



Early administration of terbutaline in severe pediatric asthma may reduce incidence of acute respiratory failure

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ABSTRACT

Background: Severe pediatric asthma, if not immediately and aggressively treated, may progress to acute respiratory failure requiring mechanical ventilation in the pediatric intensive care unit (PICU). Intravenous (IV) terbutaline, a β_2 agonist, is dispensed when the initial treatment does not improve the clinical condition. **Objective:** To investigate the influence of early initiation of IV terbutaline on the incidence of acute respiratory failure requiring mechanical ventilation in severe pediatric asthma.

Methods: A retrospective chart review was conducted of 120 subjects (35 patients from an outside hospital emergency department [ED] with late start of terbutaline and 85 patients from the authors' hospital ED with early initiation of IV terbutaline) admitted to the PICU with severe asthma treated with continuous IV terbutaline. Responses to terbutaline treatment and outcomes were evaluated.

Results: Patients transported from outlying hospital EDs had shorter pre-PICU mean durations of IV terbutaline than those transferred from the authors' ED (0.69 ± 1.38 and 2.91 ± 2.47 hours, respectively, $P = .001$). Twenty-one of 35 patients (60%) from outlying EDs required mechanical ventilation compared with 14 of 85 patients (16%) from the authors' ED ($P = .001$). Durations of pre-PICU terbutaline infusion for patients requiring mechanical ventilation were significantly shorter than those with no such requirement ($P = .015$).

Conclusion: The results of the present study, conducted in the largest number of subjects to date, suggest that early administration of continuous terbutaline in the ED may decrease acute respiratory failure and the need for mechanical respiratory (invasive and noninvasive) support in severe pediatric asthma.

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Introduction

The goal of pharmacologic therapy in acute severe asthma exacerbations is primarily to ease the work of breathing and to ensure adequate oxygenation and ventilation. The therapy should start early and preferably before admission to an intensive care unit. Therapeutic success in severe asthma can be assessed simply by preventing an escalation of symptoms to an acute respiratory failure status requiring invasive or noninvasive mechanical ventilation.^{1,2}

Current such therapy includes corticosteroids combined with aggressive administration of inhaled or intravenous bronchodilators.^{2,3} Treatments with frequently or continuously delivered inhaled β agonists (albuterol), intermittent administration of inhaled anticholinergics (ipratropium bromide), intravenous (IV) magnesium sulfate, intermittent or continuous IV administration of β agonists (terbutaline), phosphodiesterase inhibitors (aminophylline), dissociative anesthetics (ketamine), and inhalational anesthetics (halothane) have been used in severe asthma; all have been proved effective in ameliorating patients' bronchospasm by various

degrees. Preventing asthma from deteriorating to acute respiratory failure is very important because it decreases morbidity, mortality, and treatment costs within the pediatric intensive care unit (PICU). To that end, the National Asthma Educational Program has recommended the use of systemic, selective β agonists, such as terbutaline, in patients with severe asthma exacerbation.⁴

The present study focused on the efficacy of continuous IV administration of terbutaline in the pre-PICU phase in severe pediatric asthma. To the best of the authors' knowledge, no prospective randomized clinical trials have been published concerning the efficacy of continuous IV terbutaline in pediatric patients and there is a need for adequately powered clinical data on this subject.⁵ In limited previous studies, it has been shown that terbutaline is safe for use in a wide dose range in this patient population.⁶ The authors tested the hypothesis that early administration of intravenous terbutaline, well before admission to the PICU, is beneficial in preventing acute respiratory failure resulting in a need for mechanical respiratory support.

Methods

The study received approval from the institutional review board of the North Shore–Long Island Jewish Health System

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(no 11-094B). A retrospective chart review was conducted of patients admitted to the PICU with severe asthma treated with a continuous IV infusion of terbutaline during a 3-year period (2007–2010). The following parameters were documented: patient demographics, vital signs, loading and continuous IV dosages, requirement for and types of respiratory support, and outcomes of PICU management. Patients were categorized into 2 groups. The first group of patients was transported to the authors' PICU from emergency departments (EDs) of outlying nontertiary care hospitals. These patients were started on terbutaline treatment later in the course of the episode and thus had a shorter duration of terbutaline treatment in the pre-PICU phase. The second group of patients was transferred from the authors' hospital ED to the PICU. These patients had a longer duration of terbutaline treatment during the pre-PICU phase. All patients had similar degrees of respiratory distress before terbutaline infusion as evidenced by vital signs data (Table 1). Patients in the 2 groups received 3 doses of albuterol nebulizer treatment, IV steroids, and 1 dose of IV magnesium before initiation of terbutaline infusion. All patients received nebulized β_2 agonists at doses of 2.5 mg/3 mL 3 times back to back, plus 2 mg/kg of IV methylprednisolone as the loading dose, plus 25 to 50 mg/kg of IV magnesium to a maximum dose of 2 g. This treatment was administered to all patients before IV terbutaline. The duration of pre-PICU terbutaline treatment in these patients and their responses to and the outcome of terbutaline treatment were evaluated.

Statistical Analysis

Demographics and vital signs (respiratory rate and heart rate) before initiation of terbutaline drips in the 2 groups of patients were compared by the Student *t* test. Durations of IV terbutaline treatments during the pre-PICU phase also were compared using the Student *t* test. Durations of pre-PICU IV terbutaline treatment for patients not requiring any mechanical respiratory support, patients successfully treated by noninvasive support (bilevel positive airway pressure), and those requiring invasive mechanical ventilation through tracheal tubes were analyzed by analysis of variance. Nonparametric data on the breakdown of the number of patients with or without mechanical ventilation in the 2 groups were analyzed by the χ^2 test. The null hypothesis at a *P* value less than or equal to .05 was rejected. Minitab (Minitab, Inc, State College, Pennsylvania) was used in all statistical analyses.

Results

One hundred twenty patients were studied (42 girls and 78 boys, mean age 6.8 ± 4.2 years). Patients' race distribution was 64 African Americans (53%), 29 whites (24%), 15 Hispanics (13%), and 12 Asians (10%). One hundred eighteen patients survived and 2 patients died (brain death) in the PICU of a previous episode of cardiac arrest at home. Thirty-five patients were transferred from outlying EDs and 85 patients were transferred from the authors' ED (Fig 1). These 2 groups of patients had a similar age distribution and there was no difference in their respiratory rate or heart rate before terbutaline treatment, initial terbutaline loading doses, and

maximum continuous IV doses. Of the 35 patients who were transferred to the PICU from outlying EDs, 25 (71%) had their terbutaline started after arrival in the PICU, rendering their pre-PICU IV terbutaline period 0. In contrast, only 17 of 85 patients (20%) who were admitted to the PICU from the authors' ED had their terbutaline started in the PICU (*P* = .001). For the 17 patients from the authors' hospital ED, the time lapse from the start of terbutaline drip in the ED to transfer to the PICU was very short (<30 minutes). Therefore, these patients were included in the PICU group.

Overall, patients who were transported from outlying hospital EDs had a significantly shorter mean pre-PICU duration of IV terbutaline treatment than those transferred from the authors' ED (0.69 ± 1.38 and 2.91 ± 2.47 hours, respectively, *P* = .000). Twenty-one patients from outlying hospital EDs (60%) and 23 from the authors' hospital ED (27%) required noninvasive or invasive mechanical ventilation (*P* = .001; Table 1). Throughout the course of their illness, 76 patients (63%) did not require respiratory mechanical support of any kind. Periods of pre-PICU terbutaline infusion for spontaneously breathing patients, patients requiring noninvasive ventilation, and patients requiring endotracheal intubation were 2.61 ± 2.47 , 2.04 ± 2.54 , and 0.97 ± 1.59 hours, respectively (*P* = .015; Fig 2).

Discussion

The results of this study suggest that early administration of IV terbutaline in severe pediatric asthma may decrease the incidence of acute respiratory failure. The overall data indicate that the need for mechanical ventilation is significantly decreased in this group of patients (*P* = .001). The authors believe the difference in the need for respiratory support is linked to the length of terbutaline administration during the pre-PICU phase, which also was significantly different between the 2 groups of patients studied (*P* = .001). The present study represents one of the more detailed investigations on the use of terbutaline in patients with severe asthma. There is a clear need for the delineation of different aspects of IV terbutaline in these cases. The particular feature addressed in this study was the duration of IV terbutaline during the pre-PICU phase. The present study, representing the largest collection of patients, shows that the duration of the pre-PICU phase of IV terbutaline administration is an important factor that needs to be closely monitored and considered by clinicians.

Asthma exacerbation often can progress to acute respiratory failure requiring mechanical ventilation.^{2,7,8} Although studies have not suggested a recent increase in the incidence of pediatric asthma, the pediatric mortality rate from asthma has increased in recent decades.^{9,10} Inhaled β agonist therapy and systemic administration of corticosteroids continue to be the treatment of choice for acute asthma exacerbations.^{11–16} However, despite this therapy, some pediatric patients deteriorate to an acute respiratory failure status and require invasive or noninvasive mechanical ventilation (bilevel positive airway pressure).^{17–21} One explanation for such an occurrence is based on the fact that severe bronchospasm does not allow sufficient inhaled medication to be topically effective.

Table 1
Patient data

Patient group	n	Age (y)	Loading dose (μ g/kg)	Maximum IV drip dose (μ g/kg/min)	RR before IV terbutaline	HR before IV terbutaline	Duration of pre-PICU terbutaline (h)	MV
Outlying hospital EDs	35	8.43 ± 4.89	4.2 ± 0.7	0.8 ± 0.6	39.4 ± 14.1	139.9 ± 20.5	0.69 ± 1.38	21/35 (60%)
Authors' hospital ED	85	6.26 ± 3.94	4.4 ± 0.6	0.7 ± 0.6	40.2 ± 13.4	143.8 ± 23.7	2.91 ± 2.47^a	23/85 (27%)
<i>P</i> value		NS (>.05)	NS (>.05)	NS (>.05)	NS (>.05)	NS (>.05)	.000 ^a	.001

Abbreviations: ED, emergency department; HR, heart rate; IV, intravenous; MV, mechanical ventilation; NS, not significant; PICU, pediatric intensive care unit; RR, respiratory rate.

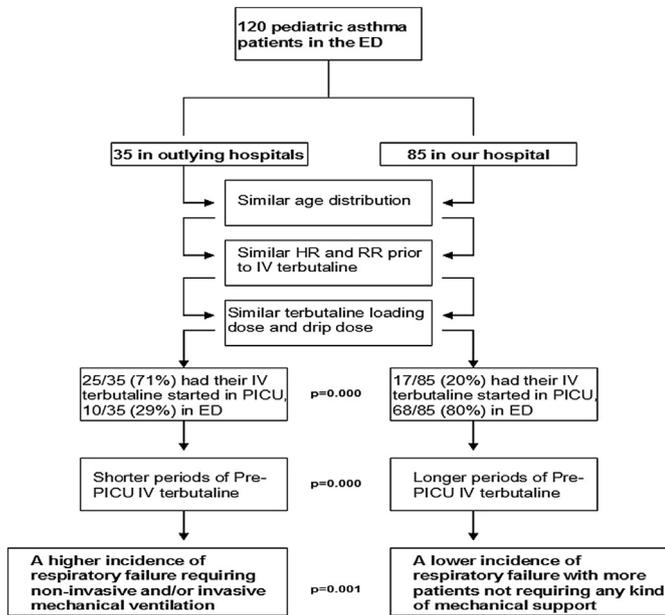


Figure 1. Diagrammatic representation of the study. ED, emergency department; HR, heart rate; IV, intravenous; PICU, pediatric intensive care unit; RR, respiratory rate.

In contrast, IV β agonist administration, such as terbutaline, could be more effective than inhaled β agonists, because it exerts bronchodilation through systemic distribution.^{22,23} However, detailed powered studies in this area are lacking.⁵ IV terbutaline has a very rapid onset of effect. It is recommended that patients receive a significant bolus dose of 2 to 10 $\mu\text{g}/\text{kg}$ followed by an initial continuous infusion dose of 0.1 to 0.4 $\mu\text{g}/\text{kg}/\text{min}$. This dose should be increased further to achieve the desired relief from a patient's bronchospasm, and vigilant clinical monitoring is paramount to detect and possibly prevent terbutaline toxicity. All terbutaline-treated patients in the present study received a dose within the recommended range. Obviously, in severe asthma, if inhaled treatment is not immediately effective, then a more effective treatment should be administered without delay. The present study investigated the efficacy of IV terbutaline treatment in lowering the incidence of acute respiratory failure in pediatric patients with severe asthma.

Two categories of patients described in the present report were similar in disease severity and required admission to the PICU. These 2 groups also did not differ from each other significantly in demographics, vital signs before terbutaline treatment, and

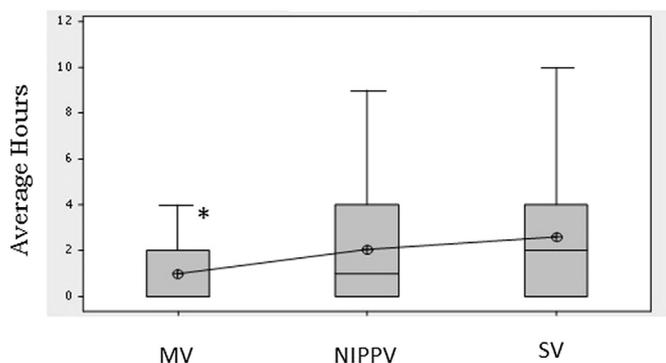


Figure 2. Hours of terbutaline administration before arriving in the pediatric intensive care unit ($P = .015$). MV, mechanical ventilation; NIPPV, noninvasive positive pressure ventilation (bilevel positive airway pressure); SV, spontaneous ventilation.

terbutaline doses. Accordingly, the data on vital signs do not support the notion that patients from outlying hospitals were not sicker. The only difference in the clinical management of these patients was the timing of initiation of terbutaline treatment. Most study patients in outlying hospitals did not receive IV terbutaline in the ED at all, or terbutaline was administered just for a brief period before transfer to the PICU, effectively decreasing the duration of average pre-PICU terbutaline treatment, and this group of patients had a significantly higher incidence of respiratory failure requiring noninvasive or invasive mechanical ventilation.

This study was not designed to provide an explanation as to why different pre-PICU IV terbutaline periods of treatment existed in these 2 groups of patients. The authors postulate that it has to do with the care providers' comfort level and/or experience in using IV β agonists. Although some EDs, such as the one in the authors' pediatric hospital, provide a tertiary care level of management with a readily available pediatric critical care consultation service, others may need to use different patient management strategies for lack of resources. Moreover, it is possible that outlying, nontertiary care hospital pediatric EDs tend to call for transport of their critically ill pediatric patients soon after the initial patient assessment and stabilization; in such cases, IV terbutaline often may be postponed until an experienced transport team arrives, and occasionally it is administered only at the patients' arrival in the PICU of the referral center. Thus, for transported patients, as in the present study, IV terbutaline treatment often may be delayed, resulting in a brief pre-PICU period of treatment and, therefore, may cause further clinical deterioration. This also explains the higher incidence of mechanical ventilation in these patients.

One of the limitations of the study is that it is a retrospective analysis; thus, the only available comparative measurements on the severity of asthma between groups were the vital signs data. Although respiratory rates and heart rates are considered well-accepted measurements, additional parameters, such as arterial blood gas data and lactate levels, might be desirable but were not available for comparison. The authors agree that there is a need for a prospective study comparing IV terbutaline with other second-line treatment modalities in a larger group of pediatric patients with severe asthma.

In conclusion, these data clearly demonstrate a difference in IV terbutaline management of these 2 groups and a different outcome regarding their overall morbidity. The present results provide solid ground on which to speculate that early administration of IV terbutaline might be beneficial in preventing acute respiratory failure in pediatric patients with asthma. However, more studies, preferably prospective, will be needed to ascertain that suspicion.

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