Regular vs Ad-lib Albuterol for Patients Hospitalized With Acute Asthma*

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Study objectives: **Inhaled, short-acting β-agonists and systemic corticosteroids form the mainstay of therapy in acute asthma exacerbation. Asthma, however, is an inflammatory disease of the airways, and its underlying pathology is not impacted by short-acting β-agonists. While the efficacy of ad-lib β-agonist administration in outpatient management of asthma symptoms is well established, little data exist to support this strategy in patients with acute, severe asthma. We postulate that as long as patients hospitalized with severe asthma exacerbation receive systemic corticosteroids, regular, scheduled administration of short-acting β-agonists is unnecessary. Similar therapeutic outcomes can be achieved with the ad-lib administration of the short-acting β-agonists.**

Design: **Prospective, randomized, double-blind, placebo-controlled trial.**

Setting: **Pulmonary floor of a 600-bed municipal hospital.**

Patients or participants: **Sixty-two patients hospitalized for acute asthma.**

Interventions: **Patients were randomized to receive either albuterol nebulizations (regular albuterol group) or saline solution nebulizations (ad-lib group) every 4 h with management of breakthrough symptoms with albuterol metered-dose inhaler or nebulizations for both groups. All patients received systemic corticosteroids. Peak expiratory flows, asthma symptoms, and need for rescue bronchodilator were followed up on each patient until discharge.**

Results: **There was no significant difference in the length of hospitalization (median length, 48 h for ad-lib group vs 57.5 h for regular albuterol group, $p = 0.82$), rate of improvement in peak flow, or symptoms between the two groups. Ad-lib β-agonist use compared to regular albuterol scheduled use resulted in a significant reduction in the total number of albuterol treatments administered (median, 7 treatments vs 19 treatments, $p = 0.001$) during hospitalization.**

Conclusions: **In the management of asthma exacerbation, ad-lib administration of albuterol is therapeutically as effective as regular, scheduled administration. This method of drug administration also reduces the total dose of β-agonists received by the hospitalized patient.**

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Key words: adrenergic β-agonists; asthma; bronchodilator; drug therapy; randomized control trial

Abbreviations: ED = emergency department; IQR = interquartile range; MDI = metered-dose inhaler; NAEPP = National Asthma Education and Prevention Program; PEFR = peak expiratory flow rate

Asthma is an increasingly important cause of chronic morbidity among children and adults worldwide. High prevalence rates have been reported, particularly in many developed countries, as have increasing morbidity, hospital admission rates, use of medical services and, in some countries, increasing mortality rates.[1–3] The standard of care for hospitalized asthma patients includes the administration of systemic corticosteroids and β_2-agonists at regular intervals.[4–8]

However, there is no firm evidence to indicate the optimal schedule of treatment with short-acting β agonists for patients with acute exacerbation of asthma. We performed a survey of the respiratory departments in the greater New York area teaching hospitals (unpublished data). It showed that patients admitted with acute asthma exacerbation are started

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on a regular, scheduled treatment regimen of nebulized short-acting β_2-agonists, such as albuterol, 2.5 mg q4h, with additional 2.5 to 10 mg every 1 to 4 h as needed for breakthrough symptoms. Our own practice with β_2-agonist administration in our institution is similar.

Airway obstruction in asthma exacerbation is a complex event with varying degrees of bronchospasm, inflammation, and mucus plugging. Inflammation is thought to be central to the pathogenesis of the disease, as it contributes not only to airflow obstruction but to bronchial hyperresponsiveness.[9,10] Corticosteroids have been shown to reduce the airway cellular infiltrate in asthma, reduce airway smooth-muscle proliferation, inhibit procollagen synthesis, and cause vasoconstriction.[11] β-agonists are effective bronchodilators[12,13] but are largely devoid of antiinflammatory activity.[14] Even though they offer temporary clinical improvement, the underlying inflammation persists.[15,16] In fact, excessive use of β-agonists may be associated with increased bronchial hyperreactivity[16,17] and morbidity and mortality,[18] especially in elderly patients and those with poorly controlled asthma.

We reasoned that this may also hold true for the hospitalized patients with exacerbation of asthma and that their clinical improvement is largely due to the administration of corticosteroids, which play a central role in controlling the inflammatory cascade. Regular, scheduled administration of albuterol treatments probably does little to alter the clinical course. We then hypothesized that the patients who received albuterol, only when required, for symptom relief (ad-lib albuterol group) would recover as quickly as the patients who are treated with regularly scheduled albuterol every 4 h in addition to the rescue treatments of albuterol for breakthrough symptoms (regular albuterol group). They would probably require less of the total dose of β-agonist during hospitalization.

Materials and Methods

Patient Selection

Patients who presented to the emergency department (ED) of Jacobi Medical Center with acute exacerbation of asthma as defined in the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report II[5] were eligible to participate in the study if they met the following criteria: (1) a known history of asthma, (2) age 18 to 70 years, (3) ability to perform peak expiratory flow maneuver with good effort, and (4) ability to clearly communicate their symptoms. Patients were excluded if they met the following criteria: (1) required mechanical ventilation, (2) were pregnant, (3) had a smoking history > 20 pack-years, or (4) had a serious systemic disease, such as congestive heart failure, renal failure, or pulmonary disease other than asthma, such as pneumonia, tuberculosis, cancer, bronchiectasis, interstitial lung disease, sarcoidosis, pleural disease, kyphoscoliosis, and COPD.

Study Design

The study was conducted as a prospective, randomized, double-blind, placebo-controlled trial. The Committee of Clinical Investigations of Albert Einstein College of Medicine approved the study protocol. While being screened, the patients were routinely treated with inhaled β-agonists by metered-dose inhaler (MDI) or nebulizer and anticholinergics by nebulizer every 20 min, with oxygen to achieve oxygen saturations of $\geq 92\%$ and oral or IV corticosteroids if there was no immediate, complete reversal of obstruction. If the patient met the eligibility criteria, an informed, written consent was obtained, and he/she was started on the study protocol within 6 h of their arrival at the ED. Patients were randomly assigned to receive either nebulized albuterol (albuterol sulfate inhalation solution 0.5%, 0.5 mL to be mixed with 2.5 mL of normal saline solution q4h [Warrick Pharmaceuticals; Reno, NV]) or placebo nebulizations q4h (0.9% saline solution, 0.5 mL to be mixed with 2.5 mL of normal saline solution [Airlife Baxter Healthcare; Valencia, CA]).

In addition to the treatments of albuterol or saline nebulizations every 4 h, both groups of patients also received albuterol treatments (nebulizations or MDI) on an as-needed basis for breakthrough symptoms. Therefore, in terms of albuterol dosing, one group would receive albuterol every 4 h plus ad-lib treatments (regular albuterol group) and the other group would receive only ad-lib treatments (ad-lib albuterol group).

A pulmonary function technician not participating in the study generated a randomization sequence in blocks of six (three albuterol sulfate solution and three saline solution in each block) and assigned random sequential numbers. Codes for the numbers were kept in a sealed envelope to be opened at the completion of the study or in a medical emergency. The albuterol sulfate solution and the saline solution were dispensed from identical glass vials with code numbers to accomplish blinding. One physician enrolled all the patients in the study in sequence. To ensure double blinding, the physicians evaluating the patients and the patients themselves were unaware of the group to which they were assigned.

Baseline peak expiratory flow rate (PEFR),[19] expressed as percentage of the predicted peak flow, and a "symptom severity score" were recorded for each patient on a flow sheet at the start of the study, then 4 h, 8 h, and 12 h after induction into the study and then twice daily (9 AM and 5 PM) thereafter until discharge. The PEFR was measured using a Wright peak flow meter (Armstrong Industries; Northbrook, IL). The symptom severity score was based on the patient's subjective perception of the severity of his symptoms. A score of 0 to 3 was assigned each for shortness of breath, chest tightness, wheezing and cough (0 for none, 1 for mild, 2 for moderate, and 3 for severe), and a total score was calculated as the sum of each individual score, allowing a maximum of 12. A higher score reflected a greater severity of symptoms, and a decreasing score indicated improvement. Each patient received the nebulized study medication (albuterol or normal saline solution) every 4 h during the entire period of his stay in hospital except when asleep. An albuterol MDI (85 μg per actuation; Warrick Pharmaceuticals) was left at the patient's bedside, and the patients were instructed to use it for breakthrough asthma symptoms.

The MDI technique was reviewed and corrected, if necessary, at the start of the protocol. The patients were instructed to make a record of the number of albuterol MDI doses (each dose comprised of two MDI puffs) used for the breakthrough asthma symptoms in a diary left at their bedside. The entries were