

Comparison of the effects of nebulized terbutaline with or without intravenous betamethasone on exhaled nitric oxide in children with acute asthma attack

Ming-Yung Lee¹, Yi-Giien Tsai¹, Kuender D. Yang², Chih-Hsing Hung^{3,4}

¹Department of Pediatrics, Tri-service General Hospital, National Defense Medical Center, Taipei;

²Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung University, Kaohsiung;

³Department of Pediatrics, Faculty of Pediatrics, College of Medicine, Kaohsiung Medical University, Kaohsiung; and ⁴Department of Pediatrics, Kaohsiung Medical, University Chung-Ho Memorial Hospital, Kaohsiung Medical University, Taiwan

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Background and Purpose: Exhaled nitric oxide (eNO), a non-invasive marker that reflects the degree of airway inflammation, may be useful for assessing the response to anti-inflammatory treatment of asthma. The purpose of this randomized prospective study was to compare the effect of a nebulized terbutaline plus a single intravenous dose of betamethasone at baseline followed by a second of terbutaline at 6 h with the effect of the same protocol of nebulized terbutaline alone on airway inflammation of acute asthmatic children as demonstrated by eNO levels.

Methods: Children visiting the emergency department due to acute asthma attack were recruited. All enrolled patients had fluorescent assay-proven hypersensitivity to *Dermatophagoides pteronyssinus*. Patients were randomized to receive either nebulized terbutaline plus intravenous betamethasone (experimental group, n = 11) or nebulized terbutaline alone (control group, n = 11) at baseline followed by a second dose of nebulized terbutaline alone 6 h later.

Results: Exhaled NO concentrations were significantly reduced in the experimental group at 7 h (40.25 ± 12.43 vs 28.88 ± 18.02 ppb; $p=0.005$) and 12 h (40.25 ± 12.43 vs 30.11 ± 18.16 ppb; $p=0.007$) after treatment. The eNO level in the experimental group was also reduced at 7 h (28.88 ± 18.02 vs 38.12 ± 16.50 ppb; $p=0.034$) and 12 h (30.11 ± 18.16 vs 39.36 ± 17.63 ppb; $p=0.035$) compared to the control group. The change of eNO concentration was correlated to the change of peak expiratory flow rate (PEFR) [$r = -0.678$; $p=0.022$] and pulmonary index scores ($r = 0.606$; $p=0.048$) at 7 h after treatment in the betamethasone group.

Conclusion: Nebulized terbutaline given at baseline and 6 h later was significantly more effective in improving PEFR and asthmatic symptoms (pulmonary index scores) for at least 12 h when the initial dose was administered in combination with intravenous betamethasone.

Key words: Asthma, betamethasone, breath tests, nitric oxide, terbutaline

Introduction

Acute asthma attack is caused by exacerbation of airway inflammation. Corticosteroid therapy of asthma can prevent asthma attack and reduce airway inflammation [1,2]. Systemic administration of corticosteroid has

been shown to be efficacious for pediatric patients hospitalized with acute asthma [3]. Although intravenous corticosteroids are considered to comprise an important part of treatment of severe asthma, the speed of their anti-inflammatory effects in asthmatic children is not known [3].

Exhaled nitric oxide (eNO) is a sensitive and noninvasive indicator for assessing the response to corticosteroid therapy after administration for 5 days [4] and 3 weeks [5]. In our previous study, eNO was decreased within 7 h after nebulized budesonide

Corresponding author: Dr. Chih-Hsing Hung, Department of Pediatrics, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung Medical University, #100, Tz-You 1st Road, Kaohsiung 807, Taiwan.
E-mail: pedhung@hotmail.com

treatment [6]. In this study, we compared the effects of nebulized terbutaline with or without intravenous betamethasone on clinical and laboratory variables, including pulmonary index score (PIS), eNO and peak expiratory flow rate (PEFR) in children with acute asthma. We compared the time required for these 2 therapies to reduce airway inflammation as demonstrated by decreased eNO concentrations.

Methods

Subjects

This study used a randomized, prospective and investigator-blinded design. A total of 30 children (aged 6-18 years) with acute asthma attack who visited our emergency department were enrolled after informed consent was obtained from their parents. Asthmatic subjects recruited for this study had all experienced several episodes of asthma in the previous 1 year and had fluorescent immunoabsorbent assay-proven hypersensitivity to *Dermatophagoides pteronyssinus* (*Der p*; Multiple Allergen Simultaneous Test, Medical Pharmacy Enterprise, CO, USA). *Der p* hypersensitivity was selected as an inclusion criterion since *Der p* was reported to be responsible for 92% of asthma hypersensitivity in Taiwan [7], and also because evidence showed that eNO concentrations were elevated in children with atopic asthma but not in those with non-atopic asthma [8]. Patients were excluded if they had used any kind of corticosteroid, theophylline, cromolyn, or leukotriene receptor antagonist within the 4 weeks prior to the start of the study. If a patient's condition worsened (PIS >13) during the treatment, hospitalization was arranged and the patient was withdrawn from the study protocol [6].

Study design

The study protocol was approved by the Clinical Trial Review Board of Tri-Service General Hospital. Patients were randomly assigned to receive either terbutaline plus betamethasone (experimental group) or terbutaline alone (control group). The control group received a 0.1 mg/kg dose of terbutaline in a 3 mL isotonic sodium chloride solution (Bricanyl; Astra-Zeneca, London, UK) administered with a hand-held disposable updraft nebulizer (Whisper Jet; Intec, Marquest Medical Products, Englewood, CO, USA) every 6 h for 2 doses [9]. The experimental group received the same dose of terbutaline (0.1 mg/kg per dose) combined with intravenous betamethasone (0.05 mg/kg; maximal 2 mg;

Rinderon; Shionogi, Taiwan) [10] on enrollment, followed by terbutaline nebulization alone 6 h after the initial treatment.

During the subsequent 12 h, all children were closely monitored by a physician. The eNO concentration, PEFR, PIS and blood pressure were measured before and 1, 3, 6, 7 and 12 h after initial treatment. The PIS was measured according to the results of examinations including wheezing, respiratory rate, accessory muscle use, inspiratory to expiratory ratio, and oxygen saturation [11]. A score of 0 to 3 was assigned to each variable and the final scores could range from 0 to 15, with 15 being the most severe condition. PEFR was measured by using a peak flow meter (Astech Co., Port Washington, NY, USA).

Measurement of eNO

The measurement of eNO was performed using a chemiluminescent analyzer (NOA 280; Sievers Instrument, Inc., Boulder, CO, USA) with the validated, single-breath technique. The patient inhaled to total lung capacity and then exhaled slowly against a fixed resistance at a constant mouth pressure (15 cm H₂O) corresponding to expiratory flow (75 mL/s), a maneuver that facilitates velopharyngeal closure and avoids nasal NO contamination [6,12]. To maintain a steady air flow, the mouth pressure was displayed on a computer screen as a prompt for the children. The eNO values were recorded from the plateau at the end of exhalation. Data were only recorded when 3 measurements revealed less than 10% variability. Most patients could complete 3 measurements without the need for further trials. These values were represented by their mean. Ambient NO levels were monitored during the studies. Only measurements with ambient NO levels less than 10 ppb were analyzed [6].

Statistical analysis

Demographic data of the experimental and control groups including age, gender, initial eNO, PIS, PEFR and blood pressure were compared by 1-way analysis of variance. Changes of eNO, PIS and PEFR between the 2 groups at 0, 1, 3, 6, 7, and 12 h after initial treatment were analyzed by the Wilcoxon signed rank test. Differences between the 2 groups were analyzed by using the Mann-Whitney *U* test. Correlations of eNO level to PEFR and PIS in the experimental and control groups were measured by Pearson correlation. A 2-tailed *p* value less than 0.05 was considered significant.

Table 1. Baseline characteristics of the patients in the experimental and control groups

Assessment	Nebulized terbutaline plus intravenous betamethasone	Nebulized terbutaline (control group)	<i>p</i>
	Mean ± SD	Mean ± SD	
Gender ratio (F/M)	5/6	4/7	0.73
Age (years)	9.91 ± 2.21	10.36 ± 2.91	0.88
Respiration rate (/min)	39.92 ± 7.24	35.67 ± 7.08	0.19
Systolic pressure (mm Hg)	105.91 ± 9.70	100.36 ± 12.51	0.24
Diastolic pressure (mm Hg)	70.64 ± 8.21	67.09 ± 7.76	0.22
NO (ppb)	40.25 ± 12.43	39.21 ± 19.56	0.75
PIS	9.00 ± 1.67	8.45 ± 1.75	0.90
PEFR (L/min)	99.09 ± 49.89	89.09 ± 18.14	0.97

Abbreviations: SD = standard deviation; F = female; M = male; NO = nitric oxide; PIS = pulmonary index score; PEFR = peak expiratory flow rate

Results

A total of 30 children with acute asthma attack were enrolled in this study. Eleven control subjects and 11 patients in the experimental group completed the study. Three patients who had a PIS of more than 13 after treatment were removed from the study and hospitalized. Another 5 patients were removed from the study protocol because of ambient NO concentration more than 10 ppb at the time of eNO measurement.

The baseline characteristics of patients in the experimental and control groups are compared in Table 1. There were no significant differences in the characteristics of patients in the control and experimental groups in age, gender, eNO concentration and blood pressure. The severity of asthma attack at entry as reflected by mean PEFR and PIS was similar in the 2 groups. There were no significant changes in blood pressure between baseline and 12 h after treatment in each group.

Effects of nebulized terbutaline plus intravenous betamethasone

The combined use of intravenous betamethasone and nebulized terbutaline inhalation significantly improved PEFR and PIS within 1 h ($p=0.003$ and $p=0.002$, respectively) and the significance of this effect remained at 12 h ($p=0.02$ and $p=0.02$, respectively) following the interim dose of terbutaline at 6 h. PEFR was also significantly improved in the experimental group compared to the control group after terbutaline treatment at 6 h ($p=0.043$) while PIS was not significantly different after treatment between groups after treatment at 6 h ($p=0.06$). The eNO level was significantly reduced at 7 ($p=0.005$) and 12 h ($p=0.007$) in the experimental group. The eNO level in the experimental group was also reduced at 7 ($p=0.034$) and 12 h ($p=0.035$) compared to the control group (Table 2).

Effects of nebulized terbutaline

In the control group, the first dose of nebulized terbutaline significantly improved PEFR and PIS at 1 h

Table 2. Comparison of changes of peak expiratory flow rate (PEFR), pulmonary index score (PIS) and exhaled nitric oxide (eNO) before and after treatment in the experimental and control groups

Time (h)	PEFR (L/min) [mean ± SD]		PIS (mean ± SD)		eNO (ppb) [mean ± SD]	
	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
0	99.09 ± 49.89	89.09 ± 18.14	9.00 ± 1.67	8.45 ± 1.75	40.25 ± 12.43	39.21 ± 19.56
1	145.45 ± 59.39 ^a	131.82 ± 44.96 ^a	6.27 ± 2.15 ^a	6.00 ± 1.41 ^a	40.97 ± 15.64	42.05 ± 23.96
3	145.45 ± 62.03 ^a	118.18 ± 39.45 ^a	5.64 ± 2.50 ^a	5.45 ± 2.34 ^a	34.52 ± 18.92	42.83 ± 26.38
6	147.27 ± 66.50 ^{a,b}	93.64 ± 37.82	5.36 ± 2.06 ^a	7.90 ± 1.45	32.34 ± 11.26	37.46 ± 18.80
7	181.82 ± 55.10 ^a	124.18 ± 54.49	5.27 ± 2.00 ^a	6.18 ± 1.94 ^a	28.88 ± 18.02 ^{a,b}	38.12 ± 16.50
12	190.90 ± 60.57 ^{a,b}	139.64 ± 57.74 ^a	3.55 ± 1.04 ^{a,b}	6.45 ± 1.69 ^a	30.11 ± 18.16 ^{a,b}	39.36 ± 17.63

^a $p < 0.05$ after treatment.

^b $p < 0.05$ between experimental group and control group.

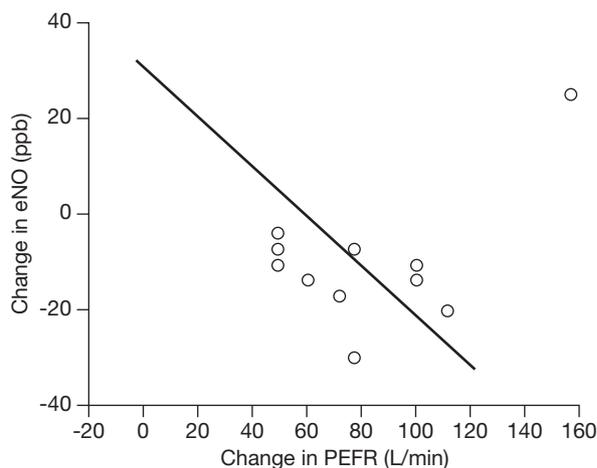


Fig. 1. Correlation between changes in exhaled nitric oxide (eNO) levels and peak expiratory flow rate (PEFR) at 7 h after initial treatment with nebulized terbutaline plus intravenous betamethasone with a second dose of terbutaline given at 6 h ($r = -0.678$; $p = 0.022$).

after treatment ($p = 0.003$ and $p = 0.007$, respectively); however, this effect was significant only up to 3 h ($p = 0.014$ and $p = 0.003$, respectively) and was not significant at 6 h ($p = 0.75$ and $p = 0.259$, respectively) [Table 2]. The improvement in symptoms thus diminished unless a second dose of terbutaline inhalation was given after the initial treatment. The eNO level was not significantly affected by nebulized terbutaline inhalation during the study period.

Correlation of eNO level with PEFR and PIS

In the experimental group, the decrease in eNO level was significantly correlated with the increase in PEFR 7 h after the initial treatment ($r = 0.678$ and $p = 0.022$) [Fig. 1], and with the decrease in PIS 7 h after initial treatment ($r = 0.606$ and $p = 0.048$) [Fig. 2]. In the control group, however, no significant correlation was found between changes of eNO and PIS or between changes of eNO and PEFR during the study period.

Discussion

eNO is a noninvasive marker of airway inflammation. Several studies have demonstrated increased eNO concentration in patients during acute asthma attacks [6,8]. NO is formed from L-arginine through the action of nitric oxide synthase (NOS), which exists as the constitutive and inducible form. The inducible NOS expression strongly associated with eNO concentration can be upregulated in infiltrating

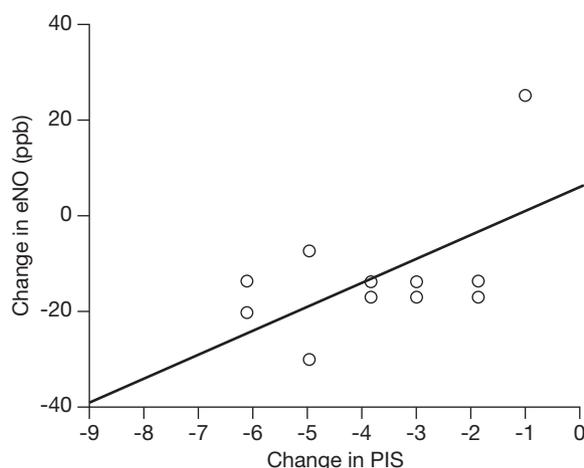


Fig. 2. Correlation between changes in exhaled nitric oxide (eNO) level and pulmonary index score (PIS) at 7 h after initial treatment with nebulized terbutaline and intravenous beta-methasone with a second dose of terbutaline given at 6 h ($r = 0.606$; $p = 0.048$).

inflammatory cells such as eosinophils and macrophages [13-15].

Although spirometry and peak flow meter are used to monitor asthmatic status, neither can reflect the degree of airway inflammation of asthma. Bronchoalveolar lavage and biopsy can measure airway inflammation directly but these techniques are not suitable for use in children. While eNO is elevated during acute asthma attack and decreased after different kinds of anti-inflammatory therapy, such as corticosteroid and leukotriene antagonists [4,16], whether elevated eNO can predict future deterioration of asthma remains unclear. If a correlation between eNO fluctuations and disease activity can be demonstrated, measurement of eNO may be beneficial in the management of asthma. Repeated eNO measurements may provide guidance on the extent to which the dosage of corticosteroid should be adjusted. This may protect asthmatic children from the side effects of excessive corticosteroid use or premature cessation of corticosteroid therapy.

Baraldi et al reported that oral prednisolone, 1 mg/kg/day for 5 days, could significantly decrease eNO levels in children with asthma [4]. Another study in which inhaled steroids were administered to asthmatic children for 10 days also demonstrated a significant decrease in eNO levels [17]. In our previous study, nebulized budesonide effectively decreased eNO and improved symptoms within 6 h in children with atopic asthma [6]. In this study, eNO was significantly reduced 7-12 h after intravenous corticosteroid therapy combined

with nebulized terbutaline at baseline followed by a second dose of nebulized terbutaline at 6 h, and it was decreased compared to the control group. A previous study identified at least 2 subgroups of difficult asthma in children: one with persistently raised eNO levels despite treatment with oral prednisolone, indicating ongoing steroid insensitive inflammation, and another with normal levels of eNO [18]. Whether steroid treatment can effectively decrease eNO in non-atopic asthma remains unclear.

Parenteral administration of corticosteroids has been shown to be effective for children hospitalized with acute asthma [19-21]. A short course of intravenous corticosteroid therapy also had no significant side effects [21]. Intravenous corticosteroid therapy was beneficial in treating pediatric status asthmaticus [19]. Becker et al suggested that oral prednisone was as effective as intravenous corticosteroids in children hospitalized with asthma [21]. A single dose of intramuscular betamethasone was safe and as efficacious as oral prednisone (daily for 7 days) in preventing the relapse of acute asthma [22]. The greater effect of intramuscular betamethasone than oral prednisolone on bronchial obstruction may be due to its longer biological half-life or to some unidentified property of its metabolites [23]. Betamethasone is also thought to be a more potent steroid than prednisolone, especially in prednisolone-resistant asthma [23]. Hence, a single dose of intravenous betamethasone is frequently used in our emergency department for treating asthma. Betamethasone, a long-acting corticosteroid, has a longer biological half-life (36 h) and its pharmacokinetic behavior is not affected by the route of administration [23,24]. Plasma thyrotropin and cortisol concentrations were suppressed immediately after an intravenous bolus dose of betamethasone, but these changes were reversed by 3 to 5 days after treatment [25].

Intravenous administration of steroid in asthmatic children may result in more systemic side effects than topical administration. A previous study found that a 3-day course of oral betamethasone had obvious systemic effects that could be detected by urine cortisol, serum cortisol or the bone formation and resorption markers, but treatment with high-dose inhaled budesonide for 10 days did not produce significant systemic effects in early childhood asthma [2]. Nebulized corticosteroid therapy may be a good consideration during acute asthma attack in children. Intravenous steroid therapy can be effective and should be reserved for treating pediatric status asthmaticus

because these patients may be too dyspneic to swallow or inhale medications [19].

In this study, combined betamethasone plus nebulized terbutaline significantly improved PEF and PIS at 1 h after treatment, and after an interim dose of terbutaline in both groups at 6 h, this significant difference in effect was maintained at 12 h. By contrast, eNO was significantly improved only at 7 and 12 h after treatment. These findings suggest that eNO is more sensitive than PEF and PIS in detecting changes in airway inflammation [16], and may be a useful marker to monitor rapid change of acute airway inflammation during steroid therapy for acute asthma attack.

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