

Terbutaline nebulization and epinephrine injection in treating acute asthmatic children

Lin Y-Z, Hsieh K-H, Chang L-F, Chu C-Y. Terbutaline nebulization and epinephrine injection in treating acute asthmatic children. *Pediatr Allergy Immunol* 1996; 7: 95-99.

Ninety children with acute asthma, equally divided into two study groups, were studied to compare the efficacy and safety of nebulized terbutaline with injected epinephrine in the treatment of acute exacerbation. The terbutaline group received 2 ml (5.0 mg) terbutaline solution diluted with 2 ml 0.9% saline for inhalation over 10 minutes; the epinephrine group received 0.01 ml/kg of 1:1000 epinephrine (maximum 0.3 ml) through subcutaneous injection at deltoid area. Spirometry, pulse oximetry, and clinical severity scoring system were evaluated at baseline and again 15 minutes after treatment. The baseline data of the two groups were not significantly different. The clinical severity score and spirometry of both groups were significantly improved after treatment. Compared with the terbutaline group, the epinephrine group had better mean oxygen saturation (SaO_2 ; $p < 0.001$), frequency of oxygen desaturation ($p = 0.0028$) and forced expiratory flow 25-75% ($\text{FEF}_{25-75\%}$, $p = 0.027$). For those patients with initial forced expiratory volume in one second (FEV_1) lower than 60% of predicted value, epinephrine treatment was more effective in the improvement of FEV_1 , $\text{FEF}_{25-75\%}$, and oxygen saturation (SaO_2) ($p = 0.011$, 0.012 , and 0.006 , respectively). A significantly higher rate of adverse effects occurred in patients given epinephrine (47% vs 11%, $p = 0.0002$); these included pallor, tremor, dizziness, headache, palpitation, soreness of legs, numbness of extremities, cold sweating, general weakness and nausea. Considering the general trend to noninvasive therapy in children and the more frequent adverse effects after epinephrine injection, such nebulized beta-2 agonists as terbutaline appear preferable for initial therapy of acute asthma if oxygen is supplemented to prevent possible hypoxemia. However, parenteral epinephrine still is worth trying, particularly in any severe, life-threatening attack.

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Keywords: terbutaline; epinephrine; acute asthma; children

Received September 7, 1995
Accepted February 7, 1996

The initial therapy for acute asthma in children in hospitals is usually a subcutaneous epinephrine injection or nebulized beta-2 agonist. Although epinephrine has been the standard therapeutic agent for acute asthma for many years, and is still considered to be an effective alternate treatment for pediatric acute asthma in children, (1, 2) there is a trend to emphasize the treatment of acute asthma by aerosolized beta-2 selective agonists. One of the beta-2 agonists, terbutaline in nebulized form, has been on Taiwan market and used by our hospitals for years. The treatment with nebulized terbutaline in children with acute asthma has been proved to be effective in our previous study (3). Despite the fact that the effect of beta-2 agonists on acute asthma has been well documented, no study comparing nebulized terbutaline with injected epinephrine has been reported of childhood acute asthma in Taiwan.

The purpose of this study was to compare the efficacy and safety of nebulized terbutaline with injected epinephrine in childhood asthmatic patients during an acute exacerbation using clinical scoring system, spirometry measurement and oxygen saturation (SaO_2) as parameters.

Material and methods

Patients

Patients presenting at the Pediatric Allergy Outpatient Clinic of the Taipei Municipal Chung Hsiao Hospital were enrolled in this study if they met standard American Thoracic Society criteria for the diagnosis of asthma (4) and had histories of wheezing disease for which they were receiving either chronic or episodic bronchodilator therapy. Patients were eligible for study if they were at least five years of

Table 1. Demographic characteristics of patients before treatment.

	Terbutaline group (n=45)	Epinephrine group (n=45)
Sex, M/F	29/16	24/21
Age, yr (range)	7.78 (0.35) 5–12	7.47 (0.31) 5–12
Number of patients treated with oral bronchodilators before study*	19	15
Duration of symptom (days)	3.80 (0.45)	3.80 (0.44)
Clinical severity score	4.64 (0.21)	5.11 (0.22)
FVC (%)	71.59 (3.03)	69.77 (2.96)
FEV ₁ (%)	65.45 (3.08)	65.81 (3.05)
FEF _{25–75%} (%)	59.74 (4.33)	65.73 (4.39)
SaO ₂ (%)	95.8 (0.3)	96.4 (0.3)
Pulse rate (beats/min)	115 (2.7)	116 (2.8)

* still within the expected pharmacologic effect of the drugs. The spirometric data are expressed as % predicted value. Figures in parentheses are SEM.

age, and able to perform spirometry. Patients with complications of pneumonia, congestive heart failure, foreign body aspiration or bronchopulmonary dysplasia were excluded. Patients who had received any aerosolized beta-agonist within six hours before presentation were also excluded. In one period of time, all eligible patients were given nebulized terbutaline and, in another, injected epinephrine.

Treatment protocols

The two treatments were started after clinical severity score, baseline pulmonary function tests, SaO₂ and pulse rate had been measured. The terbutaline group received 5.0 mg (2 ml) of terbutaline solution (Bricanyl; Astra, Sodertalje, Sweden) diluted with 2 ml normal saline (4 ml in total) and delivered by an air compressor nebuliser (Pulmo-Aide, Model No. 5610D; DeVilbiss) driven by air at a flow rate of 8 L/min. A mouthpiece was applied during inhalation. Patients were instructed to take deep breaths freely, but slowly. When tapping the solution container did not generate further aerosol, the patient's mouthpiece was removed. This procedure usually took 10 minutes. The epinephrine group received subcutaneous injection at deltoid area of epinephrine at a dose of 0.01 ml/kg of 1:1000 epinephrine (maximum, 0.3 ml). Measurements of clinical severity scores, spirometry, SaO₂ and pulse rate were repeated 15 min after treatment. Any signs or symptoms suggestive of adverse effect whether observed by parents and/or doctors or as complaints from patients were recorded.

Evaluation

Clinical severity scores

Clinical severity was assessed according to Tal et al. (5). The parameters included respiratory rate,

Table 2. Clinical and laboratory parameters after treatment.

	Terbutaline group	Epinephrine group	p value#
Clinical severity score	2.53 (0.30)*	2.69 (0.23)*	NS
FVC (%)	80.97 (3.37)*	80.49 (2.60)*	NS
FEV ₁ (%)	72.61 (3.32)*	77.48 (2.60)*	NS
FEF _{25–75%} (%)	65.34 (4.39)***	80.36 (5.04)*	0.027
SaO ₂ (%)	95.4 (0.3)	97.2 (0.2)**	<0.001
Pulse rate (beats/min)	115 (2.9)	118 (2.8)	NS

NS: not significant

p value calculated by unpaired Student's t-test except that of clinical severity score (Wilcoxon signed rank sum test). * p<0.001; ** p=0.001; *** p=0.045 when compared with values of the same group before treatment by paired Student's t-test. Figures in parentheses are SEM.

wheezing, cyanosis and accessory respiratory muscle utilization. Each item scored from 0–3. The evaluation was done by the same senior pediatrician (LF Change) throughout the study. The scores were then added to give a single clinical severity score.

Spirometry

Pulmonary functions including forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), and forced expiratory flow 25–75% (FEF_{25–75%}), were measured in all patients using standard spirometry (Vitalograph Compact, Cat No. 42.000; Vitalograph, Vitalograph Ltd., England). The FVC, FEV₁, and FEF_{25–75%} values of at least three consecutive efforts were determined, using the curve having the best FEV₁ as defined by the American Thoracic Society (6). The values were expressed as percentages of the predicted normal values for age, sex and height.

Oxygen saturation and pulse rate

Oxygen saturation (SaO₂) and pulse rate were recorded using a pulse oximeter (Model ACCUSAT™, Datascope Corp., Paramus, NJ); measurement was through the nail bed of index finger. SaO₂ values were accepted only if they were stable in 5 s on a pulse oximeter screen during reading.

Statistics

Results were expressed as mean±standard error of mean (SEM). The two-tailed Wilcoxon signed rank sum test was used for statistical analysis of the clinical severity scores. The two-tailed Student's test was used for statistical analysis of spirometry and pulse oximetry at baseline and after treatment. Paired tests were used within the same group and unpaired tests, between groups. The sex and medication and comparative frequency of the decrease of SaO₂ and adverse effects after treatment were assessed by the

Table 3. Demographic characteristics of patients with initial FEV₁ less than 60%

	Terbutaline group (n=17)	Epinephrine group (n=18)
Sex, M/F	9/8	10/8
Age, yr (range)	7.12 (0.53) 5-11	7.56 (0.51) 5-12
Number of patients treated with oral bronchodilators before study*	7	5
Duration of symptom (days)	3.24 (0.76)	3.17 (0.73)
Clinical severity score	5.47 (0.36)	6.06 (0.34)
FVC (%)	53.45 (4.53)	52.72 (3.35)
FEV ₁ (%)	44.60 (3.08)	45.66 (2.27)
FEF _{25-75%} (%)	36.31 (3.68)	41.69 (4.92)
SaO ₂ (%)	94.9 (0.5)	95.7 (0.3)
Pulse rate (beats/min)	121 (4.3)	122 (5.0)

* still within the expected pharmacologic effect of the drugs. The spirometric data are expressed as % predicted value. Figures in parentheses are SEM

Pearson chi-square test. A p value of less than 0.05 was considered statistically significant.

Results

A total of 90 patients were enrolled in this study, 45 patients in each group. Table 1 shows demographic characteristics of the two groups. At the time of entry into the study, the two groups were not significantly different with respect to age, sex, clinical severity score, FVC, FEV₁, FEF_{25-75%}, SaO₂ or pulse rate.

The results after treatment for both groups are shown in Table 2. The clinical severity score and all parameters of spirometry of both groups were significantly improved after treatment. The SaO₂ was increased in the epinephrine group, but not in the terbutaline group. The pulse rate showed no significant change. After treatment, the SaO₂ and the FEF_{25-75%} of the terbutaline group were significantly lower than those of the epinephrine group, but the improvement in clinical severity score and pulmonary functions (other than FEF_{25-75%}) was comparable between the two groups. The pulse rate was not significant either. Twenty (44%) children in the terbutaline group and seven (16%) in the epinephrine group had a decreased SaO₂ after treatment (p=0.0028).

Seventeen patients in the terbutaline group and 18 patients in the epinephrine group had an initial FEV₁ less than 60% of predicted value; they were classified as a severely asthmatic group. At their entry into study, the two subgroups were also not significantly different with respect to age, sex, clinical severity score, FVC, FEV₁, FEF_{25-75%}, SaO₂ or pulse rate (Table 3). In those patients, the epinephrine treatment also exerted greater improvement in FEV₁,

Table 4. Clinical and laboratory parameters after treatment in patients with initial FEV₁ less than 60%.

	Terbutaline group (n=17)	Epinephrine group (n=18)	p value#
Clinical severity score	3.59 (0.54)	3.56 (0.31)	NS
FVC (%)	63.69 (5.90)	69.37 (3.57)	NS
FEV ₁ (%)	51.19 (3.93)	65.01 (3.26)	0.011
FEF _{25-75%} (%)	41.87 (4.58)	59.25 (4.63)	0.012
SaO ₂ (%)	95.1 (0.3)	96.5 (0.3)	0.006
Pulse rate (beats/min)	120 (4.7)	125 (4.7)	NS

NS: not significant

p value computed by unpaired Student's t-test except for clinical severity score (Wilcoxon signed rank sum test). Figures in parentheses are SEM.

FEF_{25-75%} and SaO₂ (p=0.011, 0.012, and 0.006, respectively, Table 4).

Adverse effects, including pallor (11 cases), tremor (5), dizziness (5), headache (4), palpitation (4), soreness of legs (3), numbness of extremities (2), cold sweating (2), general weakness (1), nausea (1), were found in 21 of 45 (47%) patients given epinephrine. On the contrary, only 5 of 45 (11%) patients given nebulized terbutaline were noted to have dizziness (2), pallor (2), and tremor (1). Significantly fewer adverse effects were found in the terbutaline group (p=0.0002).

Discussion

The results of this study showed that both nebulized terbutaline and injected epinephrine were effective in reducing clinical severity and airway obstruction in children with acute asthma, but the injected epinephrine was better than the nebulized terbutaline, particularly in severely asthmatic patients, regarding improvement of SaO₂ and pulmonary function, although accompanied with greater adverse effects.

There is a possibility that the optimal bronchodilator effect of nebulized terbutaline had not been reached 15 min after therapy. When given by inhalation, 75% of maximal bronchodilator effect is achieved within 5 minutes (1), and, by 10 minutes, 80 to 90% has usually been achieved (7), but 15-60 minutes are required to reach maximum effect (8). The above description is based on the studies of a metered dose inhaler which can be administered in seconds. For nebulization, which takes about 10 min to complete, the drug effect actually starts soon after the first inhalation and then accumulates thereafter. When the pulmonary function test was rechecked 15 min after therapy as in this study, 25 min had elapsed after the first inhalation. In the study performed by Becker et al., no more bronchodilator effects were seen at 30 min as compared with those at

15 min after nebulization therapy (9) and, in the study of Baughman et al (10), the spirometric results at 30 min after nebulization treatment were nearly the same as those at 2 min. As to the epinephrine, maximal effect usually was reached at 15 min after therapy (9, 10). Therefore, the inferior bronchodilation effect of nebulized terbutaline found in this study could hardly be ascribed to suboptimal timing when the pulmonary function was re-measured 15 min after therapy.

There have been a few studies comparing injected epinephrine and aerosolized beta-2 adrenergic agents for relieving acute symptoms of asthma (9–12). The aerosolized beta-2 agonists have been shown to be as effective as epinephrine in terms of speed of onset, magnitude of improvement and duration of activity. Use of the aerosol route reportedly obviated the adverse effects encountered with the administration of injected epinephrine. Nonetheless, epinephrine still remains one of the commonly used adrenergic agent in an Emergency Room or office setting for treatment of a child with acute symptoms of asthma. In a multicenter study of Pediatric Emergency Services in the United States up to 1988, beta agonist injection still remained the initial intervention of choice in 79% of the surveyed institutions, among which 81% chose epinephrine as the injectable agonist (13). The relative complexity of administration resulting in increased personnel time is the probable cause for the lack of universal acceptance of inhaled agents. To present knowledge, only the study performed by Becker et al. (9) has compared the effect of epinephrine and beta-2 agonist on arterial oxygenation. Their study found epinephrine treatment significantly increased the PaO_2 of acute asthmatic children while no change was seen after salbutamol treatment; but there was no significant difference between the mean PaO_2 of the two groups. Our study, using SaO_2 as indicator, revealed the epinephrine treatment not only significantly increased the SaO_2 of acute asthmatic children but also obtained significantly higher SaO_2 than the terbutaline treatment did. The reason for the discrepancy may be that there are more cases in the study here (45 instead of 20 in each group), making a difference in reaching a significant level.

The phenomenon of hypoxemia or oxygen desaturation after inhalation of selective beta-2 agonists in asthmatic children has been noted in a few reports (14–16). The causes for oxygen desaturation have been suggested by some authors to result from a change in ventilation-perfusion ratio (16, 17), others have proposed that this was a response to changes of pH and osmolality of the nebulized solutions (18–21) which have been well documented to produce bronchoconstriction in asthmatic subjects (21, 22). The temperature drop during aerosol inhalation may

also contribute to bronchoconstriction (23). All these factors can cool and irritate the airways and curtail the bronchodilating effect of terbutaline. Further, in severe asthmatic patients, the airways may be so constricted and impacted by sputum that the terbutaline aerosol can hardly penetrate into the lungs evenly. Thus, terbutaline treatment is a little less favorable than epinephrine treatment when improvement of pulmonary function and oxygen saturation are particularly concerned. It should be specially mentioned that in Ros's study the oxygen was not routinely administered to all wheezing patients in 67% of the surveyed pediatric emergency institutions (13).

The major factor that makes the nebulized terbutaline treatment superior to the injected epinephrine treatment in this study was, obviously, less frequent adverse effects. However, in a busy hospital Emergency Room or physician's office, it is often more expeditious to give an epinephrine injection than to deliver the drug via nebulization. This problem can be partially resolved when a source of compressed air and oxygen, nebulizer, and accessories are readily available in a well-equipped hospital or office. Considering the general trend to noninvasive therapy in children and much more frequent adverse effects after epinephrine treatment, such nebulized beta-2 agonists, as terbutaline appear preferable for initial therapy of acute asthma if oxygen is supplemented to prevent possible hypoxemia. However, in case of severe attack, parenteral epinephrine still is very useful.

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