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Original Research Article

Efficacy of salbutamol/ketotifen combination in the treatment of pediatric asthma, and its effect on serum levels of endothelin-1, nitric oxide, and circulating endothelial cells

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Abstract

Purpose: *To investigate the clinical efficacy of salbutamol in combination with ketotifen in the treatment of pediatric asthma, and its effect on serum levels of endothelin-1 (ET-1), nitric oxide (NO), and circulating endothelial cells (CEC).*
Methods: *Pediatric asthma patients (n = 100) admitted to Liyang Hospital of Chinese Medicine from March 2019 to March 2021, were randomly divided into control group and study group, with 50 patients in each group. Control group was treated with salbutamol, while the study group received a combination of salbutamol and ketotifen. Treatment effectiveness, lung function indicator levels, and serum levels of ET-1, NO, and CEC were determined before and after treatment. Incidence of adverse reaction (ARR), onset time, and disappearance time of clinical manifestations were recorded.*
Results: *There were no significant differences in serum levels of ET-1, NO, and CEC between the two groups before treatment, but the study group had significantly higher effectiveness, better levels of lung function indicators, and lower serum levels of ET-1, NO, and CEC ($p > 0.05$). Furthermore, the study group showed a lower ARR, and shorter onset and disappearance times of clinical manifestations than control group ($p < 0.05$).*
Conclusion: *The combination of salbutamol and ketotifen enhances the recovery of pediatric asthma patients, and thus is a promising strategy for treating pediatric asthma. However, this combination therapy merits further large-scale investigation prior to its adoption in clinical practice.*

Keywords: *Salbutamol, Ketotifen, Pediatric asthma, Serum ET-1, NO, CEC*

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INTRODUCTION

Pediatric asthma is a common respiratory disease in children, and at onset, it is often accompanied by tachypnea, cough, and a feeling of suffocation [1]. It may be life-threatening if the affected child does not receive timely treatment and care. Oxygen supply and aspiration of sputum are the main treatments for pediatric asthma [2]. However, clinical practice has shown that both methods only relieve the suffering of patients at the onset of disease, without

achieving any radical curative effect [3]. Drug treatment is necessary for reducing pediatric asthma-associated morbidity, and for improving therapy. Salbutamol is often used for treating bronchial asthma and bronchitis. It relieves asthma and prevents and treats bronchospasm [4]. Ketotifen is often used in the treatment of pediatric asthma, and clinical data have shown that it is more effective in pediatric asthma than in adult asthma [5]. It has been reported that ketotifen enhances the efficacy of salbutamol, resulting in better therapeutic outcomes in a shorter period [6]. This study was carried out to determine the clinical efficacy of salbutamol in combination with ketotifen in the treatment of pediatric asthma patients, and the effect of the combined treatment on serum levels of endothelin-1 (ET-1), nitric oxide (NO), and circulating endothelial cell (CEC).

METHODS

General information on patients

A total of 100 pediatric asthma patients (aged 1 - 8 years) who were admitted at Liyang Hospital of Chinese Medicine from March 2019 to March 2021, were randomly divided into control group and study group using the coin-tossing method, with 50 patients in each group. This study was approved by the Ethics Committee of Liyang Hospital of Chinese Medicine (approval no. 20190128), and it followed the guidelines of the Declaration of Helsinki [7]. Patient family members agreed to join the study and voluntarily signed the informed consent form.

Inclusion/exclusion criteria

Inclusion criteria

Patients who met the clinical manifestations of pediatric asthma, those aged at least 1 year, patients without congenital disease, and patients without respiratory or circulatory system diseases, were included.

Exclusion criteria

The excluded patients were those with other organ diseases, patients who did not meet the criteria for surgical treatment, and patients who used other surgical treatments at periods close to the time of study.

Treatments

Salbutamol was used for patients in the control group. Salbutamol nebulized inhalant (Weifang Zhongshi Pharmaceutical Co. Ltd; NMPA approval no. H37023628; specification: 14 g) was inhaled by the patient by pressing it twice each time, and it was administered once every 4 h when patients were under normal conditions, and once at the onset. Efficacy was monitored after 3 months of continuous administration.

The study group was treated with combination of salbutamol and ketotifen. Salbutamol was used following the same method outlined for the control group. Ketotifen (Shandong Renhetang Pharmaceutical Co. Ltd, China; NMPA approval no. H37022603; specification: 1 mg) was given at a dose of 1 mg tablet twice a day for 3 months. Effectiveness/efficacy was recorded.

Evaluation of parameters/indices

Treatment effectiveness, lung function indicator levels, serum levels of ET-1, NO, and CEC before and after treatment, adverse reaction rate (ARR), and onset and disappearance time of clinical manifestations in patients in both groups, were assessed.

Efficacy/effectiveness

If the clinical manifestations in patients disappeared, without relapse for a long time, and the patients had no adverse reaction during treatment, the treatment outcome was classified as *markedly effective*. If patients had significant relief from clinical manifestations, longer intermittent stages between two onset times, and no serious adverse reactions, the treatment was *effective*. However, if patients had no obvious mitigation of clinical manifestations, but had severe adverse reactions, the treatment was *ineffective.*

Lung functions

The measured indicators of lung function comprised forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF).

Serum indices

Serum ET-1 level was measured with radioimmunoassay, while NO level was measured using the nitrate reductase assay (NRA). The CEC level was measured by counting the amount of serum CEC after using sodium citrate anticoagulant.

Statistical analysis

The SPSS 20.0 software package was used for data processing, while GraphPad Prism 7

software (GraphPad Software, San Diego, USA) was used for graphical data. Enumeration data and measurement data are expressed as numbers and percentages (n (%)), and mean± standard deviation (SD), respectively. Differences between groups were compared using χ^2 test and *t*-test, respectively, and differences were considered statistically significant at $p < 0.05$.

RESULTS

There were no statistically significant differences in baseline data of patients between the two groups ($p > 0.05$), as shown in Table 1.

Effectiveness of treatment

The treatment effectiveness in study group was significantly higher than that in the control group ($p < 0.05$), as shown in Figure 1.

Levels of lung function indicators

Patients in the study group had significantly better lung function indicators than those in the control group ($p < 0.05$; Table 2).

Serum levels of ET-1, NO, and CEC

Figure 2 shows that ET-1 levels in the study and control groups were 166.24 ± 21.50 and 166.79 ± 21.04 ng/L before treatment, while after treatment, serum ET-1 levels were 98.74 ± 11.08 and 122.60 ± 15.53 ng/L, respectively. Figure 3 shows that NO levels in the study group and control group were 123.45 ± 17.64 and 123.96 ± 17.55 μmol/L before treatment, while after treatment, serum NO levels were 73.25 ± 10.88 and 101.22 ± 12.35 μmol/L, respectively.

As shown in Figure 4, CEC levels in the study and control groups were 8.22 ± 0.68 and 8.30 ± 0.70 n/0.9 μL, respectively, before treatment. After treatment, the corresponding serum CEC levels were 4.21 ± 0.25 and 6.11 ± 0.37 n/0.9 μL, respectively.

Incidence of adverse reactions

The ARR of study group was significantly lower than that of control group ($p < 0.05$), as shown in Table 3.

Table 1: Comparison of baseline data between the 2 groups (mean ± SD; n = 50)

Group		Study group	Control group	χ^2/t	*P*-value
Gender (male/female)		23/27	21/29	0.16	0.69
Age (years)		4.72±1.08	4.85±1.17	0.58	0.57
Height (cm)		80.28±11.06	81.00±11.09	0.33	0.75
Weight (kg)		31.49±6.68	31.40±6.81	0.07	0.95
Duration of disease (months)		8.41±1.52	8.44±1.60	0.10	0.92
Degree of asthma	Mild (n)	18	16	0.18	0.67
	Moderate (n)	14	17	0.42	0.52
	Severe (n)	18	17	0.04	0.83
Congenital disease		No	No		

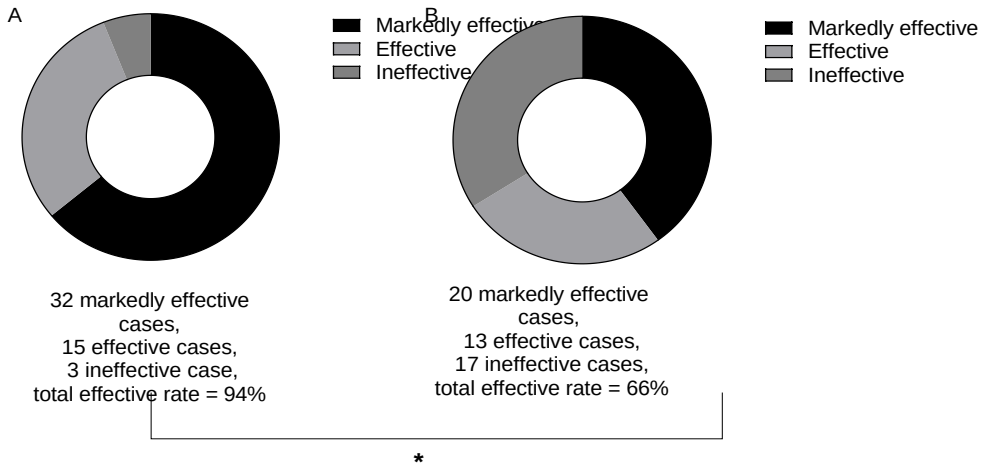

Figure 1: Between-group comparison of treatment effectiveness. *$P < 0.001$, treatment effectiveness differed significantly between the two groups ($\chi^2 = 12.25$)

Table 2: Between-group comparison of lung function indicators (n = 50)

Group	FEV1 (L)	FVC (L)	PEF (L/s)
Study	2.71±0.44	3.00±0.47	7.55±0.69
Control	2.25±0.28	2.390.33	6.43±0.51
t	6.24	7.51	9.23
P-value	<0.001	<0.001	<0.001

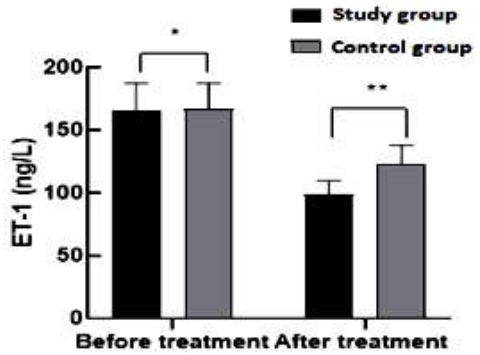

Figure 2: Between-group comparison of serum ET-1 levels. *P = 0.90, no significant difference in ET-1 levels between the two groups before treatment; **p < 0.001, serum ET-1 levels between the two groups after treatment

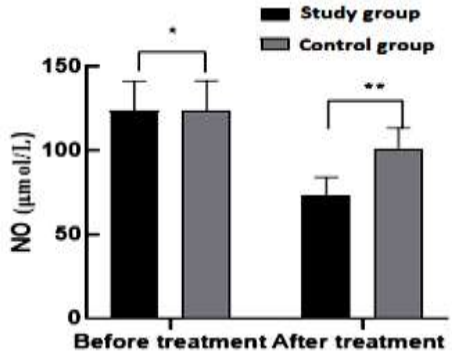

Figure 3: Between-group comparison of serum NO levels. *P = 0.89, no significant difference in NO levels between the two groups before treatment; **p < 0.001, significant difference in NO levels between the two groups after treatment

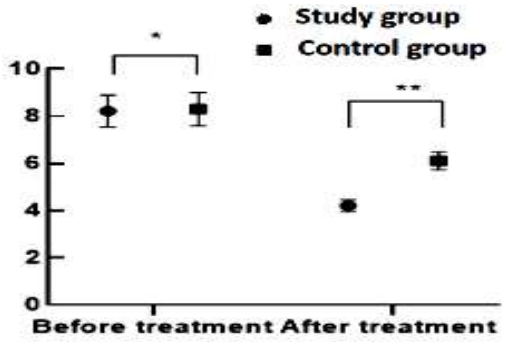

Figure 4: Between-group comparison of serum CEC levels. *P = 0.56, no significant difference in CEC levels between the two groups before treatment; **p < 0.001, significant difference in CEC levels between the two groups after treatment

Table 3: Between-group comparison of ARR

Group	Nausea	Intense cardiac activity	Fatigue	Total incidence (%)
Study	1	0	1	4%
Control	3	1	4	16%
χ^2				4.00
P-value				0.046

Onset and disappearance times of clinical manifestations

The study group had significantly shorter onset time and disappearance time of clinical manifestations than the control group *(p < 0.05)*, as shown in Table 4.

Table 4: Between-group comparison of onset time and disappearance time of clinical manifestations (mean ± SD, n = 50)

Group	Onset time (days)	Extinction time of clinical manifestations (days)
Study	0.97±0.02	12.68±1.69
Control	1.47±0.11	15.56±1.99
T	31.62	7.80
P-value	<0.001	<0.001

DISCUSSION

Asthma is a chronic respiratory disease caused by multiple factors such as climate, temperature, excessive exercise, heavy heart load, and allergies [8,9]. The main manifestations of asthma are shortness of breath and distress. Prompt remedy is necessary for patients at the onset of the disease. Currently, drug intake is the most effective treatment for asthma in clinics. Some drugs are suitable for rescue at the onset of diseases, and some drugs are indicated for treatment at non-emergency times [10,11].

Salbutamol aerosol is used against asthma both at onset period and at premorbid period. It is a selective β2 receptor agonist which relaxes smooth muscles and mitigates bronchospasm. When spray-inhaled, it directly acts on the trachea and bronchi, increases the speed of secretions discharged from the airway, and prevents bucking and other symptoms on trachea caused by blockage of secretions [12,13]. Ketotifen exerts its action mainly on cell membrane tissue and maintains the stability of smooth muscle [14]. In a way, ketotifen enhances the potency of salbutamol. Hence, this study investigated the clinical effects of salbutamol, alone and in combination with ketotifen, on pediatric asthma patients.

The clinical efficacy, degree of lung function improvement, serum levels of ET-1, NO and CEC, as well as ARR of study group treated with combination of salbutamol and ketotifen were significantly superior to those of the control group that was given salbutamol alone. It is known that ET-1 increases interleukin level and activates phosphodiesterase in humans, and its elevation causes respiratory tract injury, resulting in exacerbation of asthma, which is detrimental to recovery of patients [15]. When NO reacts with oxygen, a free radical that aggravates inflammatory reactions in patients is generated. Higher serum NO contents produce more free radicals, causing greater damage to the airway tissue [16]. The level of CEC is a reflection of the degree of damage to pulmonary vascular endothelial cells. In effect, higher CEC levels imply more severe damage in pulmonary vascular endothelial cell, leading to more intense inflammatory manifestations in patients and aggravation of asthma [17].

In the present study, after treatment, serum levels of ET-1, CEC and NO in patients in study group were decreased significantly, and the decreases were greater than those in control group. Therefore, it may be reasonably concluded that patients in study group had a clearly lowered risk of asthma after treatment. In a previous study [18], it was reported that pediatric asthma patients given combination treatment with salbutamol and ketotifen had significantly improved serum levels of pro-inflammatory factors and improved lung function. The findings in this study are consistent with this report, thereby indicating the reliability of the results obtained here.

Limitations of this study

This study used a single source of cases and small sample size. It is not a multi-center and double-blind study. Thus, the findings may have elements of bias. Moreover, the study did not include follow-up disease management of long-term efficacy in patients. Therefore, there is need to improve the study design, increase sample size, carry out multi-center research, and extend follow-up observation time, in order to obtain more accurate clinical data.

CONCLUSION

This study has demonstrated the therapeutic effect of salbutamol in combination with ketotifen, on pediatric asthma patients. The combination treatment significantly reduces serum levels of ET-1, CEC and NO, thereby enhancing the recovery of patients. However, further clinical trials are recommended before application in clinical practice.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Wei Jiang and Yu Di conceived and designed the study, and drafted the manuscript. Wei Jiang, Ye Wang, and Yu Di collected, analyzed and interpreted the data. Ye Wang and Yu Di revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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