Use of aerosol inhalation treatment with budesonide and terbutaline sulfate on acute pediatric asthmatic bronchitis

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Abstract. The use of oxygen-driven aerosol inhalation therapy with budesonide (suspension) and terbutaline sulfate for the treatment of pediatric asthmatic bronchitis was studied. Sixty pediatric patients diagnosed with asthmatic bronchitis in Xuzhou Children's Hospital during the period comprising April 2013 to December 2015 were enrolled in the study. After randomly dividing the patients into a control (conventional dexamethasone drip) and a treatment group (inhalation of budesonide with terbutaline sulfate) of 30 patients each, the symptoms were treated using antibiotics when necessary. The results of our evaluation showed the overall effective rate of treatment in the control group was 73.33% (40% with marked improvement, 33.33% with some improvement and 26.67% with no improvement) and that in the treatment group was 96.67% (73.73% with marked improvement, 23.33% with some improvement and only 3.33% with no improvement) with a statistically significant difference ($p<0.05$). The pulmonary functions of all pediatric patients showed no statistically significant differences in the pulmonary function indexes between the two groups before treatment ($p>0.05$). However, the differences in FEV1, FVC, FEV1/FVC and PEF between control and treatment groups before and after treatment were statistically significant ($p<0.05$), with overall improvement being higher in the treatment group. Finally, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level in patients of the two groups improved significantly after treatment ($p<0.05$). The ESR and CRP level in the treatment group were improved to a higher degree than those in the control group ($p<0.05$). There were only minor adverse reactions in two patients in the treatment group, and the overall rate of adverse reactions was not significantly different between the two groups ($p>0.05$). Based on our evaluation the aerosol inhalation therapy of budesonide (suspension) with terbutaline sulfate has definite curative effects and is safe to use on pediatric asthmatic bronchitis patients. The approach is superior to the conventional dexamethasone treatment and is worth studying in larger populations for recommending it widely.

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Introduction

The etiological agents causing pediatric asthmatic bronchitis are many and include rhinovirus, parainfluenza and influenza virus, adenovirus, respiratory syncytial virus and *Mycoplasma pneumoniae*; and most cases are complicated with a bacterial infection (1,2). Overt asthma may follow repeated attacks in some children due to their allergic constitution. The trachea and bronchi of infants and young children are relatively narrow and small, and the surrounding resistance fibers are not yet well developed, therefore the swelling of the mucous membrane caused by infection or other pathological irritants, leads to increased tracheal stenosis and airflow resistance. During inflammation, secretions increase and become stickier, making it more difficult for the affected individual to discharge them by expectoration and resulting in wheezing. We report here the use of an aerosol inhalation therapy of budesonide (suspension) with terbutaline sulfate (atomized liquid) for the treatment of pediatric asthmatic bronchitis in the Department of Pediatrics of our hospital, and the clinical results on the patients.

Materials and methods

Clinical data. Sixty child patients with asthmatic bronchitis admitted and treated in Xuzhou Children's Hospital from April 2013 to December 2015 were enrolled in the study. A treatment group (n=30) and a control group (n=30) were randomly established. There were 16 males and 14 females aged 1-5 years in the treatment group; and 17 males and 13 females aged 1-5 years in the control group. All child patients met the diagnostic criteria in 'Practical Paidonosology' written by Zhu Futang (1); all of them presented persistent coughing, broncho-spams, dyspnea, wheezing rales and medium-fine moist rales heard in both lungs. Infant asthma was excluded as a diagnosis in all of the patients. There were no complications of heart or respiratory failure. No statistically significant differences in the age, sex and disease status of patients were found between the two groups ($p>0.05$). The Ethics Committee of Xuzhou

Children's Hospital approved this study, and families of the patients signed written informed consents.

Inclusion criteria. The diagnostic criteria in 'Practical Paidonosology' (3) applied to all the patients.

Exclusion criteria. The exclusion criteria for this study were taken from the literature (4,5). They included active bleeding, history of recent nasal or facial surgery, severe chronic respiratory failure or the use of long-term non-invasive ventilator-assisted ventilation, severe pulmonary heart disease, right heart failure, or other severe organ diseases (uncontrolled hypertension, diabetes, hepatic or renal dysfunction), and any type of mental disease. Additionally, the participation in the study was terminated if a patient could not continue the treatment due to side effects of drugs, or could not tolerate the aerosol inhalation therapy.

Treatment method. The two groups received the same conventional therapy in order to reduce secretion production, relieving cough, improving oxygen uptake and provide anti-infective therapy. The control group was treated with an intravenous drip of dexamethasone (0.1-0.3 mg/kg/day) (Yangze Pharma, Taizhou, China). The treatment group was treated with oxygen-driven aerosol inhalation of budesonide (suspension) at a dose of 0.5-1.0 mg combined with terbutaline (atomized liquid) (both from Yangze Pharma) at a dose of 2.5 mg terbutaline for children with body weight of <20 kg, and 5.0 mg for those weighing >20 kg. The budesonide suspension was used for inhalation, 1-2 times/day, during a 10-15 min period each time. The duration of the clinical symptoms like coughing, shortness of breath, bronchospasm and lung rales, and the appearance of any adverse reactions were recorded.

Observational indexes

Determination of clinical efficacy. Changes in clinical symptoms were recorded and classified in one of the three categories. There was marked improvement when pulmonary rales disappeared, the coughing was significantly reduced or disappeared, and the sputum amount was reduced by >70%. Some improvement meant pulmonary rales and coughing were reduced and sputum amount was reduced by 30-70%. An ineffective treatment occurred when pulmonary rales and coughing were not improved, and sputum amount was reduced by <30%. The effective rate in each group was calculated by the equation: Effective rate = (marked improvement + some improvement)/total number x100%.

Determination of pulmonary functions. An SN65511-type pulmonary function detector was used to examine each patient before and after treatment. The indexes detected included the forced expiratory volume at 1 sec (FEV1), the forced vital capacity (FVC), the ratio of forced expiratory volume at 1 sec to the forced vital capacity (FEV1/FVC) and the peak expiratory flow (PEF).

Determination of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. Venous blood was collected from all patients in the control and treatment groups before and after treatment to detect the ESR and CRP level. The average levels in the two groups were compared before and after the treatment.

Table I. General data of patients.

General condition	Control group (n=30)	Treatment group (n=30)
Sex (male/female)	17/13	16/14
Age (years)	4.29±0.49	4.89±0.29
Course of disease (years)	1.94±0.34	1.66±0.38
FEV1 l) before treatment	1.22±0.08	1.20±0.08
FVC (l) before treatment	2.02±0.32	2.05±0.39
FEV1/FVC before treatment	0.62±0.08	0.60±0.10
PEF (l/min) before treatment	2.32±0.17	2.32±0.10
ESR (mm/h) before treatment	44.80±21.00	46.40±16.25
CRP (mg/l) before treatment	42.50±16.16	42.78±19.09

FEV1, forced expiratory volume; FVC, forced vital capacity; FEV1/FVC forced expiratory volume 1/forced vital capacity; PEF, peak expiratory flow; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

S*afety assessment*. Adverse events occurring during the course of the treatment of the control and treatment groups were recorded and used for statistical analysis.

Statistical analysis. The SPSS 19.0 software (IBM SPSS, Armonk, NY, USA) was used for analysis. Measurement data were presented as mean ± standard deviation; paired design t-test was used for the comparison in the same group, and the independent sample t-test was used for intergroup comparison; finally, the rank-sum test was used for ranked data. $p<0.05$ indicates a statistically significant difference.

Results

General data. A total of 60 child patients diagnosed with asthmatic bronchitis in the respiratory department of our hospital from January 2012 to March 2013 meeting the inclusion criteria were selected and randomly divided into a control group (n=30) and a treatment group (n=30). No statistically significant differences were found between the two groups when taking into account general factors such as sex ratio, age, course of disease, pulmonary function indexes (FEV1, FVC, FEV1/FVC, PEF), or ESR and CRP ($p>0.05$, Table I).

Comparison of clinical effect. In the control group, 12 patients (40%) experienced marked improvement, 10 patients had some improvement (33.33%) and the treatment was not effective for 8 patients (26.67%), making the total effective rate 73.33%. By contrast, in the treatment group, 22 patients (73.73%) had marked improvement, 7 had some improvement (23.33%) and only 1 patient continued to experience symptoms without improvement (ineffective treatment in 3.33%). The total effective rate in the treatment group reached 96.67%. There were statistically significant differences between the two groups ($p<0.05$), and the curative effect was more significant in the treatment group (Table II).

Table II. Comparison of clinical effects.

	Marked improvement	Some improvement	Ineffective	Total effective rate
Control group (n=30)	12 (40.00)	10 (33.33)	8 (26.67)	22 (73.33)
Treatment group (n=30)	22 (73.33)	7 (23.33)	1 (3.33)	29 (96.67)
Total	34 (56.67)	17 (28.33)	9 (15.00)	60 (100.00)
χ^2 value		3.28		-
P-value		0.006		-

Table III. Comparison of pulmonary functions in pediatric patients before treatment (mean ± standard deviation).

Group	FEV1 (l)	FVC (l)	FEV1/FVC	PEF (l/min)
Control group	1.22±0.08	2.02±0.32	0.62±0.08	2.32±0.17
Treatment group	1.20±0.08	2.05±0.39	0.60±0.10	2.32±0.10

FEV1, forced expiratory volume; FVC, forced vital capacity; FEV1/FVC forced expiratory volume 1/forced vital capacity; PEF, peak expiratory flow.

Table IV. Comparison of pulmonary functions in pediatric patients after treatment (mean ± standard deviation).

Group	FEV1 (l)	FVC (l)	FEV1/FVC	PEF (l/min)
Control group	1.64±0.22[a]	2.48±0.26[a]	0.66±0.06[a]	3.23±0.28[a]
Treatment group	1.99±0.21[a,b]	2.82±0.36[a,b]	0.71±0.05[a,b]	4.08±0.31[a,b]

[a]P<0.05, compared with that before treatment. [b]P<0.05, compared with control group. FEV1, forced expiratory volume; FVC, forced vital capacity; FEV1/FVC forced expiratory volume 1/forced vital capacity; PEF, peak expiratory flow.

Table V. ESR and CRP level of patients in the two groups before and after treatment.

	ESR (mm/h)		CRP (mg/l)	
Group	Before treatment	After treatment	Before treatment	After treatment
Control group	44.80±21.00	32.66±16.30[a]	42.50±16.16	30.30±15.03[a]
Treatment group	46.40±16.25	26.09±16.83[a,b]	42.78±19.09	23.55±15.49[a,b]

[a]P<0.05, compared with that before treatment. [b]P<0.05, compared with control group. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Improvement of pulmonary function. There were no statistically significant differences in the pulmonary function test results between the two groups before treatment (p>0.05). However, the differences in FEV1, FVC, FEV1/FVC and PEF in the control and treatment groups before and after treatment were statistically significant (p<0.05) with improvement after treatment in both cases. The improvement was larger in the treatment group than that in the control group (p<0.05, Tables III and IV).

Determination of ESR and CRP. After treatment, the ESR and CRP level in patients of the two groups were significantly decreased, and the differences were statistically significant compared with those before treatment (p<0.05). However, both ESR and CRP level in the treatment group improved more significantly in the treatment group (p<0.05, Table V).

Safety assessment. During the whole process, 2 patients in the treatment group suffered from nausea, pharynx discomfort and other mild symptoms due to the aerosol inhalation of drugs. The symptoms were relieved after patients were asked to rest appropriately during the aerosol inhalation and rinse the mouth after the aerosol inhalation. There were no significant

differences in the number of cases experiencing adverse reactions between the two groups ($p>0.05$).

Discussion

Terbutaline sulfate is a kind of highly-selective β2 receptor stimulant (6), and it transforms adenosine triphosphate (ATP) into cyclic adenosine monophosphate mainly through the activation of adenylate cyclase (AC), increases the concentration of cAMP in cells, and the information is transferred to protein kinase A (PKA) via cAMP; through the dephosphorylation of PKA, the phosphorylation of myosin is inhibited, thereby activating the Ca^{2+} pump and causing the outflow of Ca^{2+} in cells; so the intracellular structure is changed, the sarcomere is prolonged, and the airway smooth muscles are relaxed, finally causing bronchiectasis (7). Terbutaline sulfate not only plays a prominent role in the expansion of bronchi, but also acts on epithelial cells of bronchi mucosa, which causes the movement of ions and water into the airway, enhances the clearance function of cilia, reduces sputum secretion and decreases vascular permeability, and inhibits the release of inflammatory mediators. It is particularly critical in the treatment of acute episodes of pediatric asthmatic bronchitis (8,9).

Budesonide suspension is the only glucocorticoid drug used for aerosol inhalation at present (10). As a kind of potent glucocorticoid drug, it has a good anti-inflammatory effect, so it has been widely used clinically (11). Budesonide has a strong inhibiting effect on papilla cells, neutrophilic granulocyte, lymphocytes and other cells, and histamine, leukotrienes and other media, and it can reach the target organs quickly in a higher concentration, effectively avoiding the possible adverse reactions caused by systemic administration, and its effects are significant. In terms of treating bronchiectasis, the data show that the inhalation of high-dose glucocorticoids can have a positive effect on the inflammatory parameters and key symptoms (12). Aerosol inhalation of terbutaline sulfate combined with budesonide has a good therapeutic effect on acute episode of asthma (13), and it has been widely recognized clinically because of its good safety. Budesonide can increase the sensitivity of cell membrane β2 receptor and reduce the drug resistance of β2 receptor, and the combination of both can dilate the airway, improve breathing, and give full play to the advantages of local anti-inflammation, reducing sputum secretion and promoting sputum drainage, thus, fundamentally improving the repeated infection - obstruction - infection model caused by long-term inflammation (14-16). The differences in curative effects between the treatment and control groups were statistically significant ($p<0.05$), showing that this treatment can significantly improve patients' cough, sputum and other symptoms, accelerate the disappearance of pulmonary rales and change the symptoms after treatment significantly, which takes effect quickly with fewer side effects. At the same time, it is recommended to rinse the mouth after inhalation and keep the mouth clean in the application process to prevent double infection due to the low intraoral immunity. The method is simple and easy to be accepted by the patient with high security, which can also be promoted and applied in the relatively imperfect regions (17).

Asthmatic bronchitis, mostly caused by the virus, *Mycoplasma* and *Chlamydia*, can be complicated with bacterial infection, most child patients have allergic constitution or a family history of allergies, and some can be converted to asthma (17). Pathogen damages the respiratory epithelium, exposing and damaging the airway epithelium nerve endings, causing the cholinergic nerve hypersensitivity, which induces the airway hyper-responsiveness, causes the airway smooth muscle contraction, glandular secretion and airway hyperactivity; some viruses can inhibit β2 receptor function, leading to airway smooth muscle contraction, loss of relaxation state, and leading to the surrounding small airway contraction and wheezing (18). Traditional treatment methods are mostly based on infection control coupled with systemic glucocorticoid drugs. Usually, an intravenous drip of dexamethasone is used, but the systemic application of hormone makes the distribution concentration of drug lower in the throat, trachea and bronchus (the intended target organs), and dexamethasone being a long-acting hormone which needs to be transformed in the liver before taking effect, accumulates with continuous administration producing multiple adverse reactions (18). In addition, β-hydroxysteroid dehydrogenase in airway epithelial cells can inactivate dexamethasone, so the clinical application of dexamethasone is limited (19,20).

Terbutaline is a kind of selective adrenergic β2 receptor agonist, which can relax bronchial smooth muscles, inhibit the release of endogenous spasmogenic substances and endogenous neurotransmitter-induced edema, and improve the clearance ability of bronchial mucosa cilia. Its aerosol is characterized by rapid onset, good effect and fewer adverse reactions, and has been widely used in China (6,21). Budesonide is a kind of newly-synthesized non-halogenated adrenal cortical hormone, which has a high glucocorticoid receptor binding and strong anti-inflammatory effect, twice that of beclomethasone dipropionate. It can contract the microvessel, reduce inflammation exudation, ease edema and telangiectasia, and inhibit the movement of inflammatory cells to the inflammatory site. It can also prevent the release of allergic neurotransmitters, reduce the activity of various allergic neurotransmitters, enhance the responsiveness of airway β2 adrenergic receptor, effectively eliminate airway inflammation, significantly reduce the symptoms of bronchospasm contraction, inhibit allergens and reduce the bronchial hyper-responsiveness (22). The aerosol inhalation of budesonide and terbutaline in the treatment of pediatric asthmatic bronchitis has the following advantages: i) On the basis of bronchus expansion via terbutaline, budesonide lowers the airway reaction and reduces the inflammatory exudation, and chymotrypsin decomposes the mucin in sputum, so that secretions can be discharged easily. There are fewer systemic adverse reactions, the systemic application of antibiotic can be reduced, and the drug resistance and adverse drug reactions can also be reduced (23); ii) aerosol inhalation can improve the local drug levels, 70% of drugs can act directly on the lesion, so small-dose drug treatment can produce good anti-inflammatory effects; there are fewer systemic adverse reactions caused by aerosol inhalation; 10% budesonide can be absorbed by the respiratory mucosa into the blood circulation and rapidly inactivated in the liver, thereby losing its hormone activity (24), and iii) aerosol inhalation does not require special skills, only 10-15 min needed each time, so it is simple and convenient with good compliance for patients

and low medical costs, and generally accepted by the families of the patients (25).

In conclusion, we consider that the aerosol inhalation therapy of budesonide suspension combined with terbutaline sulfate atomized liquid has definite curative effects on pediatric asthmatic bronchitis, which is worthy of clinical popularization and application.

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