Randomised trial of intravenous salbutamol in early management of acute severe asthma in children

Gary J Browne, Antonio S Penna, Xan Phung, Michael Soo

Summary
Background The mainstay of treatment for acute asthma in children is nebulised β-adrenergic agents such as salbutamol, given with corticosteroids. However, penetration of the drug to the small airways is impeded by obstruction so intravenous salbutamol may be more effective. We assessed the use of intravenous salbutamol in the management of children with acute severe asthma in a double-blind randomised study.

Methods Children who presented to the Emergency Department of Westmead Hospital, Sydney, Australia with asthma were assessed with a clinical assessment scale, and those with severe acute asthma were given nebulised salbutamol at a dose of 2·5 mg (age <2 years) or 5·0 mg (age >2 years), made up to 4 mL with saline. Children who did not improve were eligible to enter phase one of the study. In this phase (0 h–2 h) treatment was by a standard protocol: nebulised salbutamol at the above dose; 4 L/min or 6 L/min continuous oxygen until oxygen saturation reached 93% in room air for at least 30 min; a bolus of intravenous hydrocortisone 5 mg/kg given over 3 min; and then 15 µg/kg intravenous salbutamol or saline, depending on randomised allocation. In phase two (2 h–24 h) the children were given nebulised salbutamol continuously then at 30 min, 1 h, 2 h, 3 h, and 4 h, according to need. All children were transferred to the ward once they were ready to start hourly nebulisation. The primary endpoints were recovery time (no longer requiring inhaled salbutamol) and persistent moderate to severe asthma 2 h after randomisation. Analyses were by intention-to-treat although no withdrawals occurred.

Findings The recovery time (time to cessation of nebulised salbutamol every 30 min) was 4 h in the 14 children allocated intravenous salbutamol compared with 11·5 h for the 15 children in the control group. 2 (14%) of the intravenous salbutamol group compared with 8 (53%) of the control group needed oxygen to maintain oxygen saturation at 93% room air. The intravenous salbutamol group were ready for discharge from the emergency department 9·7 h earlier than the control group. No clinically significant side-effects were found in either group.

Interpretation Addition of a 10 min infusion of salbutamol in the early treatment of children with acute severe asthma has the potential to curtail the clinical progression of asthma, reduce demand placed on hospital resources, and improve the quality of health care provided to the acutely sick child with asthma.

Lancet 1997; 349: 301–05

Introduction
Asthma is an inflammatory disease typified by airway hyper-reactivity and obstruction, producing airway resistance with a reduction in air flow. The mainstay of treatment of acute asthma in children is β-adrenergic agents such as salbutamol administered in 2·5 mg to 5·0 mg doses as frequently as every 20 min or even as a continuous nebulisation together with corticosteroids. Methylxanthines, which have low therapeutic indices, are less frequently used in acute asthma because of frequent side-effects. There has been controversy as to whether administration of intravenous bronchodilators is as good, if not better, than nebulised bronchodilators in acute asthma. Studies in adults comparing the two routes of administration give conflicting results. One review suggests that systemic absorption of drug from either route was not appreciated and may have been a confounding factor that led to the opposing results. In acute asthma, penetration of drug to the affected small airways is impeded and therefore initial therapeutic responses may be a result of drug reaching the receptors from the systemic circulation. In these circumstances, if bronchodilatation occurs predominantly in response to systemic absorption of the drug, the systemic (ie, intravenous) administration of bronchodilators early in the treatment of acute asthma may bring about an earlier clinical response before inflammation makes the airways less bronchodilator responsive.

Nebulised β-adrenergic bronchodilators produce plasma drug concentrations in the 20–40 ng/mL range, within 2 h of the start of therapy. Similar plasma salbutamol concentrations could be achieved with a 10 min infusion at a rate of 1·5 µg kg⁻¹ min⁻¹. This dosage regimen was derived by linear pharmacokinetic modelling with parameters obtained from salbutamol studies in adults. Intravenous bronchodilator therapy is reserved for children with severe asthma who do not respond to nebulised bronchodilators. This therapy is generally undertaken in paediatric intensive-care units, where dosage regimens for salbutamol range from 2 µg kg⁻¹ min⁻¹ to 15 µg kg⁻¹ min⁻¹ for long periods of time (>12 h) producing extremely high plasma salbutamol concentrations (200–600 ng/mL) without serious side-effects. In children with severe asthma nebuliser therapy can be unreliable because successful delivery depends on delivery technique and tidal volume both of
Which are highly variable.

In this study we investigated the clinical effects of a short intravenous infusion of salbutamol in the early emergency-department management of children with acute severe asthma.

**Patients and methods**

In this double-blind, randomised, placebo-controlled study we evaluated 29 patients in the Children’s Emergency Department of Westmead Hospital, Sydney, Australia between Dec 12, 1994, and Sept 12, 1995. The study was approved by the Ethics Committee of Westmead Hospital.

Initial assessment took place at the emergency department triage desk. All children with acute severe asthma were eligible to enter the study. The severity of asthma was assessed on a standard clinical assessment scale (National Australian Asthma Campaign guidelines). Patients were graded as having mild, moderate, or severe asthma, with only those who were graded as severe being eligible for the study. Patients were classified as having severe asthma if they had all four features of respiratory distress (wheeze, sternal retraction, accessory muscle use, dyspnoea) or had any of the absolute criteria (cyanosis, pulse paradoxus, altered consciousness, or a silent chest on auscultation). Children with acute severe asthma were immediately referred to an acute treatment area and assessed by a physician. All formal study assessments were then done by trained assistants.

All children with acute severe asthma were given salbutamol nebuliser therapy consisting of 4 mL saline with 2·5 mg salbutamol for children of 2 years younger or 5·0 mg of salbutamol for those older than 2 years.2

The parents or guardians of children who met the eligibility criteria of the study were approached, and once consent was obtained, the child was enrolled into the study. If, on repeat clinical assessment patients had not improved from the first baseline assessment 30 min after initial nebulisation, the study protocol was instituted.

The following children were excluded from the study: those with mild moderate asthma; those who had presented at imminent risk of respiratory arrest (life-threatening asthma); those for whom consent was not obtained; children with congenital heart disease or a family history or past episode of supraventricular tachycardia; those with underlying respiratory illness other than asthma or diabetes mellitus or glucose intolerance; those weighing less than 10 kg or younger than 12 months or weighing more than 50 kg or older than 12 years; and those who had already had the maximum amount of intravenous study drug preparation for that day.

The study was done in two phases. The first phase was for 2 h and took place in the emergency department under the strict supervision of the primary investigators. All patients were fully monitored. During the second phase of the study (the subsequent 22 h), the researchers closely monitored clinical progress on the medical wards. During the first phase, the treatment followed a standard protocol. In the second phase, asthma treatment was supervised by the hospital’s six admitting paediatric physicians. Clinical management decisions and changes in medication regimens (frequency of nebulisation) were the responsibility of these physicians and their staff, and followed a standard hospital protocol. All children were admitted to the same medical ward.

**Phase one**

In phase one each child was given treatment according to a standard protocol. Each child was given high-dose salbutamol via a nebuliser. The dose of salbutamol was 2·5 mg or 5·0 mg (<2 years or >2 years), given with saline to a volume of 4 mL. Doses were given every 20 min with continuous oxygen at 4 L/min or 6 L/min if the oxygen saturation was less than 93% in room air. The patients remained on oxygen therapy until oxygen saturation was maintained above 93% for 30 min.

When intravenous salbutamol treatment started an intravenous cannula was inserted into an antecubital vein. Before any intravenous drugs were given, 5 mL blood was taken for potassium and glucose testing. Intravenous hydrocortisone 5 mg/kg was then given as a bolus over 3 min immediately followed by an infusion of either saline or 15 µg/kg salbutamol, depending on randomisation, administered over 10 min. The cannula was flushed with 5–10 mL saline after the saline or salbutamol was administered and then it was capped.

Randomisation was done on a per-patient basis. The hospital pharmacy was responsible for randomisation of the intravenous solutions, which were prepared according to a table of random numbers, in syringes, and under sterile conditions. The numbers were used in sequence and a salbutamol solution was prepared if the number was even and a saline solution if the number was odd. A total of 50 mL (in five syringes) was prepared and contained either saline or salbutamol (15 µg/mL), instructions were to administer 1 mL/kg. The same solution was prepared each day until that particular formulation was used up. The next solution to be used was that which was next in numerical sequence. Solutions were identical in appearance, and the randomisation allocation was held by the pharmacy and released only when all clinical and laboratory assessments were completed. Thus, attending staff, investigators, and patients were unaware of treatment allocation.

All children were monitored by continuous oximetry and electrocardiography, and by measurement of respiratory rate every 15 min, blood pressure at the beginning and end of phase
The intravenous salbutamol group was less dependent on medical oxygen, with only two (14%) of 14 patients on oxygen at the end of phase one of the study compared with eight (53%) of 15 patients in the control group (p=0.05). Because oxygen was titrated to maintain

Statistical analysis

The two main outcome variables were: the mean recovery time of each group (defined as the time from randomisation to when patients no longer needed nebulised salbutamol at a given frequency); and the odds of the number of patients of each group with each of the clinical signs of asthma that were moderate to severe, 2 h after randomisation. A pulmonary index score was calculated retrospectively from the same data. This score is a sensitive (100%) and specific (67%) predictor of the need for hospital admission (when a cut off for pulmonary index score of at least seven is used). Also examined were the odds of number of patients of each group experiencing salbutamol-related side effects, and means of the quantitative variable (respiratory rate, pulse rate, plasma potassium and glucose).

The confidence intervals of means of continuous data and significance levels were calculated by Student’s t statistics. For respiratory rate, heart rate, and serum biochemistry, changes from baseline was used. Fisher’s exact test was used to calculate the significance level of categorical data. For the most important outcome variable (ie, cessation of hourly nebulised salbutamol), multiple regression analysis was used to identify variables of prognostic importance, and corrected for any baseline differences between groups in these variables and in variables of physiological importance (respiratory and pulse rate).

For data on mean recovery time, and 2 h clinical assessments, there was no loss to follow-up. Because complete compliance was achieved and there were no patient withdrawals after randomisation, analysis by intention-to-treat was not needed. No subgroup or cohort analysis was done.

Results

50 patients were admitted to the high-dependency ward with asthma during the period of active recruitment, of which 37 met the entry criteria, and 29 consented to participate in the study. There were no deviations from protocol. 14 patients were allocated intravenous salbutamol and 15 were allocated saline (figure 1).

The patients ranged in age from 1 year to 12 years (mean 8·38 years in the intravenous salbutamol group and 6·25 years in the control group). All patients in both groups had severe asthma at the baseline clinical assessment. This was also reflected in the proportions with a pulmonary index score of seven or more. Baseline demographic, clinical, and biochemical characteristics of both groups were similar (table 1).

Time taken from the start of the study to each step down in the frequency of nebulised salbutamol therapy (recovery time) is shown in table 2. Recovery time (to cessation of salbutamol every 30 min) was only 4 h for the intravenous group compared with 11·1 h in controls (p=0·03); and time to cessation of hourly nebuliser was 11·5 h compared with 21·2 h required by the control group (p=0·02). Patients in the intravenous salbutamol group were ready for discharge from the emergency department 9·7 h earlier than controls, with discharge readiness defined as start of hourly inhaled salbutamol therapy. This difference between the groups remained significant (p<0·05) even after correction for the baseline differences in variables found (on multiple regression analysis) to be important predictors of prognosis (cyanosis, level of consciousness, dyspnoea), as well as differences in respiratory rate, pulse rate, fatigue, and accessory muscle use.

The intravenous salbutamol group was less dependent on medical oxygen, with only two (14%) of 14 patients on oxygen at the end of phase one of the study compared with eight (53%) of 15 patients in the control group (p=0·05). Because oxygen was titrated to maintain

---

**Figure 1: Trial profile**

Followed up (n=15)  
Completed study (n=15)  
Randomised to receive nebulised salbutamol and intravenous hydrocortisone then intravenous saline (n=15)  
Completed study (n=14)  
Randomised to receive nebulised salbutamol and intravenous hydrocortisone then intravenous salbutamol (n=14)  

---

One, peak expiratory flow rate at each assessment in children over the age of 7 years. At 1 h, a blood sample was taken from the arm without the cannula to allow potassium and glucose testing. Each patient was also assessed before starting the study at 1 and at 2 h into the study using the clinical assessment scale. All potential adverse effects were recorded. These included tachycardia, premature ventricular contractions, palpitations, muscle tremor, agitation, headache, dizziness, insomnia, hyperglycaemia, nausea, and vomiting.

**Phase two**

Phase two of the study began at 2 h and finished at 24 h. The child’s clinical progress was monitored at 4 h, 8 h, 12 h, and 24 h. Clinical side-effects of salbutamol (tachycardia, tremor, and hyperactivity) were also recorded at each assessment. Inhaled salbutamol therapy during phase two was in accord with a standard hospital protocol of high-dose salbutamol administered first of all continuously, then every 30 min then at 1 h, 2 h, 3 h, and 4 h, depending on clinical state. When the child was ready to start hourly nebulised salbutamol he or she was transferred to the ward. The frequency of inhaled salbutamol treatment in the medical ward was assessed with the clinical assessment scale by the admitting medical-team physician. The research assistants closely observed patients during this phase of the study and used the clinical assessment scale. Thereafter all patients were followed up until discharge.

Patients were withdrawn (but still analysed under intention-to-treat) from the study in the following circumstances: any clinical deterioration during the study; if the heart rate was persistently greater than 200 beats/min for longer than 5 min; clinical deterioration during the study; if the heart rate was enough to justify intravenous cannulation (such as a 25% reduction in time to cessation of hourly nebuliser treatment). The study had been in progress for 9 months when the study was amalgamated with the Royal Alexandra Hospital at Westmead. A single interim analysis of the data was undertaken by an independent party. The analysis showed highly significant differences between the two groups, therefore the study was terminated.

To assess the effectiveness of blinding, the physicians who administered the intravenous solution were surveyed and asked whether they thought they had given salbutamol or saline at the time of the bolus infusion.
oxygen saturation above 93%, the oxygen dependence, rather than oxygen saturation itself, was the variable reflecting desaturation.

The intravenous salbutamol group showed more rapid clinical improvement by the end of phase one of the study; five (36%) of 14 patients had persistent moderate to severe asthma compared with 14 (93%) of 15 control patients (p<0·002). Only six (43%) of 14 patients in the intravenous salbutamol group had persistent severe asthma (pulmonary index score \( \geq 7 \)) compared to 14 (93%) of the 15 controls (p=0·02). Use of accessory muscles was present in six (43%) of the intravenous salbutamol group and in all the controls (p<0·001; figure 2).

The differences between the groups for wheeze (p=0·06) and dyspnoea (p=0·07) were not statistically significant. There were no statistically significant differences in changes to respiratory rate or heart rate at the end of phase one of the study. Peak-flow measurements were not reproducible during the early phase of therapy in these patients and therefore were excluded from the final statistical analysis.

At 1 h, the average plasma glucose concentrations for the intravenous salbutamol and control groups were 7·9 mmol/L and 6·39 mmol/L, respectively; the concentrations of potassium were 3·88 mmol/L and 4·23 mmol/L, respectively. Differences in rises in plasma glucose and falls in plasma potassium at 1 h between the two groups were not significant.

The differences in side-effects were not statistically or clinically significant. The only exception was a higher proportion of tremor at 2 h in the intravenous salbutamol group compared with the control group (p<0·02).

Of the 24 physicians' guesses as to whether the patient received salbutamol or saline, 50% guessed correctly, consistent with chance, as would happen with effective blinding. Even if all the five non-responding physicians guessed correctly, the correct guessing rate would only be 58·6%.

**Discussion**

Regimens of frequent high-dose salbutamol rely on large quantities of inhaled salbutamol being delivered in the initial few hours of therapy to achieve the desired clinical response. If salbutamol is given in this way therapeutic plasma concentrations can be achieved by the end of a 2-h period. The underlying hypothesis in this study was that a child with severe asthma would have a more rapid response if plasma salbutamol concentrations could be achieved within the first 10 to 15 min of the start of therapy. This hypothesis assumes that there is a relation between plasma salbutamol concentration and response time and that the airways in acute asthma respond predominantly to salbutamol via the systemic route rather than via the local (luminal) route. Our study gives support to this hypothesis and the underlying assumptions.

In hypercapnic adult asthmatic patients, intravenous salbutamol was thought not to be beneficial over high-dose inhaled salbutamol treatment. Bronchodilator resistance due to obstruction from inflammation may have already occurred, since the administration of intravenous salbutamol was delayed until admission of patients into the intensive-care unit in that study. We took advantage of a small window of time that exists between initial presentation and the point at which...
inflammation hinders airway responsiveness to bronchodilators. The value of taking advantage of this opportunity was most evident during phase one of the study, when patients were given an intravenous bolus of salbutamol. There was clear clinical improvement in these patients and less than half of them had persistent severe asthma compared with more than 90% of patients who had conventional nebuliser regimens. These patients also had a significantly shorter time to stabilisation (as evident by earlier readiness for discharge from the emergency department), earlier stabilisation in oxygen saturation (evident by reduced dependence on medical oxygen to maintain an oxygen saturation >93%), and reduced need for more frequent inhaled salbutamol therapy during study phase two. No clinical deterioration in relation to intravenous salbutamol was documented clinically or on oxygenation.

Corticosteroids were administered as part of the routine management of severe asthma in this study. The study was designed to give all patients a similar dosage regimen of an accepted corticosteroid on their entry into the study.

No significant side-effects were documented in either group. Limb tremor was seen in several patients in the intravenous group but this was not clinically significant. We expected that tachycardia and hypokalaemia might be more prominent in the intravenous salbutamol group but found no such difference.

This study demonstrates the effectiveness and advantages of early intravenous therapy, which ensures reliable delivery of both salbutamol and corticosteroid in a painless manner if a topical anaesthetic is applied early. Many children with acute severe asthma on conventional treatment eventually require intravenous drug therapy which may often be delayed. The delays may lead to a protracted clinical course with loss of effective airway bronchodilation due to progressive inflammation.

The potential to curtail severe asthma attacks with reduction in stabilisation time and earlier discharge can have several possible effects on emergency departments. The early clinical improvement may lead to reduced patient dependency, with savings to nursing and medical staff time and resources. In a busy emergency-department environment, frequent nebuliser administration may be difficult and therapy may be delayed. Earlier clinical improvement as seen in the intravenous salbutamol group reduces the overall need for frequent intravenous maintenance salbutamol therapy and may eliminate these difficulties. Reduced stabilisation time allows for early discharge from the emergency department, which in turn has the potential to increase efficiency by maintaining high patient turnover.

One of the limitations of this study was the fact that ipratropium bromide was not investigated. This agent was not routinely used in our hospital at the time of the study for the management of acute asthma. Evidence that came to light after the beginning of this trial suggests that ipratropium bromide may be of value when combined with inhaled salbutamol.21

This study shows the benefits and safety of the use of 15 mg/kg intravenous salbutamol administered as a single infusion over 10 min in the early management of acute severe childhood asthma. The infusion achieved a rapid clinical response with no significant side-effects. The use of intravenous salbutamol in the initial treatment of children with acute severe asthma in the emergency department has the potential to shorten the duration of severe attacks and reduce overall need for inhaled salbutamol. Intravenous salbutamol therapy should not be reserved for the intensive-care unit,21 since the advantages of its early use in the emergency department have been clearly demonstrated in this study.

References