Effect of Continuously Nebulized Ipratropium Bromide Plus Albuterol on Emergency Department Length of Stay and Hospital Admission Rates in Patients With Acute Bronchospasm*

A Randomized, Controlled Trial

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Objective: To compare the outcome of patients with acute bronchospasm treated with continuously nebulized albuterol plus ipratropium bromide vs albuterol alone.

Setting: The Emergency Department (ED) at the University of California San Francisco Medical Center.

Participants: Patients ≥ 18 years old presenting to the ED with acute bronchospasm and a peak expiratory flow rate (PEFR) of < 70% predicted.

Interventions: This was a prospective, randomized, double-blind, placebo-controlled trial. Subjects were treated with either a combination of albuterol (10 mg/h) plus ipratropium bromide (1.0 mg/h) or albuterol alone via continuous nebulization for a maximum of 3 h. Vital signs, Borg dyspnea score, and PEFR were recorded hourly. Primary outcome measures were improvement in PEFR, hospital admission rates, and length of stay in the ED.

Measurements and results: Data was analyzed for 67 subjects. The mean age (± SD) was 47.5 ± 18.8, and mean initial PEFR was 44.8 ± 12.5% of predicted. The median length of stay for all subjects was 225 min, and 31% of all subjects were admitted. Patients given combination therapy averaged 6.3% greater improvement in PEFR compared with control subjects (95% confidence interval [CI], −15% to 27%). The odds ratio for admission with combination therapy was 0.88 (95% CI, 0.28 to 2.8). The median length of stay in the ED was 35 min shorter for those receiving combination treatment (210 vs 245 min; p = 0.03). However, when adjusted for initial PEFR, there was no statistically significant difference (p = 0.26).

Conclusion: Although the direction of all three outcome measures favored combination therapy, there was no statistically significant difference between ED patients with acute bronchospasm receiving continuous albuterol plus ipratropium bromide and those receiving albuterol alone.

Key words: acute disease; albuterol administration and dosage/therapeutic use; asthma; chronic obstructive pulmonary disease; comparative study; emergency service; hospitals; ipratropium administration and dosage/therapeutic use; treatment outcome

Abbreviations: CI = confidence interval; ED = emergency department; NHLBI = National Heart, Lung, and Blood Institute; PEFR = peak expiratory flow rate; RT = respiratory therapist

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Ipratropium bromide, an anticholinergic bronchodilator, is considered to be a first-line therapy for stable patients with COPD1–3 and is also gaining acceptance as adjunctive outpatient therapy for patients with asthma.3–6 However, its role in the treatment of acutely ill patients with bronchospasm remains unclear. Recent guidelines for the treatment

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of both asthma and COPD exacerbations in the emergency department (ED) recommend using ipratropium in most patients, but the ability of this therapy to improve outcome has not been proven. A number of studies comparing β-agonist therapy alone with a combination of β-agonist plus ipratropium bromide in patients experiencing acute bronchospasm demonstrate greater improvement in pulmonary function for those receiving combination therapy. However, studies that have looked at clinical outcomes have yielded conflicting results.

The goal of this study was to determine whether combination therapy with β-agonist and ipratropium bromide for patients with acute bronchospasm was superior to β-agonist therapy alone. Many EDs now use continuous nebulizer therapy for treatment of acute bronchospasm, in accord with recent studies and guidelines suggesting that, in comparison to intermittent nebulization, outcomes in more severely ill patients are improved. However, prior studies comparing combination therapy to standard therapy have used only intermittent treatments. We hypothesized that patients with acute bronchospasm given continuous combination therapy with β-agonist and ipratropium bromide will have greater improvement in pulmonary function, fewer hospitalizations, and shorter stays in the ED than those given continuous β-agonist alone.

**Materials and Methods**

This was a prospective, randomized, double-blind, placebo-controlled trial conducted at the ED of the University of California San Francisco Medical Center between May 1994 and October 1995. This department sees approximately 21,000 patients annually, with approximately 370 visits per adult patients with acute bronchospasm. Patients 18 years of age or older presenting with an episode of acute bronchospasm were eligible for inclusion. On admission to the ED, all patients with acute bronchospasm immediately received a bronchodilator treatment with a hand-held, small-volume nebulizer containing 2.5 mg albuterol in 3 mL normal saline. Patients who had just received bronchodilator treatment in an ambulance or hospital clinic were not included in the study. (Fig 1). Predicted values for PEFR were obtained from the nomogram of Knudson et al. The best of three attempts was used for this and all subsequent PEFR measurements. ED physicians identified eligible patients and notified a respiratory therapist (RT) to enroll patients, prepare treatments, and collect vital sign and PEFR data. Patients were excluded if they were pregnant, had pneumonia or congestive heart failure, or required immediate intubation. This study was approved by the Committee on Human Research at the University of California at San Francisco, and all patients gave written informed consent.

After enrollment, subjects were placed on a cardiac monitor and the baseline heart rate, respiratory rate, BP, and oxygen saturation levels were recorded. The RT obtained baseline PEFR using a flow meter (Asthac Peak Flow Meter; Center Laboratories; Port Washington, NY), and subjects were asked to rate their level of dyspnea using the modified Borg dyspnea scale.

Following baseline measurements, all subjects received 60 mg oral prednisone and began continuous nebulizer therapy with either a combination of albuterol at 10 mg/h plus ipratropium bromide at 1.0 mg/h (combination treatment) or albuterol plus saline at 10 mg/h (control treatment). The combination and control treatments were prepared by the hospital pharmacy in random sequence using a random number table and were placed in identical 4-oz brown-tinted bottles, which were then numbered consecutively. Both treatments contained 33.4 mg (5 mg/mL or 67 mL) albuterol. The combination therapy also contained 3.34 mg (5 mg/mL or 16.7 mL) ipratropium. Both therapies were mixed with normal saline to create a total volume of 100 mL/bottle. For each study patient, the RT selected the next numbered bottle in sequence and placed the contents in a nebulizer (Heart; Vortran Medical Technology, Sacramento, CA). The treatments were delivered via aerosol mask at 10 L/min. Most of the patients received the medicated aerosol driven by compressed air, with supplemental oxygen by nasal cannula as needed. However, if the patient’s oxygen saturation was ≤ 90%, oxygen was used to power the nebulizer. Vital signs, Borg dyspnea score, presence of arrhythmias and tremor, and PEFR were recorded hourly by the RT.

The following information was recorded for each subject: age, height, weight, history of hospitalization, history of intubation for bronchospastic disease, smoking history, and current medications. A smoking history was defined as the use of any regular cigarette for a year or more, at present or in the past. Subjects also were asked whether they had been given a diagnosis of asthma or COPD from their primary physician, and the clinical diagnosis was recorded.

Treatment was administered for a maximum of 3 h. Subjects could be discharged to home during the study period; they were...
not required to stay for the full 3 h of treatment. If the decision to admit a patient to the hospital was made before the study period ended, the study drug and monitoring were continued until the patient left the ED. Additional medications were not given during the study period. Treating physicians and RTs remained blinded to the study drug after the study period and were free to give additional medications after the study period ended.

Admission and discharge criteria were based on the 1991 guidelines in the National Asthma Education Program Expert Panel Report of the National Heart, Lung, and Blood Institute (NHLBI).22 According to these recommendations, patients should be treated in the ED until their PEFR reaches 70% of predicted, or until they have received 4 h of treatment. At this point, patients with PEFRs between 40 and 70% of predicted may be discharged provided that they do not have significant clinical symptomatology or significant risk factors for poor outcome. Therefore, during the 3-h study period, treating physicians were permitted to discharge patients only if their PEFR reached 70% of predicted. After the study period, physicians were permitted to use clinical parameters, PEFR, and other risk factors to determine disposition. Prior to initiating the study, physicians were informed both verbally and by memo about the discharge guidelines contained in the NHLBI report, but use of these guidelines was not mandatory. Disposition decisions made by house staff were approved by the ED attending physician.

The RT, treating physician, and patient were blinded to treatment, and the code for drug assignment was not known to the investigators until data for all patients had been entered into the study database.

Primary outcome measures were improvement in PEFR, hospital admission rate, and length of stay in the ED. Secondary measures were improvement in heart rate, respiratory rate, dyspnea score at the end of treatment, and side effects for each study group.

Statistical Analysis

Analyses of three outcome measures were performed. Repeated-measures models with an autoregressive correlation structure were used to analyze the improvements in PEFR, relative to baseline value, at 1, 2, and 3 h. Logistic regression and Fisher's exact test were used to analyze the probability of admission vs discharge, with odds ratios used as summary statistics. Length of stay was defined as the time from entry into the study to discharge, with those admitted being counted as having the longest possible stay. Statistical methods used for this measure were unaffected by the exact length of time chosen for these patients, so an arbitrary time longer than any of the observed times was chosen. Length of stay was summarized for each treatment group by the median, and the two groups were compared by the nonparametric Wilcoxon test. Kaplan-Meier curves of the proportion not yet discharged vs time were used to provide a graphical summary of discharge times. Improvement in respiratory rate, heart rate, and Borg dyspnea score at the end of treatment were compared using the two-tailed Student's t test.

Baseline characteristics were compared using Fisher's Exact Test for categorical variables and the two-tailed Student's t test for continuous variables. Because the randomization was imbalanced on smoking history and the baseline percent of predicted PEFR, controlled analyses were performed. Multivariate repeated-measures models and logistic regressions included these two covariates in addition to treatment. Wilcoxon tests controlled for these covariates by stratifying on smoking history and three levels of baseline PEFR: $\geq 25$%; 26 to 49%; and $\geq 50$% of predicted. Additional covariates were also included in the regression models, but because of the limited number of subjects, no further stratification was possible for the Wilcoxon test.

This study had the power to detect a difference between treatment groups in final PEFR of 25%, using a two-tailed $\alpha$ of 0.05 and $\beta$ of 0.20. Analyses were performed using the Statistical Analysis System (SAS Institute; Cary, NC) procedures Proc Mixed, Proc Logistic, Proc Freq, and Proc Lifetest.

Results

Seventy-three patients were enrolled in the study; six patients were excluded. Three patients had PEFRs that were $\geq 70$% predicted, one patient had pneumonia, one had congestive heart failure, and one required transfer to the ICU for respiratory failure before beginning therapy. Analyses were performed on the 67 remaining patients. Three patients were enrolled twice; one was enrolled three times. The mean age ($\pm$ SD) for all patients was 47.5 $\pm$ 18.8 years. Seventy percent of patients were women. The mean initial PEFR was 44.8 $\pm$ 12.5% of predicted (range, 19 to 69% of predicted). Twenty-one of the enrollees in the study (31%) were admitted. Fifty-seven patients (85%) identified themselves as having asthma, and 10 (15%) as having COPD. These patients were evenly distributed in the two treatment groups.

There were 465 patients who presented to the ED with acute bronchospasm during the study period but were not enrolled in the study. In this group of patients, the mean age was 46.5 years and 67% were female. Eighty-eight percent had asthma, and 12% had COPD. The admission rate among these patients was 23%.

There were two statistically significant differences in the baseline characteristics of the treatment groups (Table 1). The control group by chance had a significantly lower initial PEFR than the combination therapy group. The control group also had a significantly higher percentage of patients with a history of smoking. Analyses of improvement in PEFR, length of stay, and admission rate were initially adjusted for both of these baseline characteristics. Because the adjustment for the percentage of smokers did not affect the results, all of the outcome measures were adjusted for baseline PEFR only.

Additionally, the group receiving combination therapy had a higher proportion of patients who previously had been hospitalized and intubated, while there were more patients in the control group who previously had been prescribed ipratropium bromide for home use. However, none of these differences reached statistical significance.
Improvement in PEFR

Among all subjects, the mean PEFR increased from an initial 44.8% to 66.24% of predicted at the end of treatment (improvement from baseline, 49.65%). Subjects receiving combination therapy had a 56% improvement from baseline (95% CI, 35 to 78%), and control subjects had a 43% improvement from baseline (95% CI, 28 to 58%). After adjusting for initial differences in PEFR, the subjects who received combination therapy had an overall 6.3% (95% CI, 2.15 to 27%) greater improvement in PEFR from baseline (repeated-measures model using all three time points) than those who received albuterol only. No statistically significant difference in improvement in PEFR could be demonstrated between treatment groups at 1, 2, or 3 h, whether calculated as the absolute change from baseline in the percent predicted PEFR (Fig 2), the absolute change in PEFR (L/min), or the percent change in PEFR.

Length of Stay

The median length of stay in the ED for all subjects was 225 min. Patients in the combination therapy group had a median stay of 210 min (95% CI, 180 to 226 min), and control subjects had a median stay of 245 min (95% CI, 220 min to “admitted”) (Wilcoxon test, p = 0.03; Fig 3). (Numeric values for the upper CI limits are not assigned because admitted patients were assumed to have the longest possible length of stay and were not assigned a specific numeric value.) When adjusted for base-line differences in initial PEFR, the difference in length of stay in the ED between treatment groups was not statistically significant (Wilcoxon test, p = 0.26).

Hospital Admissions

Twenty-one of the subjects (31.3%) were admitted. The mean final PEFR for discharged patients was 74 ± 22% of predicted (median, 76%), and the mean final PEFR for admitted patients was 49 ± 20% (median, 49%).

![Figure 2. Change in percent predicted PEFR from baseline. The mean change from baseline in PEFR is expressed as the absolute change in percent predicted. The difference between groups receiving combination treatment and control treatment was not significant at 1, 2, or 3 h. Error bars represent standard error.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21911/)
Eight patients (23%) who received combination therapy and 13 control subjects (39%) were admitted. Adjusting for initial PEFR, the odds ratio for admission for the combination therapy group was 0.88 (95% CI, 0.28 to 2.8).

**Clinical Parameters**

No statistically significant differences between treatment groups were found in respiratory rate, heart rate, and Borg dyspnea score at 1, 2, and 3 h of treatment. At the end of treatment, improvements in respiratory rate, heart rate, and Borg dyspnea score from baseline were the same for both treatment groups (Table 2).

**Asthma Only**

The 57 patients who had a clinical diagnosis of asthma were analyzed separately for all three outcomes. There were no qualitative differences between the results for this group and those for the group as a whole.

**Complications**

No patient required intubation. One patient in the control group returned within 24 h of treatment because of a failure to improve and a rash on her hands. No arrhythmias other than sinus tachycardia were noted in either group. There were no statistically significant differences in the incidence of tremor between groups. Four patients reported minor side effects: one had emesis; two complained of dry mouth; and one complained of headache. All four patients were in the control group.

**Discussion**

We conducted a randomized and blinded study comparing the outcomes of ED patients with acute bronchospasm treated via continuous nebulization with either a combination of ipratropium plus albuterol or albuterol alone. Although the direction of the results for all three outcome measures suggests some clinical benefit from combination therapy, we were unable to demonstrate a statistically significant difference in improvement in PEFR, hospital admission rate, or length of stay in the ED.

Although recent recommendations by both the American Thoracic Society and the NHLBI program advocate the use of ipratropium for most acutely ill patients with bronchospasm, only two previous studies in adults have examined whether combination therapy affects clinically important outcomes. Shrestha et al found a statistically significant

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**Figure 3.** Length of stay in the ED. Kaplan-Meier survival curves demonstrate the difference in length of stay for patients by showing the proportion of patients in each treatment group remaining in the ED at any time. Patients who were admitted were assigned the longest length of stay.
shorter length of stay in the ED (91 min) in patients with COPD treated with a combination of hourly nebulized isethionate and a low dose of inhaled ipratropium (54 μg or 3 puffs after the first isethionate treatment, and 36 μg after the second and fourth). However, this study did not control for the use of steroids, it administered IV aminophylline to all patients, and it used a less potent and less β-selective β-agonist than is currently recommended. In an unblinded study with a 2-h limit on length of stay, McFadden et al.17 found no statistically significant difference in admission rates or time in the ED with the addition of 0.5 mg of ipratropium bromide to intermittent treatments with nebulized albuterol.

Two pediatric studies have looked at admission rates but not at length of stay. Schuh et al.15 found that children experiencing acute exacerbations of asthma (FEV₁ ≤ 50% predicted) who received three 0.25-mg doses of ipratropium had a significantly greater improvement in spirometry than those who received no ipratropium or one dose, but a statistically significant difference in admission rate was found only among patients whose initial FEV₁ was ≤ 30% of predicted. Qureshi et al.16 demonstrated a statistically significant difference in improvement in FEV₁ favoring combination therapy using 0.5 mg ipratropium with the first and third albuterol nebulizer treatment for children with asthma, but they found no statistically significant difference in admission rates. In both studies, subjects were required to remain in the ED for the entire treatment period, so that length of stay was not an outcome variable.

Our study differs from previous studies in that it was designed to evaluate both admission rates and length of stay, and used a protocol that incorporated the consensus guidelines with regard to the choice of β-agonist, use of steroids, length of treatment, and discharge criteria.22 Moreover, unlike previous studies, we delivered the ipratropium continuously. Recent trials indicate that continuous nebulization of β-agonist may result in better outcomes in patients with PEFRs of ≤ 200 L/min and this mode of bronchodilator delivery is now recommended by the expert panel of the NHLBI for patients with PEFRs of < 50% of predicted.23 Because prior studies have not administered combination therapy via continuous nebulization, it was necessary to determine the optimum ipratropium regimen. The standard dose of ipratropium bromide for intermittent nebulization in adults is 0.5 mg.25 We charged the nebulizers with the equivalent of 1.0 mg/h to be certain that patients received at least 0.5 mg in the same time frame that they would have if using a small-volume nebulizer. The lack of side effects in patients who received ipratropium suggests that continuous nebulization at this dose is well-tolerated.

In our study, patients who received combination therapy had a 6.3% greater improvement in PEFR than those who received standard therapy. Although this was not statistically significant in our study population, the magnitude of the difference is similar to the 7.3% greater improvement in FEV₁ found by Qureshi et al. The design of our trial necessarily limits the opportunity to observe significant differences in changes in PEFR, in order to permit observations regarding length of stay. Patients were eligible for discharge at any time during the treatment period that their PEFR reached 70% of predicted.22 This study feature imposed a ceiling on the maximum change from baseline that could be achieved before patients left the study, and it allowed patients who were responding more slowly to eventually reach the PEFR of faster responders. Shrestha et al., using a similar design in which patients with COPD exacerbations could be discharged during the study period, demonstrated a statistically significant shorter length of stay for patients receiving combination therapy but no statistically significant difference in spirometry.

While we were unable to demonstrate a statistically significant difference in the effects of combination and standard therapy, all three outcome measures demonstrated a trend in favor of combination therapy. The consistency of these findings suggests that ipratropium may improve the clinical course of ED patients with bronchospasm. Only one study, by Schuh et al., has demonstrated a statistically significant difference in admission rates in favor of combination therapy, and this was seen only in the sickest patients, where the admission rate was 83% for those treated with standard therapy. This would suggest that for the ED population as a whole, very large numbers of patients are needed to detect statistically significant reductions in admission rates. Nevertheless, if the true odds of admission for patients treated with combination therapy is 12% lower than that of patients given standard therapy, as our study suggests, this would certainly warrant the use of ipratropium in most patients, given the substantially higher cost of admission compared with that of the drug. Similarly, if the length of ED stay were indeed 35 min shorter with combination therapy, as estimated here, this would have a substantial impact on ED treatment costs, overcrowding, and patient satisfaction.

Limitations

Two baseline characteristics were not similar between treatment groups, but we adjusted for these differences in our statistical analyses. Although we permitted some physician discretion with regard to
admission and discharge decisions at the end of the study period, the mean PEFRs for discharged and admitted patients indicate that the treating physicians adhered well to the guidelines suggested by the 1991 NHLBI expert panel. We did not perform follow-up on our patients to see whether one form of treatment resulted in a greater incidence of relapse or a shorter hospitalization. Because only those patients with PEFRs of < 70% of predicted were eligible for enrollment, the study population was somewhat more ill than the ED patients with bronchospasm who were not enrolled, as reflected in the higher admission rate for study patients. Study patients were otherwise similar to nonenrolled patients with regard to age, gender, and diagnosis of asthma or COPD. Because only three of our subjects had initial PEFRs that were ≤ 25% of predicted, we cannot comment on the effect of adding ipratropium to the regimen of patients who present with this degree of bronchospasm.

We did not attempt to distinguish strictly between patients with asthma and COPD using the definitions of the American Thoracic Society. These definitions are difficult to apply in an ED setting, especially since there is considerable overlap with regard to the reversibility of airway obstruction in the two diseases. Furthermore, the number of patients in our study with a working diagnosis of COPD was small. However, when we separately analyzed results for those patients with a clinical diagnosis of asthma, the results were qualitatively the same.

We acknowledge that the use of PEFR as a measure of the degree of bronchospasm is not ideal. PEFR is affected by the degree and timing of expiratory effort, and has more variability than FEV1. Most EDs rely on PEFR because it can be measured without the assistance of an RT. Nevertheless, clinical changes may not be reliably reflected in a PEFR measurement.

Finally, the width of the CIs for our results makes it inadvisable to draw firm conclusions about the effects of ipratropium on these outcomes. Larger studies are needed to determine conclusively any impact of ipratropium on care in the ED.

CONCLUSION

Although there were small differences in PEFR, the likelihood of admission, and length of stay, which favored combination therapy, a statistically significant advantage in clinical outcomes could not be demonstrated in ED patients with acute bronchospasm receiving continuous ipratropium plus albuterol compared with patients receiving albuterol alone. Larger studies may demonstrate a clinically useful role for ipratropium in acutely ill patients.

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