذه البخاخات في علاج الربو المزمن متوسط أو عالي الشدة. كان الغرض من هذه الدراسة مقارنة الفعالية والسلامة السريريتين لثلاث أنظمة علاجية في المرضى العراقيين المصابين بالربو المزمن متوسط أو عالي الشدة. تضمنت هذه الدراسة ثلاث مجاميع, في كل مجموعة 15 مريضا. تم اعطاء المرضى بخاخ البيكلوميثازون مفردا 1500–2000 مكغ يوميا أو البيكلوميثازون 750–1000 مكغ مع أقراص الأمينوفيللين الفموية ذات التحرير المحور 450 مغ يوميا أو البيكلوميثازون 750–1000 مكغ مع أقراص المونتيلوكاست الفموية 10 مغ يوميا لمدة 4–5 أسابيع. تم مراجعة المرضى بعد مرور أسبوعين و 4–5 أسابيع من أول زيارة. نتجت فروق معنوية ضمن كل مجموعة من حيث التحسن في معلمات فحص وظائف الرئة وسجل أعراض الربو في حين لم تسجل فروق معنوية بين المجاميع. فيما يخص الأعراض الجانبية فان مجموعة البخاخ مع الأمينوفيللين فقط أظهرت أعراضا جانبية خطيرة في بعض المرضى. أستنتج من هذه الدراسة أن اعطاء دواء ثان مع بخاخ البيكلوميثازون كان مهما لغرض استخدام جرع أقل هذا البخاخ كما وأستنتج أن المونتيلوكاست أأمن من الأمينوفيللين من حيث الأعراض الجانبية الخطيرة لذا فان أقراص الأمينوفيللين تعتبر بديلا عن أقراص

المونتيلوكاست كأدوية مضافة الى جرع متوسطة من بخاخات الكورتيكوستيرويدات في علاج الربو المزمن متوسط أو عالي الشدة.

Abstract:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The treatment guidelines recommend the use of a second controller drug in addition to medium doses of inhaled corticosteroids (ICSs) rather than the use of high doses ICS alone in the treatment of moderate-severe persistent asthma. This study was conducted to compare the clinical efficacy and safety of three treatment regimens in Iraqi patients with moderate-severe persistent asthma.

The study included three groups; each group included 15 patients. Patients were administered beclomethasone inhaler alone 1500-2000 µg/day, beclomethasone inhaler 750-1000 µg/day plus oral controlled release aminophylline tablets 450 mg/day or beclomethasone inhaler 750-1000 µg/day plus oral montelukast tablets 10 mg/day for 4-5 weeks. Patients were followed 2 weeks and 4-5 weeks after the baseline visit. In all of the three groups, significant improvements were noticed in pulmonary function test parameters (FEV1, FVC, FEF50%) and the asthma symptom records (day-time symptoms, night-time symptoms, number of salbutamol puffs per 24 hours), while there were no significant differences among the groups. Regarding side effects, only the group of inhaled steroid plus aminophylline tablets showed discontinuation of drug therapy in some patients which could be attributed to the development of serious side effects.

It was concluded that the administration of a second controller agent was important to use lower doses of inhaled beclomethasone. It was concluded also that montelukast was associated with a lower incidence of serious side effects than aminophylline which could make aminophylline an alternative to montelukast as combination therapy with medium doses ICS in the treatment of moderate-severe persistent asthma.

Introduction:

Asthma is a complex condition in which many cells and cellular elements play a role. It is characterized by chronic airway inflammation, reversible airway obstruction and airway hyper-responsiveness to a variety of stimuli [1]. Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms; some of factors do both [2].

Airway inflammation is believed to be the fundamental driver of the chronic intermittent nature of asthma symptoms [3]. In asthma, all cells of the

airways are involved and become activated. Included are eosinophils, T cells, mast cells, macrophages, neutrophils, epithelial cells, fibroblasts, and bronchial smooth muscle cells [4]. Activation of these cells leads to release of pro-inflammatory mediators and cytokines [5].

Drugs currently available to treat asthma are classified as quick-relief medications or "relievers" and long-term control medications or "controllers" on the basis of their principal pharmacodynamics and clinical effects. Thus, short-acting bronchodilators such as inhaled β2- agonists or anticholinergics are considered relievers. Corticosteroids, leukotriene receptor antagonists, sustained-release theophylline products and omalizumab are considered controllers [6]. Inhalation therapy is the preferred route of administration of anti-asthmatic drugs to the airways due to its rapid, efficient and safe delivery [7].

This study was designed to compare the clinical efficacy and safety of high doses of beclomethasone inhaler alone with medium doses of inhaled beclomethasone combined with oral aminophylline tablets (controlled release) or montelukast tablets in Iraqi patients having moderate-severe persistent asthma.

Materials & Methods:

This study was conducted on patients with moderate-severe persistent asthma according to GINA 2006 guidelines [1] and NAEPP 2007 guidelines [8] at Baghdad Teaching Hospital and AL-Zahraa Center of Asthma and Allergy from December 2009 till August 2010.

This study included a baseline visit for enrolling eligible patients and two follow up visits to reassess the patients.

Patients were selected and enrolled in this study according to the following inclusion criteria: age of patients $\geq$ 12 years old, diagnosis of asthma for at least 6 months before the baseline (pretreatment) visit, use of salbutamol inhaler for quick asthma relief for at least 6 weeks before the baseline visit, non smokers or ex-smokers of less than 12 pack-years and stopped smoking for at least 3 months before the baseline visit, and baseline FEV1 of 40-80% of predicted value with an increase of at least 12% within 30 minutes of using 2-4 puffs (200-400 µg) of salbutamol inhaler.

Patients were not enrolled in the study if they had one or more of the following exclusion criteria: other illnesses that may interfere with the monitoring or control of asthma (like COPD, lung cancers or heart failure), pregnancy whether confirmed or suspected, active or history of respiratory tract infections within 2 weeks prior to the baseline visit, current regular use of more than 500 µg/day of beclomethasone inhaler or equivalent, current regular use of systemic corticosteroids (rescue high doses or regular maintenance doses),

current or history of administration of other asthma controller drugs within one week prior to baseline visit, and patients inability to comply with the inhalation technique or symptoms records. Also, patients were excluded from the study if they developed pregnancy or acute exacerbation of asthma during the study.

In the baseline visit, patients were investigated regarding asthma symptoms scores (frequency of day-time and night-time asthma attacks) and the frequency of using salbutamol inhaler/24 hours for the quick relief of asthma attacks in the two weeks prior to baseline visit. Baseline pulmonary function test was done provided that patients did not take salbutamol inhaler for at least 4 hours before the test. Then patients repeated the pulmonary function test within 30 minutes of administering 200-400 µg of salbutamol inhaler to estimate the percentage of reversibility in FEV1.

Patients were randomly assigned to one of three treatment regimens:
First group: administered beclomethasone metered dose inhaler (MDI) 1500-2000 µg/day.
Second group: administered beclomethasone MDI 750-1000 µg/day with oral controlled release aminophylline tablets 450 mg/day.
Third group: administered beclomethasone MDI 750-1000 µg/day with oral montelukast tablets 10 mg/day.

All patients were administered salbutamol MDI for quick relief of asthma attacks and they were supplied with asthma symptoms diary sheets to record day-time and night-time asthma attacks and number of puffs of salbutamol inhaler.

In the first and second follow up visits (2 and 4-5 weeks after commencing therapy respectively), patients were reevaluated regarding asthma symptoms scores and the use of salbutamol inhaler/24 hours. Pulmonary function test was repeated provided that patients did not administer salbutamol inhaler for at least 4 hours and the study medications for at least 12 hours before conducting the test. Also, patients were monitored regarding the development of side effects which could be attributed to the study medications.

Data were prepared as mean ± standard error of mean (SEM). Paired and unpaired t-tests were used for statistical analysis (using excel program) and p value < 0.05 was used as the level of significance.

Results:

Total number of patients enrolled in this study was 89. Patients who completed the course of this study (and their data were included in the results) were 45; 15 patients in each group. Patients who were excluded from the study were 44 patients due to many reasons.

Within each of the three groups there was a progressive significant increase in FEV1 value at the first and second follow up visits compared to the baseline visit and at the second follow up visit compared to the first follow up visit. There were no significant differences among the three groups at the baseline, first follow up and second follow up visits as shown in (Table- 1).

Treatment groups	Pretreatment (baseline)	2 weeks after treatment	4-5 weeks after treatment
First group	2.182 ± 0.193	$2.658 \pm 0.209^{*}$	$2.796 \pm 0.206^{*,\dagger}$
Second group	1.986 ± 0.192	$2.423 \pm 0.186^{*}$	$2.682 \pm 0.189^{*,\dagger}$
Third group	1.952 ± 0.119	$2.308 \pm 0.118^{*}$	$2.745 \pm 0.105^{*,\dagger}$

Table- 1: Forced expiratory volume in one second (FEV1) in liters.

$P^{*} < 0.05$ with respect to baseline value.

$P^{\dagger} < 0.05$ with respect to two weeks after treatment value.

In the first group FVC was significantly increased at the first follow up visit compared to the baseline value, but remained unchanged in the second follow up visit compared to the first follow up visit. In the second group FVC was significantly increased in the first and second follow up visits compared to the baseline value, but there was no significant difference between the first and second follow up visits. Unlike the first two groups, third group showed a progressive significant improvement in FVC value in both first and second follow up visits compared to the baseline visit and in the second follow up visit compared to the first follow up visit. There were no significant differences among the groups as shown in (Table-2).

Treatment groups	Pretreatment (baseline)	2 weeks after treatment	4-5 weeks after treatment
First group	2.9 ± 0.279	$3.239 \pm 0.27^{*}$	$3.216 \pm 0.277^{*}$
Second group	2.581 ± 0.171	$3.053 \pm 0.22^{*}$	$3.116 \pm 0.173^{*}$
Third group	2.707 ± 0.161	$2.99 \pm 0.174^{*}$	$3.22 \pm 0.171^{*,\dagger}$

Table 2: Forced vital capacity (FVC) in liters.

$P^{*} < 0.05$ with respect to baseline value.

$P^{\dagger} < 0.05$ with respect to two weeks after treatment value.

In all of the three groups; FEF50% at both the first and second follow up visits was significantly higher than that at the baseline visit and FEF50% in the second follow up visit was significantly increased compared to first follow up visit. There were no significant differences among the groups at the baseline, first and second follow up visits as shown in (Table-3).

Treatment groups	Pretreatment (baseline)	2 weeks after treatment	4-5 weeks after treatment
First group	2.012 ± 0.19	2.786 ± 0.251*	3.325 ± 0.288*,†
Second group	1.775 ± 0.138	2.417 ± 0.2*	2.937 ± 0.22*,†
Third group	1.904 ± 0.154	2.49 ± 0.185*	3.024 ± 0.184*,†

Tabl-3: Forced expiratory flow at 50% of vital capacity (FEF50%) in liters/second.

$P^{*} < 0.05$ with respect to baseline value.

$P^{\dagger} < 0.05$ with respect to two weeks after treatment value.

In each group day-time and night-time symptoms were significantly reduced after using the medications; the reduction was observed from the first follow up visit and continued in the second follow up visit. The symptoms were significantly reduced at the first and second follow up visits compared to the symptoms at the baseline visit; also symptoms were significantly reduced at the second follow up visit compared to the symptoms at the first follow up visit. There were no significant differences among the groups at the baseline, first and second follow up visits as shown in (Tables-4 and 5).

Treatment groups	Pretreatment (baseline)	2 weeks after treatment	4-5 weeks after treatment
First group	3.82 ± 0.32	1.284 ± 0.199*	0.404 ± 0.138*,†
Second group	4.071 ± 0.291	1.762 ± 0.3*	0.608 ± 0.255*,†
Third group	3.5±0.288	1.083±0.249*	0.591±0.188*,†

Table- 4: Day-time symptoms.

$P^{*} < 0.05$ with respect to baseline value.

$P^{\dagger} < 0.05$ with respect to two weeks after treatment value.

Treatment groups	Pretreatment (baseline)	2 weeks after treatment	4-5 weeks after treatment
First group	2.566 ± 0.222	0.546 ± 0.13*	0.182 ± 0.101*,†
Second group	2.5 ± 0.196	0.614 ± 0.11*	0.202 ± 0.078*,†
Third group	2.3 ± 0.187	0.341 ± 0.097*	0.079 ± 0.051*,†

Table -5: Night-time symptoms.

$P^{*} < 0.05$ with respect to baseline value.

$P^{\dagger} < 0.05$ with respect to two weeks after treatment value.

In each group the number of salbutamol puffs/24 hours was reduced significantly after initiating the treatment. Number of puffs was reduced significantly at both the first and second follow up visits compared to the

baseline value and at the second follow up visit compared to the first follow up visit. There were no significant differences among the groups at the baseline, first and second follow up visits as shown in (Table-6).

Treatment groups	Pretreatment (baseline)	2 weeks after treatment	4-5 weeks after treatment
First group	9.333 ± 0.804	1.702 ± 0.49*	0.659 ± 0,274*,†
Second group	10.142 ± 0.763	2.922 ± 0.528*	1.052 ± 0.443*,†
Third group	9.433 ± 0.826	1.689 ± 0.527*	0.677 ± 0.293*,†

Table- 6: Salbutamol puffs/24 hours.

$P^{*} < 0.05$ with respect to baseline value.

$P^{\dagger} < 0.05$ with respect to two weeks after treatment value.

Subjective monitoring of side effects was used as a measure of safety profile of the three treatment groups. Side effects reported in the first and second groups were infrequent, mild and tolerated by most patients like burning sensation in the mouth in the first group and headache, fatigue, dyspepsia and nausea in the second group. Five patients in the third group developed intolerable side effects namely severe palpitations and tremors (these patients were excluded and their data were dropped out of the study results).

Discussion:

Results of this study were similar to the results of other workers who showed similar significant improvements in FEV1 after using high doses of inhaled corticosteroids or lower doses of the inhaled steroids combined with either oral theophylline [(9)] or montelukast tablets [(10)]. The effects of montelukast were attributed to direct suppression of smooth muscle constriction induced by powerful muscle constrictors (cysteinyl leukotrienes) which are released during the inflammatory response [11] in addition to its anti-inflammatory effects [12]. Similarly, theophylline has anti-inflammatory, immunomodulatory and bronchodilator effects [13].

There were no significant differences among the groups regarding the improvement in FVC despite using lower doses of the inhaled steroid in the second and third groups. This was attributed to that oral aminophylline [14] and montelukast may be more likely to reach the small airways than inhaled glucocorticoids [15].

FEF50% represents the measurement of distal peripheral small airways (0.5-2 mm internal diameter) and it is the most sensitive portion of the pulmonary function test to airflow in the peripheral airways [16]. Montelukast inhibits the biosynthesis of cysteinyl leukotrienes which are potent

bronchoconstrictors and may preferentially affect the small airways more than the large airways [17], while inhaled corticosteroids have not been shown to attenuate leukotrienes production [18]. Likewise, aminophylline was shown to have anti-inflammatory and bronchodilator effects in the peripheral small airways [19]. Using higher doses of the inhaled steroid may increase the systemic absorption and bioavailability of the steroid thus increasing the concentration of the steroid reaching the peripheral airways [20].

All the groups caused nearly the same degree of significant reduction in the number of salbutamol puffs/24 hours because these groups caused nearly the same degree of significant improvement in the frequency and severity of day-time and night-time asthma attacks which was reflected on the use of this quick relief medication. Dempsy *et al* (2002) [21] showed similar results; they found that significant improvements in the number of both day-time and night-time symptoms were seen within each active treatment group compared to baseline. Wang *et al* (2005) [22] compared the effects of adding a second controller agent to inhaled beclomethasone with double doses of inhaled beclomethasone. They concluded that the regimens had the same effects on asthma control, ameliorating symptoms and improving lung function and may allow a reduction in the inhaled corticosteroid doses when treating asthma.

Side effects shown in the beclomethasone-aminophylline group could be attributed to aminophylline due to its content of theophylline. Theophylline has a narrow therapeutic index with the potential of serious adverse effects even if low dose regimens were used (such as in this study) [9]. Despite the good therapeutic efficacy of theophylline products (including aminophylline) in many studies, concerns about side effects have limited their use [23].

Conclusion:

The results could indicate that all the treatment regimens were effective in managing asthma in persistent asthmatic Iraqi patients. The results of this study clearly demonstrated the serious adverse effects that could be attributed to aminophylline tablets. On the other hand, the study also demonstrated the comparable safety and efficacy of combining oral montelukast tablets with lower doses of inhaled beclomethasone and using high doses of the inhaled beclomethasone alone. Therefore, it could be recommended that the use montelukast tablets plus lower doses of inhaled corticosteroids would be an effective strategy to control moderate-severe persistent asthma and to reduce the need for high doses of corticosteroids inhalers.

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