Single-dose intravenous salbutamol bolus for managing children with acute severe asthma in the emergency department: Reanalysis of data*

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Objective: To reanalyze data from two previous studies to provide stronger evidence of benefit for early use of single-dose intravenous bolus salbutamol in children with acute severe exacerbations of asthma.

Methods: Randomized, double-blind, placebo-controlled trial of 84 children with acute severe asthma who presented to the emergency department of the Children's Hospital at Westmead. After clinical evaluation, patients who had severe asthma were given high-dose inhaled salbutamol and had an intravenous cannula inserted. Additional treatment consisted of intravenous methylprednisolone (1 mg/kg), oxygen (6 L/min via mask if SaO$_2$ was <93%). Patients were then randomized to receive an intravenous infusion of either 15 µg/kg salbutamol or saline, with clinical progress assessed hourly for 2 hrs. All patients were admitted to the hospital and clinically monitored for the proceeding 2–24 hrs, with inhaled salbutamol treatment administered in accord with the hospital's protocol.

Despite many advances in the treatment of asthma and more effective ways of delivering bronchodilators in acute severe asthma, asthma remains the most common medical emergency in children (1–9). Children with acute severe asthma, if treated effectively in the emergency department (ED), can have the clinical progression of asthma curtailed, resulting in reduced demands placed on EDs and improving the quality of care delivered to acutely sick children (10, 11).

Clinical response to inhaled bronchodilators in asthma may vary in an individual in relation to the severity of airway obstruction (12). If airway obstruction is severe, effective delivery of inhaled drugs to the airway may be impaired, resulting in poor clinical response to treatment, with the patient in a nonresponsive phase of the illness (13). This may be exacerbated by progressive inflammatory change occurring in the bronchial wall, which renders Airways unresponsive to bronchodilators (14–16). If in acute asthma penetration of drug to the affected small airways is impeded, the initial therapeutic response may be a result of drug reaching the receptors from the systemic circulation (17–20).

We reported two studies that compared the clinical outcomes of children who frequently received nebulized bronchodilator therapy (one using salbutamol, the other using salbutamol together with ipratropium bromide) with children who were administered, in addition to frequent-dose nebulized salbutamol, a single-dose intravenous bolus of salbutamol (10, 11). These reports demonstrated more rapid clinical improvement in children managed with a single-dose intravenous bolus and showed that the addition of nebulized ipratropium bromide to nebulized salbutamol had no clinically significant benefits. These two studies used what are considered appropriate therapies for childhood asthma: One used a frequent, high-dose nebulized salbutamol alone, and the other used frequent, high-dose nebulized salbutamol in combination with ipratropium bromide.

A recent Cochrane systematic review reports that a single dose of an anticholinergic agent is not effective for the treatment of mild and moderate exacerbations and is insufficient for the treatment of severe exacerbations of asthma in children (21). Furthermore, there was no conclusive evidence that multiple doses of anticholinergic agents were of value for acute exacerbations of childhood asthma (21). In consideration of this new evidence, the aim of this study was to reanalyze our data from two previous studies to provide further evidence supporting the benefit of the early use of single-dose intravenous bolus salbutamol in children with acute severe exacerbations of asthma.
METHODS

Study Design

Both studies were double-blinded, randomized, controlled trials in evaluating the effectiveness of single-dose intravenous salbutamol in the management of acute asthma in children. The two studies were similar, including selection criteria, basic prerandomization treatment, and data collection procedures in their conduct of the research. The only difference between the two studies was an additional treatment arm introduced in study 2. Details of the study protocol were reported previously (10, 11) and are depicted diagrammatically in Figure 1 and Figure 2.

Selection Criteria for Both Studies

Children who presented to the ED with severe asthma were eligible to enter the study. Severe asthma was classified as having all four features of respiratory distress (wheezing, sternal retraction, accessory muscle use, dyspnea) or having any of the absolute criteria (cyanosis, pulsus paradoxus, altered consciousness, or a silent chest on auscultation). These children were immediately referred to an acute treatment area and assessed by a physician. All children were given salbutamol nebulizer therapy consisting of 4 mL of saline with 2.5 mg of salbutamol for children 2 yrs old and younger or 5 mg of salbutamol for children older than 2 yrs. Because all children in this study had severe asthma, they were admitted to an inpatient bed.

Exclusion Criteria. The following excluded criteria were used: any child presenting with life threatening asthma, age <12 months, presence of congenital heart disease, family history of Wolff-Parkinson-White syndrome or past supraventricular tachycardia, respiratory disease other than asthma, clinical or radiologic pneumonia, diabetes mellitus or glucose intolerance, weight <10 kg or >60 kg, and known hypersensitivity to the study drugs.

Patient Withdrawal. Patients were to be withdrawn from the study in the following circumstances: clinical deterioration during the study, heart rate persistently >200 beats/min for longer than 5 mins, signs on the electrocardiogram of hypokalemia, and withdrawal from the study by parent or guardian.

Procedures

Children with acute severe asthma presenting to the ED were eligible to enter the study. Initial evaluation occurred at the ED triage desk, and children with acute severe asthma were then immediately referred to an acute treatment area and assessed by an emergency physician. The severity of asthma was assessed using a standard clinical assessment scale, the National Australian Asthma Campaign guidelines (22), and only those patients who fulfilled these asthma criteria and had a pulmonary index score consistent with severe asthma (23) were eligible for the study. Study assessments were performed in all cases by trained research assistants. Those research assistants were medical students in their last year of medical school who were trained over
a period of 3 months by a paediatric emergency physician (GB) to recognize and categorize asthma as mild, moderate, or severe as indicated by the clinical assessment scale. Children assessed by the attending emergency physician as having acute severe asthma were given salbutamol nebulizer therapy (Aerioflo oxygen mask, Waite, Sydney, Australia, with AirlifeTM Misty-Neb, Baxter Healthcare, Deerfield, IL), consisting of 2.5 mg of salbutamol if ≤2 yrs of age or 5 mg of salbutamol if >2 yrs of age with saline to a volume of 4 mL. Consent was obtained from parents or guardians of children before inclusion in the study. After 20 mins, an assessment was made by a trained research assistant, and if the patient’s asthma was still clinically severe, the study proper commenced.

The study was conducted in two phases. The first phase, a study period of 2 hrs, occurred in the ED under the strict supervision of the primary investigators. All patients were fully monitored. The subsequent 22 hrs comprised the second phase of the study during which the researchers closely monitored clinical progress on the medical wards. During the first phase, the treatment followed a standard protocol as outlined in the National Asthma Campaign guidelines (22). During the second phase, children were admitted under one of six hospital admitting teams, with all asthma treatment supervised by the admitting physician. Clinical management decisions and changes in medication regimens (frequency of nebulization) were the responsibility of these physicians and their staff and followed a standard hospital protocol based on the National Asthma Campaign guideline criteria (22). All children were admitted to the same medical ward.

In the beginning, the child commenced high-dose inhaled salbutamol therapy and, at the same time, an intravenous cannula was inserted into an antecubital vein. The purpose was to obtain a baseline 2 mL of blood for serum potassium and glucose level assessment. Salbutamol was administered via a nebulizer at a dose of either 5 mg per 4 mL for children >2 yrs or 2.5 mg per 4 mL if ≤2 yrs. Doses were given every 20 mins together with continuous oxygen at 4 L/min. All children were monitored for hypoxia with a pulse oximeter (N-3000, Nellcor, Pleasanton, CA). Continuous oxygen at a flow rate of 6 L/min was administered to all patients if oxygen saturation (SaO2) was <93% in room air. Patients remained on oxygen therapy depending on clinical response to treatment. Once the SaO2 was maintained at >93% for a period of half an hour, oxygen therapy was weaned. This was done by using both clinical assessment and pulse oximetry until maintained at >93% in room air. This period was recorded as the time of cessation of oxygen therapy. The administration of salbutamol was accompanied with 5 mg/kg intravenous hydrocortisone as a bolus administered over 3 mins immediately followed by an infusion of the study drug administered over 10 mins. The administration of the study drugs, as depicted in Figure 1 and 2, depended on the randomization for each study.

Children were assigned to the study in a block randomization fashion, with investigators, attending staff, and patients blinded to treatment. The hospital pharmacy was responsible for randomization of the intravenous solutions, which were prepared by them in syringes under sterile conditions. The randomization code was broken when all clinical and laboratory assessments were complete.

Phase 2 of the study began at 2 hrs and finished at 24 hrs. The child’s clinical progress was monitored at 4, 8, 12, and 24 hrs. Clinical side effects of salbutamol (tachycardia, tremor, and hyperactivity) were also recorded at each assessment. Ongoing inhaled salbutamol therapy during phase 2 was in accord with a standard hospital protocol using high-dose salbutamol administered, continuously, every half hour and at 1, 2, 3, and 4 hourly intervals, depending on clinical state as determined by the National Asthma Campaign guideline criteria (22). When the child was ready to commence hourly nebulized salbutamol, the child was transferred from the ED to the ward. The frequency of ongoing inhaled salbutamol treatment in the medical ward was determined by the admitting medical team physician by using the clinical assessment scale. The research assistants closely observed patients during this phase of the study by using the clinical assessment scale. Follow-up was performed on all patients until discharge.

Data for each study were collected prospectively and entered onto two separate electronic databases. Plasma potassium and glucose determinations were performed by the Department of Clinical Chemistry, Westmead Hospital, by using the standard multiple blood analyzer routinely in use in the department.

Study Outcomes

The primary outcomes of the studies were:

- Need for ongoing oxygen therapy.
- Mean recovery time ready to be discharged from the ED was defined as the time between randomization to the time when patients began hourly nebulized salbutamol.
- Mean recovery time ready to be discharged from hospital was defined as the time between randomization to the time when patients began nebulized salbutamol every third hour.

The secondary outcomes of the studies were:

- Changes in potassium and glucose levels within the first hour of randomization.
- Any adverse effects caused by the use of salbutamol, including tachycardia, premature ventricular contractions, palpitations, muscle tremor, agitation, headache, dizziness, insomnia, hyperglycaemia, nausea, and vomiting.

In this combined study, the same outcomes were used.

Data Collection and Analysis

Information on patient characteristics and outcomes of studies were extracted from the corresponding databases. To assess the compatibility of the two data sets, comparisons were conducted between the two control groups of the two studies and the two treatment groups of study 2. The purpose of comparing the two treatment groups in study 2 was to further confirm that intravenous bromide did not render additional clinical benefit over and above the treatment of intravenous salbutamol. Should this be established, all treatment groups in studies 1 and 2 were, in principal, no different from one another, thus combining treatment groups is acceptable. The two data sets were then combined into a single data set to be analyzed. The analyses were performed by applying analysis of variance for continuous variables and chi-square test for categorical variables.

RESULTS

Comparisons Within and Between the Two Studies. As shown in Table 1, there was no difference in the mean age, distribution of male and female patients, mean weight, and the presenting Pulmonary Index Score between the two control groups of the two studies. In terms of the primary outcomes, no statistically significant differences were found in the requirement of oxygen therapy and the mean recovery time ready to be discharged from the hospital for the two control groups either.

Comparisons were also conducted between the two treatment groups in study 2, namely, the intravenous salbutamol and the intravenous salbutamol and ipratropium bromide groups. The purpose of these comparisons was to determine whether the two treatment arms could be combined into one. The results of these analyses indicated that there was no statistically significant difference between the two groups, apart from the mean age of patients (Table 2). These results were consistent with those obtained and reported in the previous study (11). This suggested that the two treatment arms could be combined into a single group.
The results of the combined study are summarized in Tables 3 and 4. As indicated, the control and treatment groups were comparable in terms of patient characteristics. For the primary outcomes, the mean recovery time ready to be discharged from the ED for the treatment group (2.13 hrs) was significantly shorter than that of the control group (5.40 hrs, t(82) = 2.597, p < .05). Similarly, a significant difference was also found in the mean recovery time of patients ready to be discharged from the hospital between the treatment and control groups (t(82) = 2.625, p < .05), with the time for the treatment group being much shorter (17.32 hrs) than for the control (26.27 hrs).

In terms of the secondary outcomes, as expected, there was a slight decrease in the potassium level for both the treatment and control groups and an increase in the glucose level in both groups within the first hour of randomization. However, the differences between the two groups were not significant (Tables 3 and 4). The differences in side effects were also not statistically nor clinically significant.

**Clinical Status.** The intravenous salbutamol group demonstrated more rapid clinical improvement by the end of phase 1 of the study, with eight (57%) patients having persistent severe asthma compared with 14 (93%) control patients (p < .02). Using the PIS, only 6 (43%) patients in the intravenous salbutamol group had persistent severe asthma (PIS < 7), compared with 14 (93%) patients in the control group (p < .02). The intravenous salbutamol group experienced more rapid improvement at 2 hrs in the proportion that were wheezing (p < .02), had dyspnea (p < .05), and had increased accessory muscle use (p < .005). By 8 hrs postrandomization, there was still greater clinical improvement in the salbutamol group compared with the control group. The difference was significant (p < .05) for wheezing, dyspnea, and accessory muscle use. There were no statistically significant differences in respiratory rate or heart rate at the end of phase 1 of the study. Peak flow measurements were not reproducible during the early phase of therapy in these patients and were therefore excluded from the final statistical analysis.

### Table 1. Comparisons between the two control groups in the two studies

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Study 1 (n = 15)</th>
<th>Study 2 (n = 19)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr (SD)</td>
<td>5.65 (3.14)</td>
<td>6.49 (4.34)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>M</td>
<td>12 (80.0)</td>
<td>14 (73.7)</td>
<td>NS</td>
</tr>
<tr>
<td>F</td>
<td>3 (20.0)</td>
<td>5 (26.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean weight, kg (SD)</td>
<td>22.48 (10.12)</td>
<td>24.90 (11.36)</td>
<td>NS</td>
</tr>
<tr>
<td>PIS (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>&lt;7</td>
<td>1 (6.7)</td>
<td>5 (26.3)</td>
<td>NS</td>
</tr>
<tr>
<td>7–8</td>
<td>3 (20.0)</td>
<td>7 (36.8)</td>
<td>NS</td>
</tr>
<tr>
<td>9–10</td>
<td>10 (66.7)</td>
<td>6 (31.6)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1 (6.7)</td>
<td>1 (5.3)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Outcomes**
- **Oxygen therapy, n (%)**
  - Yes: 9 (60.0) vs. 6 (40.0), p = .59
  - No: 6 (40.0) vs. 4 (21.1), p = .59
- **Mean recovery time ready to be discharged from hospital, hrs (SD)**
  - Study 1: 22.92 (12.53) vs. 27.38 (18.88), p = .13
  - Study 2: 22.92 (12.53) vs. 27.38 (18.88), p = .13

PIS, Pulmonary Index Scale; NS, not significant.

### Table 2. Comparison between the two treatment groups in study 2

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Intravenous Salbutamol (n = 21)</th>
<th>Intravenous Salbutamol + Ipratropium Bromide (n = 15)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yr (SD)</td>
<td>7.21 (3.66)</td>
<td>4.36 (2.74)</td>
<td>p &lt; .05</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>M</td>
<td>15 (71.4)</td>
<td>10 (66.7)</td>
<td>NS</td>
</tr>
<tr>
<td>F</td>
<td>6 (28.6)</td>
<td>5 (33.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean weight, kg (SD)</td>
<td>23.52 (11.04)</td>
<td>19.31 (10.70)</td>
<td>NS</td>
</tr>
<tr>
<td>PIS (%)</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>&lt;7</td>
<td>4 (19.0)</td>
<td>3 (20.0)</td>
<td>NS</td>
</tr>
<tr>
<td>7–8</td>
<td>13 (61.9)</td>
<td>8 (53.3)</td>
<td>NS</td>
</tr>
<tr>
<td>9–10</td>
<td>3 (14.3)</td>
<td>4 (26.7)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1 (4.8)</td>
<td>0 (0.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Outcomes**
- **Oxygen therapy, n (%)**
  - Yes: 6 (28.6) vs. 4 (26.7), p = .59
  - No: 15 (71.4) vs. 11 (73.3), p = .59
- **Mean recovery time ready to be discharged from hospital, hrs (SD)**
  - Intravenous Salbutamol: 17.97 (13.25)
  - Intravenous Salbutamol + Ipratropium Bromide: 19.79 (19.69)

PIS, Pulmonary Index Scale; NS, not significant.

**DISCUSSION**

Asthma is an inflammatory disease typified by airway hyperreactivity and obstruction-producing airway resistance with a reduction in air flow (1). The mainstay of treatment of acute asthma in children is β2-adrenergic agents such as salbutamol delivered in frequent high doses or continuously nebulized together with corticosteroids (2–9, 24). A recent trend in the treatment of acute paediatric asthma is to decrease the use of intra-venous aminophylline (25) and increase the use of oral corticosteroids early in the patient’s visit (26). These interventions have reduced the need for intravenous catheter insertion, with corticosteroids reducing the need for hospitalization for many children. In Australia, particularly in the western Sydney region where the Children’s Hospital at Westmead is situated, the number of children presenting with acute severe asthma has increased and continues to increase, with many admitted to intensive care for a continuous infusion of intravenous salbutamol (27). We consider the use of a single-dose intravenous salbutamol bolus in the ED to be more effective in achieving earlier clinical response in a subgroup of children with acute severe asthma. In these children, intravenous access is already in place, facilitating early administration of salbutamol.
Our data show that in a subgroup of children with acute severe asthma who, in addition to receiving frequent, high-dose nebulized salbutamol, receive a single-dose intravenous salbutamol bolus of 15 μg/kg early in ED treatment demonstrate a more rapid clinical response. Children who received nebulized salbutamol were stabilized more rapidly in the ED, with a mean recovery time to ED discharge 3.27 hrs less than children in the control group. Similarly, the mean recovery time to hospital discharge was 9.5 hrs less for those receiving nebulized salbutamol.

The use of frequent, high-dose nebulized salbutamol in children with severe asthma is effective; however, clinical response may be slow. This can be caused by progressive airway obstruction from inflammation, and the children are then considered to be unresponsive to treatment (13–15, 28, 29). In these patients, continuous nebulized salbutamol is often used to prevent the phenomenon of bronchospastic rebound. This approach achieves high levels of salbutamol, but side effects are frequently reported (28, 30, 31). The use of a single-dose intravenous salbutamol bolus is a controlled way of achieving therapeutic salbutamol levels early. As shown by our data, if used early, these children are less likely to be in a nonresponsive phase of their disease with clinical improvement evident (12, 13).

No significant side effects were documented in either group during the study. Limb tremor was seen in a number of patients in the intravenous group, but this was not clinically significant. It would be expected that tachycardia, hypokalemia, and hyperglycaemia would be more prominent in the intravenous salbutamol group, but this was not the case. In our study, those children who were administered intravenous salbutamol (the equivalent of three 20 minute doses of nebulized salbutamol) received less ongoing nebulized β₂-adrenergic treatment. The use of even larger doses of intravenous salbutamol for children in the ED as recommended in intensive care.
pared with study in patients administered intrave-
14). This was most evident early on in the
haled bronchodilators less effective (12
duces signi
before in
etration of intravenous salbutamol in the ED
small sub-
group of children with acute severe
nous salbutamol bolus in a small sub-

frequent, high-dose nebulized treatment
intravenous salbutamol than with
more likely to occur with a single-dose
therapy while in the ED. The place for
one. There have been numerous reports
evaluating the effect of an anticholinergic
combination with salbutamol for the
reatment of childhood asthma. These re-
ports demonstrate a statistical improve-
ment in pulmonary function but no clinical
improvement (37–40). A recent Cochrane systematic review reported that
a single dose of an anticholinergic agent
was not effective for the treatment of
ild and moderate exacerbations and was
sufficient for the treatment of severe
exacerbations of asthma in children (21).
Furthermore, the review could not find
conclusive evidence that multiple doses
of anticholinergic agents were of value
for acute exacerbations (21). Our data
support this view, with the use of multi-
ple doses of an anticholinergic showing
no difference in clinical response in chil-

ommendations for inhaled salbutamol main-
tainment, a child can have a similar peak-

t is often not
obtainable in untrained children younger
than 7 yrs and in very sick children of all
ages. Peak flow is also subject to titration
effect. That is, by more frequent nebula-
ization, a child can have a similar peak-
flow value to one who is on a less fre-
quent nebulization schedule.

CONCLUSION

A single-dose intravenous salbutamol
bolus of 15 μg/kg administered over 10
mins in the initial treatment of children
with acute severe asthma in the ED has
the potential to shorten the duration of
severe attacks and reduce overall require-
ments for inhaled salbutamol mainte-
nance.

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