

The role of hypodermic injection with low dose of adrenaline in emergency treatment of severe asthma

Objective: To explore the effect of subcutaneous injection of low dose adrenaline on emergency treatment of severe asthma.

Methods: A total of 124 cases with severe asthma treated in our hospital from January 2016 to April 2017 were selected as the subjects and randomly divided into observation group and control group according to different emergency treatment methods, 62 cases in each group. The patients in the control group were given conventional emergency salvage after admission while those the observation group were injected low dose adrenaline with the total dose no more than 1mg. The changes and improvements in symptoms and signs such as blood oxygen saturation, heart rate and respiration were recorded in the two groups before, during and after treatment. And airway function as well as serum levels of inflammatory factors of IL-6, IL-8, IL-17 and TNF- α were compared between the two groups.

Results: Before treatment, there was no significant difference in the scores of RR, HR, SaO₂ between the two groups ($P>0.05$), while at 10 and 30 minutes after treatment, compared with the control group, the RR and HR scores were significantly lower ($P<0.001$) and SaO₂ significantly higher ($P<0.001$) in the observation group. During the treatment, the total effective rate in the two groups was on the rise, while at 30 minutes after treatment, the total effective rate was significantly higher in the observation group than in the control group ($Z=35.168$, $P<0.001$). Before treatment, no significant difference was found between the two groups in TEF 25%, TEF 50%, TEF 75% and FEV1/FV ($P>0.05$), while after treatment, the levels of TEF 25%, TEF 50%, TEF 75% and FEV1/FVC were increased in the two groups, more significantly in the observation group than in the control group, and the difference was statistically significant ($P<0.05$). Before treatment, there was no significant difference between the two groups in the levels of IL-6, IL-8, IL-17 and TNF- α ($P>0.05$), while after treatment, the levels of IL-6, IL-8, IL-17 and TNF- α were decreased in the two groups, more significantly in the observation group than in the control group, and the differences were statistically significant ($P<0.05$).

Conclusion: Compared with conventional methods in emergency severe asthma, the treatment with small dose of epinephrine is of rapid onset and has better therapeutic effects of suppressing cough, relieving spasm, relaxing smooth muscle as well as reducing capillary permeability, besides, the method, with few adverse reactions, good tolerance as well as safety enables to improve SaO₂ as well as airway function and lower serum inflammatory factors in patients, thus worthy of clinical application and spreading.

Keywords: emergency • severe asthma • small dose adrenaline • airway function • serum inflammatory factors

Introduction

According to the book "Neijing", asthma is also known as wheeze and wheezing asthma, resulting from retained phlegm in lung plus invasion of exogenous pathogen, improper diet as well as emotional maladjustment

and resulting in obstructed airway. In modern medicine [1] bronchial asthma is a syndrome caused by airway inflammation and a complex pathophysiological process involving many inflammatory cells such as pathophysiology of eosinophils, mast cells, T lymphocytes, neutrophils, airway

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epithelial cells with the induction by endogenous and exogenous factors. Its main pathological changes include contracture of small bronchial smooth muscle, dilation of blood capillary, increased permeability, rising secretion of mucous glands, edema of bronchioles mucosa and formation of mucus hitch with its main symptoms manifested as recurrent wheezing, shortness of breath, chest tightness or cough, which often take place and go worse at night or in the early morning. At present, the treatment of asthma is mainly aimed to control symptoms to avoid deterioration, maintain lung function as normal as possible and prevent irreversible airflow obstruction as well as death [2]. Related studies have proved that industrial progress, modern lifestyle and rapid change of ecological environment are important factors leading to a sharp increase in the incidence of asthma [3]. Severe asthma, as a common critical disease in emergency room, has high morbidity and mortality, and if failing to be treated timely and effectively, it will seriously threaten the life safety of patients [4]. The successful treatment of severe asthma with adrenaline has been recently reported, but there is no detailed report about the selection of the treatment time, medication method as well as curative effect and about the impact of adrenaline on airways function and on the level of serum inflammatory factors in patients [5]. In view of this, we conducted a research in this field to explore the effect of rescue treatment with small dose adrenaline on airway function

as well as serum inflammatory factors in patients with severe asthma, with the details now reported as follow.

Data and methods

General data

A total of 124 cases with severe asthma treated in our hospital from January 2016 to April 2017 were selected as the subjects, including 72 males and 52 females aged 18~68 with an average age of (37.4 ± 3.2) years. All the studies were approved by the ethical committee of affiliated hospital of north Sichuan medical college and informed consent was obtained from all patients.

Inclusion criteria

- I. Patients met the criteria for diagnosis of asthma formulated by Chinese Medical Association in 2008 and were confirmed with the disease of severe or over severe degree according to the severity grading of asthma attack (TABLE 1).
- II. Patients showed symptoms like lethargy, irritability, coma or insanity;
- III. Patients spoke in a monosyllabic way and failed to finish a sentence due to dyspnea or orthopnea;
- IV. Patients had ventilator-assisted breathing and three concave signs;
- V. Lung auscultation showed diffuse and loud wheezing in the double lungs.

Table 1. Grading of severity of condition in acute attacks of asthma

Clinical feature	Mild	Moderate	Severe	Over severe
Shortness of breath	walking or going upstairs	taking some movements	having a rest	
Body position	supine position	sitting posture	orthopnea	
Way of speaking	consecutive sentence	separate phrase	separate word	inability to speak
Mental state	possible anxiety in quiet	moderate anxiety or irritability	frequent anxiety or irritability	somnolence or mental confusion
Sweating	without	with	sweating profusely	
Breathing rate	mild increase	increase	>30times/min	
Ventilator-assisted breathing activity and three concave signs	always without	with	always with	chest and abdominal paradoxical movement
Wheeze	scattered and in the late of respiration	loud and diffuse	loud and diffuse	weakened or even disappearing
Pulse rate(time/min)	<100	100~120	>120	slower or irregular
Paradoxical pulse	without	with	always with	without, respiratory muscle fatigue
Oxygen partial pressure (inspiring air, mmHg)	normal	≥60	<60	<60
PaCO ₂ (mmHg)	<45	≤45	>45	>45
SaO ₂ (inspiring air, %)	>95	91~95	≤90	≤90

Exclusion criteria

- I. Patients refused to cooperate with the treatment;
- II. Patients had pneumothorax and severe infection complications;
- III. Patients had cardiogenic asthma, mental disease, arrhythmia, organic heart disease, severe immune system or endocrine system diseases such as diabetes, hypertension and hyperthyroidism.

The selected patients were randomly divided according to emergency treatment methods into the observation group and the control group with 62 cases in each group. There was no significant difference between the 2 groups in age, gender and degree of asthma ($P>0.05$).

Treatment methods

The emergency patients were examined after admission on vital signs such as blood pressure and pulse, oxygen was given by mask, venous access was established and ECG monitoring was conducted to closely observe the changes of symptoms and signs in patients. Routine emergency rescue was performed in the control group: patients were intravenously injected with aminophylline (Modern Shanghai Hasen Pharmaceutical Co. Ltd., specifications 2 mL: 0.25 g) 0.5 g+500 mL NaCl, plus with 80 mg methylprednisolone (Methylprednisolone Sodium Succinate for Injection, Pfizer Manufacturing Belgium NV specifications: bottle/40 mg) for intramuscular injection. Patients in the observation group were treated with small doses of epinephrine: besides the treatment in the control group, patients were given subcutaneous injection of 0.3 mg epinephrine (Shanxi Zhendong Tai Sheng Pharmaceutical Co. Ltd., specifications 0.5 mg: 0.5 mL), 10 min later, the changes (relieved or not) in symptoms and signs of patients were observed and those with no effective response were repeatedly injected with epinephrine of the same dose, with the total dose no more than 1 mg. The changes of symptoms such as blood oxygen saturation, heart rate and respiration were observed in the two groups before and after the treatment. After being successfully treated, patients were given conventional consolidation and anti-inflammation treatments.

Observation index and evaluation of curative effect

1. The changes and improvements in symptoms and signs such as blood oxygen saturation, heart rate and respiration were recorded in the two groups before, during and after treatment. The judgment standard for curative effect: patients were scored in terms of irritability, cyanosis, sweating, wheezing, blood oxygen saturation, heart rate and respiration:
 - i. The scores of irritability, cyanosis and sweating symptoms were classified as 0, 1, 2, 3 and 4 respectively corresponding to non, mild, moderate and severe and over severe degree;
 - ii. HR: the scores of HR were classified as 0, 1, 2, 3 and 4 respectively corresponding to 60-99 times per minute, 100-120 times per minute, over 120 times per minute, under 60 times per minute and over 150 times per minute;
 - iii. RR: the scores of RR were classified as 0, 1, 2, 3 and 4 respectively corresponding to 12-23 times per minute, 24 -30 times per minute, over 30 times per minute, under 12 times per minute and over 40 times per minute;
 - iv. The blood oxygen saturation (SaO_2): the scores of SaO_2 were classified as 0, 1, 2, 3 and 4 respectively corresponding to 95% ~ 100%, 90% ~ 95%, 60% ~ 90% and 60% below.
 - v. The evaluation for improvements of symptoms and signs in the patients after treatment: (1) Significantly effective: heart rate was 100 beats/min, respiratory rate was 24 times/min below, patients had stable emotion with no dyspnea and with decreased or even disappeared wheeze; (2) Effective: heart rate was within 120 beats/min, respiratory rate was 30 times/min below, patients had moderately stable emotion with certain alleviated but still existing dyspnea and obviously decreased wheeze;(3) Invalid: there were no significant improvements in heart rate, respiratory rate, emotional state, dyspnea, wheeze or auscultation.

The effective rate of treatment = [the number of significantly effective cases + the number of effective cases]/the total number of cases] * 100%.

- Airway function: lung function was detected in the two groups of patient before and after treatment; the expiratory flow rates respectively at the tidal volume of 25%, 50% and 75%, referred to as TEF 25%, TEF 50% and TEF 75%, as well as the forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were recorded with the ratio of FEV1 to FVC (FEV1/FVC) calculated, the detection was conducted by using Germany Master Scope pulmonary function testing instrument.
- Serum inflammatory factors: the fasting venous blood were collected in the two groups before and after treatment with the serum specimens centrifuged from blood samples in freezing conservation. The serum levels of IL-6, IL-8, IL-17 and TNF- α were determined by enzyme linked immunosorbent assay, and the kit was purchased from Shenzhen Jing Mei biological Co. Ltd.

Statistical treatment

SPSS 21 statistical software was used for data processing, the count data were expressed as "percentage" and assessed by χ^2 test and rank sum test was used for ranked data (Z test), the measurement data of normal distribution were described as " $(\bar{x} \pm s)$ " and analyzed

by T test, F test was used for time gradient data, and $P < 0.05$ suggested that there was difference of statistical significance.

Results

Comparison of related indexes during the treatment between the two groups

Before treatment, there was no significant difference in the scores of RR, HR, SaO₂ between the two groups ($P > 0.05$), while at 10 and 30 minutes after treatment, compared with the control group, the RR and HR scores were significantly lower ($P < 0.001$) and SaO₂ significantly higher ($P < 0.001$) in the observation group, as shown in **TABLE 2**.

Comparison of curative effect between the two groups during the treatment

During the treatment, the total effective rate in the two groups was on the rise, while at 30 minutes after treatment, the total effective rate was significantly higher in the observation group than in the control group ($Z = 35.168, P < 0.001$), as shown in **TABLE 3**.

Comparison of airway function between the two groups

Before treatment, no significant difference was found between the two groups in TEF 25%, TEF 50%, TEF 75% and FEV1/FV ($P > 0.05$), while after treatment, the levels of TEF 25%, TEF 50%, TEF 75% and FEV1/FVC were increased in the two groups, more significantly in the observation group than in the control group, and the difference was statistically significant ($P < 0.05$), as shown in **TABLE 4**.

Table 2. changes in the observed indexes during the treatment in the two groups ($\bar{x} \pm s$)

Groups	time	RR(time-min-1)	HR(time-min-1)	Symptoms score (score)
Control group (n=62)	before treatment	39.78 \pm 1.14	125.47 \pm 2.25	13.67 \pm 0.25
	at 10 min	31.66 \pm 2.17	122.34 \pm 1.93	9.87 \pm 2.14
	at 30 min	20.55 \pm 2.08	93.35 \pm 1.79	7.37 \pm 1.68
Observation group (n=62)	before treatment	37.84 \pm 1.53	125.32 \pm 2.47	13.42 \pm 1.06
	at 10 min	26.24 \pm 1.73#	116.11 \pm 1.36#	7.02 \pm 1.98#
	at 30 min	15.85 \pm 1.02#	90.04 \pm 3.18#	2.87 \pm 1.43#

Note: compared with the control group, #P < 0.001.

Table 3. Comparison of curative effect between the two groups during the treatment

Groups	Time	Invalid case (n)	Significantly effective case(n)	Effective case (n)	Total effective rate (%)
Control group(n=62)	at 10 min	32	11	19	48.39
	at 30 min	9	43	10	85.48
Observation group(n=62)	at 10 min	30	12	20	51.61
	at 30 min	1	56	5	98.39#

Note: compared with the control group, #P<0.001.

Comparison of inflammatory factors between the two groups

Before treatment, there was no significant difference between the two groups in the levels of IL-6, IL-8, IL-17 and TNF-a ($P>0.05$), while after treatment, the levels of IL-6, IL-8, IL-17 and TNF-a were decreased in the two groups, more significantly in the observation group than in the control group, and the differences were statistically significant ($P<0.05$), as shown in **TABLE 5**.

Summary

Before treatment, there was no significant difference in the scores of RR, HR, SaO₂ between the two groups ($P>0.05$), while at 10 and 30 minutes after treatment, compared with the control group, the RR and HR scores were significantly lower ($P<0.001$) and SaO₂ significantly higher ($P<0.001$) in the observation group; during the treatment, the total effective rate in the two groups was on the rise, while at 30 minutes after treatment, the total effective rate was significantly higher in the observation group than in the control group ($Z=35.168, P<0.001$). Before treatment, no significant differences was found between the two groups in TEF 25%, TEF 50%, TEF 75% and FEV1/FV ($P>0.05$), while after treatment, the levels of TEF 25%, TEF 50%, TEF 75% and FEV1/FVC were increased in the two groups, more significantly in the observation group than in the control group, and the difference was statistically significant ($P<0.05$); and before treatment, there was no significant difference between the two groups in the

levels of IL-6, IL-8, IL-17 and TNF-a ($P>0.05$), while after treatment, the levels of IL-6, IL-8, IL-17 and TNF-a were decreased in the two groups, more significantly in the observation group than in the control group, and the differences were statistically significant ($P<0.05$). According to these results, the treatment of severe asthma with small dose epinephrine, compared with other conventional emergency methods, is of rapid onset and has better therapeutic effects of suppressing cough, relieving spasm, relaxing smooth muscle as well as reducing capillary permeability, besides, the method, with few adverse reactions, good tolerance as well as safety, enables to improve SaO₂ as well as airway function and lower serum inflammatory factors in patients, thus worthy of clinical application and spreading.

Discussion

The incidence of asthma has been gradually increasing in recent years along with the aggravation of environmental pollution. At present, the disease poses a serious threat to people’s health and safety. Asthma is a chronic airway inflammation, can increase airway response in patients with such common symptoms as chest tightness, shortness of breath and wheezing, which are more obvious in the early morning and at night, usually associated with airflow obstruction. Severe asthma has urgent onset, if not effectively treated in time, it will threaten patient’s lives. Main measures for the treatment of severe asthma in clinic

Table 4. Comparison of airway function between the two groups

Groups	TEF 25% (ml/s)		TEF 50% (ml/s)		TEF 75% (ml/s)		FEV1/FVC	
	Before treatment	After treatment						
Control group (n=62)	78.42 ± 7.06	84.05 ± 6.43	107.78 ± 8.23	117.13 ± 9.63	124.77 ± 10.18	133.65 ± 9.67	75.07 ± 7.35	80.48 ± 8.15
Observation group (n=62)	78.21 ± 7.17	90.22 ± 7.67	107.44 ± 9.16	126.11 ± 9.36	124.52 ± 10.24	159.76 ± 9.12	75.12 ± 7.24	90.11 ± 7.67
t	0.672	6.125	0.523	7.668	0.196	7.339	0.742	6.892
p	0.451	0.024	0.602	0.021	0.621	0.022	0.623	0.025

Table 5. Comparison of inflammatory factors between the two groups

Groups	IL-6 (ng/L)		IL-8 (µg/L)		IL-17 (ng/L)		TNF-α(ng/L)	
	Before treatment	After treatment						
Control group (n=62)	169.52 ± 13.42	144.32 ± 21.75	52.79 ± 12.16	36.67 ± 7.21	9.63 ± 1.44	7.93 ± 1.05	1204.77 ± 78.15	716.24 ± 73.06
Observation group (n=62)	168.65 ± 14.14	126.37 ± 20.18	52.43 ± 11.75	24.76 ± 6.12	9.62 ± 1.32	5.07 ± 1.04	1205.62 ± 82.47	508.65 ± 38.92
t	0.893	7.445	0.509	6.092	0.238	7.041	0.933	5.956
p	0.325	0.019	0.415	0.026	0.726	0.018	0.548	0.031

include reducing airway resistance, lowering the permeability of capillaries as well as local anti-inflammation [6-8]. Aminophylline and methylprednisolone are commonly used for treatment of the disease in which methylprednisolone is a glucocorticoid drug that inhibits the activation and migration of inflammatory cells *in vivo* and can enhance the β_2 receptor responsiveness in respiratory tract so as to effectively relieve asthma [9,10]. Aminophylline can regulate the immunity and expand the bronchus in patients [11]. As a result, these two drugs are frequently used in the emergency treatment of disease.

The epinephrine β_2 receptor is widely distributed in alveolar wall, surface of smooth muscle cells in submucosa glands as well as the surface of the inflammatory cells [12]. Epinephrine, by binding with β_2 receptor located on the surface of mast cell membrane, can reduce the release of the detached particles and inhibit the release of allergic substances like histamine. In addition, adrenaline can promote the receptor excitement, reduce the permeability of blood vessels and facilitate β_2 receptor agonist to play its role in the airway. In the study, small dose adrenaline was used in the observation group, presenting excitatory effects of both β receptor and α receptor. In the emergency treatment after admission, the total effective rate in the observation group showed a significantly increasing trend, suggesting that small dose adrenaline can obviously control and relieve the symptoms of severe asthma with good efficacy. Furthermore, the scores of RR and HR were lower in the observation group than in the control group during the treatment, proving that the small dose of adrenaline can decrease RR and HR scores more significantly than aminophylline and methylprednisolone. Besides, the SaO_2 level and the total effective rate within 30min were both significantly higher in the observation group on the whole, indicating that within 30 min of emergency salvage, the treatment for severe asthma with small doses of adrenaline can significantly enhance curative efficacy and works faster in the basis of conventional therapy.

Bronchial hyperresponsiveness and chronic airway inflammation are the main pathological changes in asthma, the airway function in sufferers decreases significantly due to airflow obstruction and airway spasm, TEF 25%, TEF 50% as well as TEF 75% are

main reflections of small airway spasm, and FEV1/FVC can effectively reflect the degree of airflow limitation [13]. The results of this study showed that the levels of TEF 25%, TEF 50%, TEF 75% and FEV1/FVC were increased in both groups, but higher in the observation group than in the control group ($P<0.05$), indicating that airway spasm and airflow limitation are improved more significantly in the patients from the observation group.

IL-6 is mainly activated by monocyte as well as macrophage and IL-8 is mainly released by mast cells as well as eosinophilia, both of which can mediate inflammatory response, increase mucus secretion and induce airway hyperresponsiveness [14]. IL-17 is secreted by T lymphocytes, which activates inflammatory cells and promotes their aggregation in the airway so as to induce asthma. TNF- α , an important inflammatory factor with multiple effects, can stimulate inflammatory cells to gather in airway tissue and lead to the inflammatory cascade with the role of other factors like IL-6 and IL-8, thereby worsening inflammation lesions and inducing or aggravating asthma [15]. The results of this study showed that the levels of IL-6, IL-8, IL-17 and TNF- α in the two groups were decreased after treatment, with lower levels in the observation than in the control group ($P<0.05$). This illustrates that compared with the conventional treatment of aminophylline and methylprednisolone, small dose of adrenaline can significantly lower the levels of inflammatory factors in patients.

To sum up, in comparison with conventional methods in the emergency case of severe asthma, the treatment with small dose of epinephrine is of rapid onset and has better therapeutic effects of suppressing cough, relieving spasm, relaxing smooth muscle as well as reducing capillary permeability, besides, the method, with few adverse reactions, good tolerance as well as safety, enables to improve SaO_2 as well as airway function and lower serum inflammatory factors in patients, thus worthy of clinical application and spreading.

References

1. Trejo Bittar HE, Yousem SA, Wenzel SE. Pathobiology of severe asthma. *Ann. Rev. Pathol.* 10(1), 511-545 (2015).
2. Huang YJ, Nariya S, Harris JM *et al.* The airway microbiome in patients with severe asthma: associations with disease features and severity. *J. Allergy. Clin. Immunol.* 136(4), 874-884 (2015).

3. Hanania NA, Noonan M, Corren J *et al.* Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax*. 70(8), 748-756 (2015).
4. Smith SG, Chen R, Kjarsgaard M *et al.* Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia. *J. Allergy. Clin. Immunol.* 137(1), 75-86 (2016).
5. Wiebe K, Rowe BH. Nebulized racemic epinephrine used in the treatment of severe asthmatic exacerbation: a case report and literature review. *Canadian. J. Emer. Med.* 9(4), 304-308 (2007).
6. Papiris DSA, Manali ED, Kolilekas L *et al.* Acute severe asthma. *Drugs*. 69(17), 2363-2391 (2009).
7. Mitra A, Bassler D, Goodman K *et al.* Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. *Cochrane. Database. Sys. Rev.* 1(1), 101-146 (2005).
8. França-Pinto A, Mendes FA, de Carvalho-Pinto RM *et al.* Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomised controlled trial. *Thorax*. 70(8), 732-739 (2015).
9. Pedersen BK, Laursen LC, Lervang HH *et al.* Methylprednisolone pulse therapy in severe acute asthma. *Allergy*. 42(2), 154-157 (1987).
10. Engel T, Dirksen A, FråLund L *et al.* Methylprednisolone pulse therapy in acute severe asthma: A randomized, double-blind study. *Allergy*. 45(3), 224-230 (2010).
11. Lloyd SR, Sharma A. Aminophylline infusion in acute severe asthma: where do we go from here?. *Can. Fam. Phys.* 36(5), 917-920 (1990).
12. Putland M, Kerr D, Kelly AM. Adverse events associated with the use of intravenous epinephrine in emergency department patients presenting with severe asthma. *Ann. Emer. Med.* 47(6), 559-563 (2006).
13. Adoun M, Frat J P, Doré P *et al.* Comparison of nebulized epinephrine and terbutaline in patients with acute severe asthma: a controlled trial 1. *J. Crit. Care.* 19(2), 99-102 (2004).
14. Campo P, Rodríguez F, Sánchez-García S *et al.* Severe asthma workgroup-SEAIC asthma committee. Phenotypes and endotypes of uncontrolled severe asthma: new treatments. *J. Inves. Aller. Clin. Immunol.* 23(2), 76-88 (2013).
15. Song C, Luo L, Lei Z *et al.* IL-17-producing alveolar macrophages mediate allergic lung inflammation related to asthma. *J. Immunol.* 181(9), 6117-6124 (2008).