

Safety of Terbutaline for Treatment of Acute Severe Pediatric Asthma

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Objectives: The use of continuous intravenous terbutaline treatment in severe asthma attacks has been hampered by the lack of well-powered clinical trials where effects of such treatment are described in detail. Here, we aimed to provide a descriptive report on the largest cohort of severe pediatric asthma patients treated with terbutaline.

Methods: The study was conducted in a pediatric intensive care unit in a large metropolitan tertiary care university hospital on 124 patients receiving terbutaline infusion. To stratify the effect of, and determine any age-related differences of, terbutaline, the patients were divided into 3 age groups (0–6 years, 7–12 years, and 13–18 years). Clinical response and the potential harmful effects of terbutaline infusion were determined.

Results: There were significant reductions in systolic (varying between 86% and 93% of the baseline) and diastolic blood pressures (varying between 74% and 86% of the baseline level). However, the values returned to baseline level shortly after discontinuation of infusion. Terbutaline increased heart rates in all groups shortly after initiation (9%–13% above baseline), which returned to below baseline levels 1 hour after discontinuation. Serum potassium levels were also reduced in all patients compared to their baseline values after initiation of terbutaline infusion. However, none of the subjects required potassium replacement.

Conclusions: The results indicate that overall, terbutaline infusion was well tolerated without irreversible adverse effects of the treatment. Although hemodynamic and metabolic disturbances occurred, these were clinically easily managed and posed little risk in emergency department or pediatric intensive care unit.

Key Words: pediatric asthma, terbutaline, safety, adverse effects

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Asthma is an inflammatory disease of the airways causing reversible airflow obstruction, and exacerbations can be life threatening if not treated promptly. It is one of the most common chronic conditions of childhood, affecting 7.1 million children younger than 18 years in the United States, with more than half having an acute episode annually.¹ This extremely prevalent chronic condition now affects 300 million people worldwide with an ever-increasing prevalence in the developing world as a result of increased atopic sensitization and allergic reactions, and is projected to afflict 100 million more people by the year 2025 as a result of widening urbanization.²

Initial treatment of asthma exacerbations consists of oxygen if hypoxemia presents, inhaled beta 2-agonists, inhaled ipratropium bromide, and systemic steroids.^{3–5} In more severe cases, if the symptoms do not improve with initial interventions or if the clinical picture worsens, intravenous (IV) beta 2-agonists can be added to the treatment.^{4,6,7} Early administration of IV beta 2-agonists has been shown to decrease the incidence of acute respiratory failure in children with severe asthma exacerbations.⁸

Beta adrenergic drugs are the most potent bronchodilators. Terbutaline directly activates the beta adrenoceptors located in airway smooth muscle. It stimulates intracellular adenylyl cyclase, catalyzing the conversion of adenosine triphosphate to cyclic 3' 5'-adenosine monophosphate resulting in airway smooth muscle relaxation.⁹ However, concerns exist regarding the cardiac and hemodynamic safety of using continuous terbutaline.

Despite recent data demonstrating its efficacy in ameliorating the clinical symptoms of severe asthma, terbutaline is often used later in the treatment of an acute asthma exacerbation. Detailed studies documenting the effects and dosage of terbutaline and management of the patients are relatively scarce. Furthermore, studies addressing the potential adverse effects of terbutaline in asthma are limited.¹⁰

Previously, we demonstrated that early administration of terbutaline significantly reduced the incidence of acute respiratory failure in pediatric patients with severe asthma.⁸ These results have brought a renewed interest to terbutaline treatment.¹¹ In the present study, we sought to investigate and describe the adverse effects of terbutaline treatment in pediatric patients, with the hypothesis that continuous terbutaline is a safe therapy in the treatment of acute severe asthma.

METHODS

Study Design

This is a retrospective review of 124 pediatric patients who received IV terbutaline during treatment for acute severe asthma between January 2007 and January 2012 in a pediatric intensive care unit (PICU) of a tertiary children's hospital. Eighty subjects were boys and 44 were girls (Table 1). The ages of the patients varied between 8 months and 18 years; and the race distributions were black, 6; white, 31; Hispanic, 15; and Asian, 12. All subjects received 3 doses of inhaled beta 2-agonist, IV steroids, and IV magnesium before the initiation of terbutaline with only minimal or no clinical improvement based on the discretion of the primary caring physicians. The study subjects were all pediatric patients admitted with the diagnosis of acute severe asthma who did not respond to initial therapy with albuterol and atrovent nebulizers with 3 doses given plus IV steroids and magnesium infusion. We included all pediatric patients with acute severe asthma. Exclusion criteria were pneumonia, acute respiratory distress syndrome, and cardiac and renal conditions with respiratory distress.

The subjects then received a bolus of IV terbutaline at a dose of 4 to 6 µg/kg followed by an infusion that started at 0.4 µg/kg per minute and titrated to a maximum of 3 µg/kg per minute. The other drugs used were ipratropium bromide nebulization, methylprednisolone, and magnesium sulfate. Ipratropium bromide nebulization was given at 250 mg per dose diluted with 3-mL isotonic sodium chloride solution given as nebulization every 6 hours for 48 hours. Methylprednisolone was given at 2 mg/kg per dose as initial bolus followed by IV 0.5-mg/kg per dose every 6 hours. Magnesium sulfate was given as needed at 50-mg/kg per dose IV boluses over 30 minutes to a maximum dose of 2 g. Owing to the known peak effect of terbutaline ranging from 60 to 180 minutes, clinical data were collected including change in

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TABLE 1. Demographics of All Subjects Included in the Study

Age Group	No. Subjects	Sex		Race			
		F	M	Black	White	Hispanic	Asian
0–6 yr	59	22	37	31	17	6	5
7–12 yr	47	19	28	26	8	8	5
13–18 yr	18	3	15	9	6	1	2
Total	124	44	80	66	31	15	12

heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) at baseline, 1 and 4 hours during infusion, and also 1 hour after discontinuation of the terbutaline treatment. Data on the requirement of vasoactive support after start of the infusion, potassium levels before and after the infusion, occurrence of seizure activity, and electrocardiogram data were also collected.

Inhaled beta-2 therapy was discontinued after initiation of terbutaline infusion. Frequent physical examinations, improvement, or changes in vital signs were used to titrate the terbutaline infusion dose during treatment at the discretion of the physician primarily caring for the patient in the PICU. None of the patients received additional IV bronchodilator during terbutaline treatment. Intravenous steroids were continued. Hourly inhaled beta 2-agonist was started on all subjects after discontinuation of the IV terbutaline infusion. All patients with hypotension or wide pulse pressure received 3 fluid boluses with 20-mL/kg isotonic sodium chloride solution. Vasoactive support was started if the blood pressure did not improve after fluid boluses.

To delineate the possible different responses to such therapy among pediatric age groups, the subjects were divided into 3 groups for the analysis: specifically, 0- to 6-year-old group, 7- to 12-year-old group, and 13- to 18-year-old group.

Statistical Analysis

For each physiological parameter (SBP, DBP, and HR), a mixed linear model was constructed. Fixed effects were age group,

time since start of treatment, and their interaction; total infusion time, load dose, and maximum infusion dose were introduced as linear covariates. An unstructured inpatient covariance matrix was modeled. Satterthwaite corrections to denominator degrees of freedom were applied. Post hoc tests were used to compare posttreatment means with baseline mean within each age group; bootstrap-derived corrections to *P* values to adjust for multiple testing were applied. Model residuals were examined for outliers and skew. Model-generated adjusted means and standard errors are reported. SAS Statistical Analysis System 9.3 software (SAS Institute Inc, Cary, NC) was used for all statistical analysis. *P* < 0.05 was considered statistically significant.

RESULTS

All subjects showed decreases in SBP and DBP at 1 and 4 hours after initiation of terbutaline infusion compared to their baseline. After 1 hour of discontinuation of the terbutaline infusion, except in the patients in the 0- to 6-year age group, in all subjects, SBP returned to baseline (Table 2). The mean SBP varied between 86% and 93% of the baseline, and the most pronounced reduction was noticed in the 0- to 6-year age group after 4 hours. Diastolic blood pressures also significantly decreased at 1 and 4 hours after starting terbutaline infusion and returned to baseline after its discontinuation (Table 3). The mean DBPs were between 74% and 86% of the baseline in various groups, and the most prominent reduction was observed after 1 hour in the 0- to 6-year age group. The least affected group with regard to DBP was the 13- to 18-year age group in all time points. Significant increases in mean HRs were observed during the first hour of infusion, but at the fourth hour of treatment, the mean HR was not significantly elevated from baseline. After discontinuation of the terbutaline treatment, the HR for all age groups showed marked decreases to rates lower than the baseline (Table 4). The potassium levels for all age groups were reduced from the baseline level 24 hours after terbutaline infusion (*P* = 0.001; Fig. 1). In the 0- to 6-year age group, the mean serum potassium concentrations reduced from 3.90 to 3.28 mg/dL (84% of the baseline; 16%

TABLE 2. Systolic Blood Pressure of Patients Receiving IV Terbutaline

	Systolic Blood Pressure (mm Hg ± SE)			
	Baseline	1 h	4 h	1 h After Discontinuation
0–6 yr	111.43±1.52 (100%)	101.70±1.57 (91%)	95.23±0.94 (86%)	103.39±0.69 (93%)
<i>P</i>		0.0001	0.0001	0.0001
7–12 yr	112.96±1.67 (100%)	104.42±1.77 (93%)	104.11±1.76 (93%)	112.22±0.78 (100%)
<i>P</i>		0.0007	0.0001	0.969
13–18 yr	123.57±2.72 (100%)	111.41±2.82 (90%)	108.52±1.69 (88%)	115.02±1.24 (93%)
<i>P</i>		0.0001	0.0001	0.969

TABLE 3. Diastolic Blood Pressure of Patients Receiving IV Terbutaline

	Diastolic Blood Pressure (mm Hg ± SE)			
	Baseline	1 h	4 h	1 h After Discontinuation
0–6 yr	64.4±1.47 (100%)	47.71±1.36 (74%)	49.9±0.78 (77%)	60.8±0.77 (94%)
<i>P</i>		0.0001	0.0001	0.069
7–12 yr	64.21±1.64 (100%)	48.77±1.52 (75%)	53.77±0.88 (84%)	65.87±0.86 (102%)
<i>P</i>		0.0001	0.0001	0.723
13–18 yr	65.45±2.64 (100%)	45.19±2.50 (76%)	56.56±1.43 (86%)	71.07±1.38 (108%)
<i>P</i>		0.0001	0.0004	0.142

TABLE 4. Heart Rates of Patients Receiving IV Terbutaline

	Heart Rate (BPM $\pm$ SE)			
	Baseline	1 h	4 h	1 h After Discontinuation
0–6 yr	149.68 $\pm$ 2.76 (100%)	164.03 $\pm$ 2.54 (109%)	156.18 $\pm$ 2.05 (104%)	123.85 $\pm$ 1.42 (83%)
<i>P</i>		0.0001	0.03	0.0001
7–12 yr	135.93 $\pm$ 3.05 (100%)	154.51 $\pm$ 2.80 (113%)	141.24 $\pm$ 2.27 (104%)	108.18 $\pm$ 1.59 (80%)
<i>P</i>		0.0001	0.171	0.0001
13–18 yr	130.10 $\pm$ 4.95 (100%)	146.23 $\pm$ 4.55 (112%)	133.71 $\pm$ 3.68 (102%)	93.27 $\pm$ 2.55 (72%)
<i>P</i>		0.0002	0.821	0.0001

reduction), whereas in the 7- to 12-year age group, it was reduced to 3.31 mg/dL from 4.04 mg/dL (82% of the baseline; 18% reduction). Similarly, in the 13- to 18-year age group, the mean serum potassium levels was 84 % of the baseline (from 3.80 to 3.20 mg/dL; 16% reduction). However, in none of the patients, reduction in potassium concentrations reached to a clinically critical level requiring potassium replacement and therefore considered as clinically stable throughout the treatment.

Ten (8%) of the study subjects required vasoactive medication to support their blood pressure during the terbutaline infusion treatment (Table 5) for an average of 13.8 hours (range, 4–32 hours). Owing to the severity of the airway obstruction, 9 of these patients received some type of positive pressure ventilation (6, invasive; and 3, noninvasive). The duration of terbutaline infusion treatment was longer in patients who required mechanical ventilator support.

Sinus tachycardia was the only significant electrocardiogram finding. No other arrhythmia occurred in this study group. All patients developed sinus tachycardia compared to baseline after initiation of the drip. No patient developed a seizure while on the terbutaline infusion.

DISCUSSION

In the present descriptive study, a large cohort of pediatric patients was investigated for the possible adverse effects related to terbutaline infusion in acute severe pediatric asthma. Our data showed that there were significant reductions in SBP and DBP right after the initiation of the terbutaline administration. The reductions were evident throughout much of the duration of treatment; however, they returned to normal after completion of the treatment. The reductions in blood pressures were observed in all age groups and only infrequently required support by the addition of a second vasoactive medication. These results are in

agreement with those reported earlier.¹² Almost all of those who developed hypotension requiring the addition of a vasopressor for support were those who also required mechanical ventilation. This group of patients, therefore, were likely those with the most severe airway obstruction and lung hyperinflation. These are the group of patients whose intrathoracic pressure is already elevated, limiting venous return to the heart, and therefore negatively affecting cardiac output and blood pressure. With the institution of any systemic vasodilator, such as terbutaline, a significant decrease in blood pressure requiring vasoactive support is expected.

Patients for all groups had decreased potassium levels after initiation of the terbutaline drip. Although these reductions were statistically significant, they did not reach to a level of clinical significance requiring replacement.

Cardiac toxicity is considered a potential adverse effect of vigorous asthma treatment including IV beta-agonist medications.¹³ The results of our study are in agreement with the previous reports, where after initiation of terbutaline infusion, our patients demonstrated hypotension and tachycardia. Kambalipalli and Upathyayula¹² studied the potential adverse effects of terbutaline in 77 children with severe asthma and reported significant increases in HRs and reductions in diastolic blood pressures with no cardiac arrhythmias. Similarly, no documented arrhythmias occurred in our cohort.

Furthermore, regarding other known noncardiac adverse effects, none of our subjects developed seizures after terbutaline regimen.

The paucity of clinical trials investigating the addition of intravenous beta-agonists to inhaled beta-agonists has hindered reaching a reliable conclusion on the use of IV terbutaline in severe asthma treatment.^{10,14} In recent meta-analyses, Travers et al¹⁰ drew attention to this information gap and rightfully suggested the need for high-powered clinical trials to further investigate this common clinical scenario and treatment modality.

In one randomized prospective and controlled study, Bogie et al¹⁵ evaluated 49 pediatric patients in 2 groups receiving either IV terbutaline or IV saline in addition to nebulized albuterol. In the group receiving terbutaline, overall clinical indicators showed a trend toward improvement, compared to the group receiving saline, but did not reach statistical significance. Furthermore, one patient had arrhythmia and 3 patients had elevated troponin levels during terbutaline infusion.¹⁵ In our previous study, the administration of terbutaline infusion starting early during the pre-PICU period was associated with requiring significantly less ventilatory support.⁸ This study brought a renewed interest in the use of terbutaline in the treatment of severe asthma¹¹; however, the potential for adverse events related to its use is of utmost importance. Browne et al¹⁶ previously reported the safety of the use of IV salbutamol in acute severe asthma. Similarly, Chiang et al¹⁷ concluded that there was no association of cardiac toxicity with the use of terbutaline infusions in a prospective study conducted

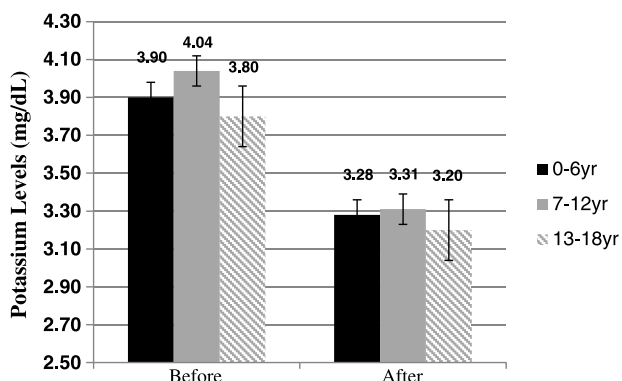
**FIGURE 1.** Potassium levels of patients receiving IV terbutaline.

TABLE 5. Data on Patients Receiving Vasoactive Medications During Terbutaline Treatment

No.	Age (yr)	Sex	Respiratory Support	Duration of Terbutaline (hr)	Max drip dose (µg/kg/min)	Medication	Max dose (µg/kg/min)	Duration of Vasoactive (hr)
1	6	F	NI	70	0.8	Epinephrine	0.02	12
2	15	M	NI	78	0.8	Epinephrine	0.01	8
3	15	M	NI	80	0.8	Epinephrine	0.05	6
4	9	M	MV	124	0.8	Epinephrine	0.05	14
5	1	M	None	8	0.5	Dopamine	5.00	12
6	11	F	MV	240	1.2	Dopamine	5.00	10
7	4	F	MV	64	3.0	Norepinephrine	0.05	4
8	14	M	MV	336	1.4	Dopamine	5.00	18
9	1	F	MV	126	0.8	Dopamine	7.50	22
10	3	F	MV	122	1.4	Norepinephrine	0.03	32

NI indicates noninvasive mechanical ventilation; MV, mechanical ventilation.

on 29 severely asthmatic patients. Our present study provides further support to this notion and adds new data to the field where detailed investigations are needed. One limitation of our study would be that our findings are gathered from a retrospective investigation at a single center. Thus, multisite involvement with prospective approach might also be needed in future studies.

CONCLUSIONS

Terbutaline infusion is a safe treatment option for children with severe asthma requiring escalation of bronchodilator therapy. Although it is associated with the development of decreased blood pressure and increased HR as well as decreased levels of serum potassium, hemodynamic support or electrolyte replacement is infrequently required.

REFERENCES

1. CDC. Centers for Disease Control and Prevention. National Center for Health Statistics, National Health Interview Survey Raw Data, 2011. Analysis by the American Lung Association Research and Health Education Division using SPSS and SUDAAN software. 2011.
2. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*. 2004;59:469–478.
3. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(5 suppl):S94–S138.
4. Kling S, Zar HJ, Levin ME, et al. Guideline for the management of acute asthma in children: 2013 update. *S Afr Med J*. 2013;103(3 Pt 3):199–207.
5. Grover S, Jindal A, Bansal A, et al. Acute bronchial asthma. *Indian J Pediatr*. 2011;78:1388–1395.
6. British Thoracic Society and Scottish Intercollegiate Guidelines Network. In: *British Guideline on the Management of Asthma, a National Clinical Guideline*. Edinburgh; 2012.
7. Jones BP, Paul A. Management of acute asthma in the pediatric patient: an evidence-based review. *Pediatr Emerg Med Pract*. 2013;10:1–23 quiz 23–24.
8. Doymaz S, Schneider J, Sagy M. Early administration of terbutaline in severe pediatric asthma may reduce incidence of acute respiratory failure. *Ann Allergy Asthma Immunol*. 2014;112:207–210.
9. Johnson M. Beta2-adrenoceptors: mechanisms of action of beta2-agonists. *Paediatr Respir Rev*. 2001;2:57–62.
10. Travers AH, Milan SJ, Jones AP, et al. Addition of intravenous beta(2)-agonists to inhaled beta(2)-agonists for acute asthma. *Cochrane Database Syst Rev*. 2012;12:CD010179.
11. Kantor DB, Phipatanakul W. Intravenous β agonists and severe pediatric asthma exacerbation: time for a closer look at terbutaline? *Ann Allergy Asthma Immunol*. 2014;112:187.
12. Kambalapalli M, Nichani S, Upadhyayula S. Safety of intravenous terbutaline in acute severe asthma: a retrospective study. *Acta Paediatr*. 2005;94:1214–1217.
13. Maguire JF, O'Rourke PP, Colan SD, et al. Cardiotoxicity during treatment of severe childhood asthma. *Pediatrics*. 1991;88:1180–1186.
14. Travers AH, Jones AP, Camargo CA Jr, et al. Intravenous beta(2)-agonists versus intravenous aminophylline for acute asthma. *Cochrane Database Syst Rev*. 2012;12:CD010256.
15. Bogie AL, Towne D, Luckett PM, et al. Comparison of intravenous terbutaline versus normal saline in pediatric patients on continuous high-dose nebulized albuterol for status asthmaticus. *Pediatr Emerg Care*. 2007;23:355–361.
16. Browne GJ, Penna AS, Phung X, et al. Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. *Lancet*. 1997;349:301–305.
17. Chiang VW, Burns JP, Rifai N, et al. Cardiac toxicity of intravenous terbutaline for the treatment of severe asthma in children: a prospective assessment. *J Pediatr*. 2000;137:73–77.