Randomized Trial of the Addition of Ipratropium Bromide to Albuterol and Corticosteroid Therapy in Children Hospitalized Because of an Acute Asthma Exacerbation

Norma Goggin, MD, MRCP; Colin Macarthur, MB, ChB, PhD; Patricia C. Parkin, MD, FRCPC

Objective: To determine whether the addition of inhaled ipratropium bromide to inhaled albuterol and systemic corticosteroid therapy was more efficacious than inhaled albuterol and systemic corticosteroids alone in the inpatient treatment of acute asthma exacerbations in children.

Design: Double-blind, randomized, placebo-controlled trial.

Setting: Pediatric inpatient unit of a tertiary urban hospital.

Participants: Eighty children (aged 1-18 years) hospitalized because of an acute asthma exacerbation.

Intervention: Children were randomized to receive either nebulized ipratropium bromide, 250 µg, or nebulized isotonic sodium chloride solution, 1 mL. All children received albuterol and systemic corticosteroids.

Main Outcome Measures: The primary outcome variable was a validated clinical asthma score, measured at baseline and every 6 hours for 36 hours. Secondary outcome measures included the forced expiratory volume in 1 second, the oxygen saturation, the number of doses of inhaled study drug, the time to an inhaled drug-dosing interval of 4 hours, and the length of the hospital stay.

Results: There were no differences between groups on baseline characteristics. The intention-to-treat analysis, using repeated-measures analysis of variance, showed no significant (P = .07) difference between the groups in the clinical asthma score over time. There were also no significant differences between groups on secondary outcomes.

Conclusion: The addition of nebulized ipratropium bromide to nebulized β2-agonist and corticosteroid therapy in the treatment of children hospitalized because of asthma (following intensive emergency department treatment) confers no extra benefit.


IN CHILDREN WITH AN acute asthma exacerbation, standard treatment consists of frequent nebulized β2-agonists and early systemic corticosteroid therapy. A recent systematic review of numerous studies and 2 subsequent studies have demonstrated that the addition of 2 to 3 doses of inhaled ipratropium bromide to β2-agonist therapy in the emergency department treatment of children with severe asthma improves lung function and reduces the hospital admission rate. The role of ipratropium bromide in the treatment of children hospitalized following emergency department treatment has not been well studied. Two studies, published more than 10 years ago, have examined the role of ipratropium bromide in the inpatient setting. The objective of this study was to determine whether the addition of inhaled ipratropium bromide to inhaled albuterol and systemic corticosteroid therapy was more efficacious than inhaled albuterol and systemic corticosteroids alone in the inpatient treatment of acute asthma in children.

RESULTS

BASELINE CHARACTERISTICS

A total of 212 patients were assessed (Figure 1). Of these patients, 113 were ineligible for the following reasons: the exacerbation was too mild (n = 35), the exacerbation was too severe (n = 4), the patients were too young (n = 7), this was the first episode of wheeze (n = 20), there was a coexistent chronic disease (n = 14), the
PARTICIPANTS AND METHODS

STUDY POPULATION

All children received initial treatment in the emergency department and were assessed for eligibility at admission to the inpatient unit. Patients were eligible if they were between the ages of 1 and 18 years and had a known history of asthma (defined as at least 1 previous episode of wheezing or a history of chronic cough that required treatment with bronchodilators or anti-inflammatory agents). Only children with moderate to severe asthma symptoms at admission to the inpatient unit (defined as requiring inhaled β₂-agonists a minimum of every 2 hours, having a forced expiratory volume in 1 second [FEV₁] of 25%-80% of the predicted value, or having a clinical asthma score of 3-9) were recruited.

Exclusion criteria were as follows: coexistent cardiac, neurological, immunosuppressive, or other chronic pulmonary disease; known hypersensitivity to the study drugs; preexisting ocular abnormalities; the need for airway intervention or admission to the critical care unit; severe asthma symptoms at admission to the inpatient unit (clinical asthma score of 10); or undue delay, ie, longer than 12 hours from the time of first treatment in the emergency department to admission to the inpatient unit.

The study was approved by the institutional Research Ethics Board. Informed parental consent was obtained; assent was obtained for children older than 7 years, and consent was obtained for adolescents 16 years and older.

STUDY DESIGN

All patients received a frequent nebulized albuterol inhalation solution (Ventolin; Glaxo Wellcome Inc, Mississauga, Ontario), 0.15 mg/kg per dose (maximum, 5-mg dose). The dosing interval was determined by the attending physician. The usual treatment in our institution is to begin with a dosing interval of a half hour to 2 hours, progressing to 2 hours, and then to 4 hours as the patient improves clinically. All children were also treated with corticosteroids using either intravenous hydrocortisone (Upjohn Abbott, Toronto, Ontario), 4 to 6 mg/kg every 6 hours, or oral prednisone (Novopharm, Toronto), 1 mg/kg once daily. The total duration of corticosteroid therapy was a minimum of 5 days.

Subjects were randomized to receive either nebulized ipratropium bromide inhalation solution (Atrovent; Boehringer Ingelheim, Burlington, Ontario), 1.0 ml (250 µg), or nebulized isotonic sodium chloride solution, 1.0 ml, as placebo. Randomization was independently performed by a research pharmacist using a table of random numbers. The dosing interval of ipratropium bromide or placebo was matched to the albuterol dosing interval. Ipratropium bromide or placebo and albuterol were mixed in the same nebulizer, suspended in isotonic sodium chloride solution, made up to a total volume of 4 ml, and delivered for 15 minutes by face mask and nebulizer (Whisper Jet; Intec Medical, Englewood, Colo) driven by compressed air or oxygen (oxygen flow rate, 6-8 L/min) if the child was receiving oxygen. Nebulizer therapy was administered by the child’s attending nurse.

Compliance was assessed by reviewing the hospital drug administrative records. The use of supplemental oxygen therapy and other concurrent therapy (eg, aminophylline) was at the discretion of the attending staff and was recorded.

Patients enrolled in the study were stratified at enrollment by 2 criteria. Children within each stratum were randomly allocated to treatment groups in blocks of 4. First, children were stratified by age (<5 or ≥5 years), given that age influences the ability to perform FEV₁, which was a secondary outcome measure. Second, children were stratified by the number of doses of nebulized ipratropium bromide administered in the emergency department (<5 or >3) because it was hypothesized that the intervention effect might vary according to prior exposure to ipratropium bromide. The cutoff number of 3 doses of ipratropium bromide was based on the results of a double-blind, randomized, controlled trial.²

Ipratropium bromide inhalation solution and isotonic sodium chloride solution are clear, colorless, and odorless liquids, and the 2 solutions were indistinguishable from one another in the liquid and nebulized states.

Table 1 shows the baseline characteristics of the 2 groups, with no significant differences between the groups. Patients in both groups received intensive treatment in the emergency department, which included approximately 8 doses of albuterol and 6 doses of ipratropium bromide over approximately 7 hours. Of the 80 randomized patients, 77 received the first dose of oral or intravenous corticosteroid in the emergency department before randomization and 3 received the first dose after randomization (2 in the ipratropium bromide–treated group and 1 in the placebo group). Nonparticipants (n=15) were similar to participants for age, sex, asthma history, asthma treatment, and duration of current symptoms.

PRIMARY OUTCOME

Both groups showed a similar improvement in clinical asthma score during the first 36 hours. At baseline, the mean (±SD) clinical asthma score was 6.1 (±1.3) in the ipratropium bromide–treated group vs 5.7 (±1.4) in the placebo group. At 36 hours, the mean (±SD) clinical asthma score had decreased to 2.4 (±1.9) in the ipratropium bromide–
treated group vs 2.6 (±2.0) in the placebo group. The intention-to-treat analysis, using repeated-measures analysis of variance, showed no significant difference between the groups in the clinical asthma score over time (P=.07) (Figure 2).

SECONDARY OUTCOMES

There were no significant differences between the groups in oxygen saturation over time (P=.16). Only 15 patients (5 in the ipratropium bromide-treated group and 10 in the placebo group) were able to perform spirometry reliably, with no significant differences between the groups in FEV₁ over time (P=.62). There were also no significant differences between the 2 groups on the other secondary outcomes (Table 2). None of the 80 patients in the study presented to the emergency department or were readmitted to the hospital within 72 hours of discharge.

SAFETY DATA

No patients reported any visual symptoms. In both groups, the heart rate decreased during the 36-hour study period. At each 6-hour measurement, the mean heart rate in the ipratropium bromide–treated group ranged between 6 and 10 beats/min faster than that in the placebo group, with a significant difference between the groups in heart rate over time (P=.01).

SUBGROUP ANALYSES

There were no significant differences in the clinical asthma score over time between the ipratropium bromide–treated group and the placebo group in 3 of the 4 subgroups: greater than 3 doses of ipratropium bromide in the emergency department (n=55, P=.13), age younger than 5 years (n=54, P=.22), and age 5 years and older (n=26, P=.35). In the subgroup of patients receiving 3

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doses of ipratropium bromide or fewer in the emergency department (n = 25) at baseline, the mean (±SD) clinical asthma score was 5.8 (±1.3) in the ipratropium bromide–treated group vs 5.7 (±1.7) in the placebo group. At 36 hours, the mean (±SD) clinical asthma score had decreased to 3.1 (±2.0) in the ipratropium bromide–treated group vs 3.5 (±2.1) in the placebo group. Using repeated-measures analysis of variance, there was a significant difference between the groups in the clinical asthma score over time (P = .04).

COINTERVENTIONS

Cointervention use in the 2 groups was similar. All patients received albuterol at an appropriate dose, 0.05 to 0.15 mg/kg. Of the 80 patients, 74 (92%) received systemic corticosteroids (with no significant [P = .95] differences between the 2 groups). Six patients did not receive systemic corticosteroids in the hospital (1 had received 5 days of corticosteroids before admission, and 5 received a dose in the emergency department and were discharged within 24 hours).

Table 1. Characteristics of Participants at Baseline*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipratropium Bromide (n = 41)</td>
<td>Placebo (n = 39)</td>
</tr>
<tr>
<td>Age, y†</td>
<td>2.9 (1.8-5.8)</td>
<td>3.7 (2.3-6.1)</td>
</tr>
<tr>
<td>Male sex‡</td>
<td>26 (63)</td>
<td>23 (69)</td>
</tr>
<tr>
<td>Lifetime episodes of wheeze‡</td>
<td>22 (54)</td>
<td>23 (59)</td>
</tr>
<tr>
<td>≥1</td>
<td>19 (46)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>8 (19)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>No. of asthma hospitalizations†</td>
<td>1.0 (0-3)</td>
<td>1.0 (0-3)</td>
</tr>
<tr>
<td>Used in the previous week†</td>
<td>38 (93)</td>
<td>35 (90)</td>
</tr>
<tr>
<td>β2-Agonist</td>
<td>28 (68)</td>
<td>27 (69)</td>
</tr>
<tr>
<td>Oral or inhaled corticosteroid</td>
<td>2.0 (1-3)</td>
<td>2.0 (1-3)</td>
</tr>
<tr>
<td>Duration of current symptoms, d†</td>
<td>8.3 (±2.7)</td>
<td>7.9 (±2.4)</td>
</tr>
<tr>
<td>No. of doses in the emergency department</td>
<td>6.9 (±2.2)</td>
<td>7.0 (±2.6)</td>
</tr>
<tr>
<td>Albuterol</td>
<td>8.3 (±2.7)</td>
<td>7.9 (±2.4)</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>6.0 (±2.3)</td>
<td>5.9 (±2.2)</td>
</tr>
<tr>
<td>Time from first treatment to the emergency department to enrolment, h</td>
<td>8.3 (±2.7)</td>
<td>7.9 (±2.4)</td>
</tr>
<tr>
<td>Baseline clinical asthma score</td>
<td>6.1 (±1.5)</td>
<td>5.7 (±1.4)</td>
</tr>
<tr>
<td>Baseline % oxygen saturation</td>
<td>93.3 (±3.1)</td>
<td>93.5 (±3.1)</td>
</tr>
<tr>
<td>Baseline heart rate, beats/min</td>
<td>150.8 (±14.6)</td>
<td>152.3 (±20.5)</td>
</tr>
</tbody>
</table>

*Data are given as mean (±SD) unless otherwise indicated. †Data are given as median (interquartile range). ‡Data are given as number (percentage) of participants.

doses of ipratropium bromide or fewer in the emergency department (n = 25) at baseline, the mean (±SD) clinical asthma score was 5.8 (±1.3) in the ipratropium bromide–treated group vs 5.7 (±1.7) in the placebo group. At 36 hours, the mean (±SD) clinical asthma score had decreased to 3.1 (±2.0) in the ipratropium bromide–treated group vs 3.5 (±2.1) in the placebo group. Using repeated-measures analysis of variance, there was a significant difference between the groups in the clinical asthma score over time (P = .04).

COINTERVENTIONS

Cointervention use in the 2 groups was similar. All patients received albuterol at an appropriate dose, 0.05 to 0.15 mg/kg. Of the 80 patients, 74 (92%) received systemic corticosteroids (with no significant [P = .95] differences between the 2 groups). Six patients did not receive systemic corticosteroids in the hospital (1 had received 5 days of corticosteroids before admission, and 5 received a dose in the emergency department and were discharged within 24 hours).
Thirty-six (45%) patients received supplemental oxygen, with no significant (P = .80) difference between the 2 groups. No patient received intravenous aminophylline or oral theophylline.

The results of this randomized controlled trial suggest that cointervention with inhaled ipratropium bromide in children (aged 1-18 years) hospitalized because of an acute asthma exacerbation, following intensive emergency department treatment with albuterol, ipratropium bromide, and corticosteroids, confers no extra benefit.

There were some limitations to the study. Most patients enrolled in the study (55 [69%] of 80) were younger than 5 years, and only 15 (19%) were able to perform FEV₁ reliably. This was anticipated a priori, because most children hospitalized with acute asthma are younger than 5 years. Therefore, we used a clinical asthma score as the primary outcome measure. This score has been shown to be reliable, valid, and responsive. The use of spirometry as an outcome measure in those with acute asthma during childhood may be limited. Highlighting the need for alternative measures of acute asthma severity. Finally, the results of this study may not be generalizable to patients admitted to intensive care units (patients with severe asthma symptoms at admission to the inpatient unit were excluded) or to patients who have not received intensive combination bronchodilator treatment in the emergency department.

The literature on the role of ipratropium bromide in the treatment of childhood asthma in the emergency department setting is comprehensive, and includes a systematic review, a meta-analysis, and 2 recent, large, randomized, controlled trials. These studies suggest that the addition of multiple doses (≤3 doses have been studied) of anticholinergic agents to β₂-agonist therapy in the initial treatment of children with severe asthma exacerbations is safe, efficacious, and cost-effective. There is no apparent benefit in children with mild to moderate asthma exacerbations. Most of these studies, however, did not include younger children.

Two studies have examined the role of ipratropium bromide in the inpatient setting. Both were published more than 10 years ago. Neither study found any benefit from the addition of ipratropium bromide to albuterol in children admitted to the hospital with an acute asthma exacerbation. The results of these studies, however, are not generalizable to current practice because bronchodilators were used infrequently (every 4-8 hours) and corticosteroids were not given to all patients.

Recently, Craven et al showed that the addition of repeated doses of ipratropium bromide to systemic corticosteroid and β₂-agonist therapy did not improve the clinical outcomes of children hospitalized with asthma. Children in this study, however, did not receive ipratropium bromide in the emergency department (which is recommended by the literature), and the dosing interval was 4 to 6 hours on the inpatient unit. This contrasts with our study, in which children received intensive ipratropium bromide therapy in the emergency department and in the inpatient unit. Before enrollment in our study, children received, on average, 6 doses of ipratropium bromide in the emergency department and within the study protocol children received a median of 13 doses of ipratropium bromide over 36 hours. Considering the evidence from studies in the emergency department and the inpatient setting together, it appears that intensive ipratropium bromide treatment, in addition to albuterol and corticosteroids, is most effective when delivered as early as possible in the treatment of an acute asthma exacerbation.

In this study, the frequent administration of ipratropium bromide appeared to be safe. The mean heart rate in both groups increased at all points, but never to a clinically worrisome level. However, the heart rate in the ipratropium bromide-treated group was slower to decrease during the study period compared with the heart rate in the placebo group (P = .01). Transient anisocoria associated with nebulized ipratropium bromide treatment has been described in children, but was not noted in this study.

The ideal dosage and dosing frequency of ipratropium bromide in the treatment of childhood asthma are not known. In this study, the standard dose of 250 µg of ipratropium bromide was used, but administration was frequent because it was matched to the frequency of administration of albuterol, which ranged from 30-minute to 4-hour intervals. Although it is theoretically possible that a benefit might have been observed with a higher dose of ipratropium bromide, it is unlikely in view of the frequent administration of the drug.

Subgroup analysis suggested that children who received 3 or fewer doses of ipratropium bromide in the emergency department did benefit from the continuation of ipratropium bromide treatment in the inpatient setting, whereas those who received more than 3 doses did not. Caution is required when interpreting subgroup analyses, because of the possibility of reaching “false-positive” conclusions because of multiple comparisons. Although the subgroup analyses were proposed a priori, this subgroup was small (n = 25) and the magnitude of the P value (P = .04) was modest. This finding, therefore, should be seen as hypothesis generating, rather than hypothesis testing.

The addition of 2 to 3 doses of inhaled ipratropium bromide to β₂-agonist therapy in the emergency department treatment of children with severe asthma improves lung function and reduces the hospital admission rate.

The role of ipratropium bromide in the treatment of children hospitalized following emergency department treatment, however, has not been well studied.

The addition of nebulized ipratropium bromide to nebulized β₂-agonist and corticosteroid therapy in the treatment of hospitalized asthmatic children (following intensive treatment in the emergency department) does not confer any clinical benefit.
Using repeated-measures analysis of variance to test for differences between groups in the clinical asthma score over time, the $P$ value approached statistical significance ($P = .07$); however, it was in the direction favoring placebo. Furthermore, given the sample size of 80 patients, this study had greater than 90% power to detect a difference in the clinical asthma score between groups of as small as 0.9 (which would not be interpreted as clinically meaningful). For length of stay, the sample size of 80 patients provided 90% power to detect a difference between groups of as small as 12½ hours, a difference considered “clinically important” by previous investigators.18

In conclusion, the sample size in this study was sufficient to detect a clinically important difference between the groups in the clinical asthma score over time. Therefore, the negative result is interpretable and it is concluded that the addition of nebulated ipratropium bromide to nebulated $\beta_2$-agonist and corticosteroid therapy in the treatment of hospitalized asthmatic children (following intensive treatment in the emergency department) does not confer any clinical benefit.

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Dr Goggin designed the trial and the research materials, trained and liaised with the research nurses, conducted the data collection, performed the initial data analysis, and produced the main drafts of the article. Dr Macarthur participated in study design and management, conducted the final data analysis, and contributed to the interpretation of results and the writing of the article. Dr Parkin, the guarantor for the article, initiated the research, provided overall direction on the study, and contributed to the design of the protocol, the analysis, the interpretation of results, and the writing of the article.

Corresponding author and reprints: Patricia C. Parkin, MD, FRCP, Division of Paediatric Medicine, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (e-mail: patricia.parkin@sickkids.ca).

REFERENCES