

## Original Research Article

# Efficacy of combined nebulized aerosol inhalation and pulmicort respules in the treatment of emergency pediatric laryngitis, and its effect on adverse reactions

Huazhen Wang<sup>1</sup>, Naiqin Han<sup>1</sup>, Nana Xu<sup>2</sup>, Qingjiao Wu<sup>3</sup>, Xiaoqing Dong<sup>4</sup>, Zhen Han<sup>4\*</sup>

<sup>1</sup>Department of Pediatrics, <sup>2</sup>Department of Obstetrics, <sup>3</sup>Department of Colour Ultrasound, <sup>4</sup>Department of Emergency Surgery, The People's Hospital of Zhangqiu District, Jinan 250200, China

\*For correspondence: **Email:** [jingyanxiebianwx@163.com](mailto:jingyanxiebianwx@163.com)

Sent for review: 20 September 2021

Revised accepted: 24 May 2022

### Abstract

**Purpose:** To determine the efficacy of combined use of nebulized epinephrine inhalation and pulmicort respules in the treatment of emergency pediatric laryngitis and, its impact on the incidence of adverse reactions.

**Methods:** A total of 100 cases of pediatric laryngitis admitted in The People's Hospital of Zhangqiu District between December 2018 and December 2020 were randomly assigned (1:1) to receive either pulmicort respules (control group) or pulmicort respules plus nebulized epinephrine inhalation treatment (study group). Outcome measures included level of effectiveness and adverse reactions.

**Results:** Pulmicort respules plus nebulized epinephrine inhalation treatment was associated with shorter remission time for dyspnea, wheeze, croup, and hoarseness versus pulmicort respules. The combination treatment produced higher total effectiveness of 96 % than pulmicort respules with total effectiveness of 82 % ( $p < 0.05$ ). After treatment, both groups had decreased serum levels of interleukin-8 (IL-8), IL-6, C-reactive protein (CRP), and tumor necrosis factor (TNF)- $\alpha$ , with markedly lower levels in the group given nebulized epinephrine inhalation in combination with pulmicort respules ( $p < 0.05$ ). Compared with patients given pulmicort respules only, those given combination treatments had a significantly shorter hospitalization time and a lower incidence of adverse reactions (4 vs 8 %;  $p < 0.05$ ).

**Conclusion:** Nebulized epinephrine inhalation in combination with pulmicort respules has high safety in the treatment of emergency pediatric laryngitis, and it significantly reduces clinical symptoms, inflammatory response, and hospital stay. However, further clinical trials are required prior to its use in clinical practice.

**Keywords:** Nebulized epinephrine inhalation, Pulmicort respules, Pediatric laryngitis, Efficacy, Adverse reactions

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

## INTRODUCTION

Pediatric laryngitis is a common acute infection in the upper respiratory tract, and it falls into the

category of diffuse inflammation of laryngeal mucosa. The incidence of pediatric laryngitis is associated with viruses and bacteria, with higher occurrence among children under-5 years old,

and often in spring [1,2]. The disease is of rapid onset, and it is characterized by symptoms such as dyspnea, wheeze, hoarseness, and croup [3].

Stenosis of the laryngeal cavity coupled with weak cartilage leads to increased lymphatic vessels and glandular tissues of laryngeal mucosa in children. Swelling of the laryngeal mucosa prompted by inflammation gives rise to laryngeal edema and obstruction. If not treated in time, the disease may be life-threatening [4]. In clinical practice, the treatment is aimed at quickly reducing laryngeal edema, inhibiting laryngeal spasms, and relieving inflammatory responses [5]. The efficacy of the combination of nebulized epinephrine inhalation and pulmicort respules in the treatment of emergency pediatric laryngitis and its impact on the adverse reactions were assessed in this study.

## METHODS

### General patient information

In this retrospective analysis, 100 pediatric laryngitis patients treated in The People's Hospital of Zhangqiu District between December 2018 and December 2020 were recruited. They were randomly assigned to a control group and an experimental group. The control group had 26 males and 24 females, aged 1 - 6 years, with a mean age of  $2.8 \pm 1.4$  years. The study group had 27 males and 23 females, aged 1 - 5 years, with a mean age of  $2.5 \pm 1.3$  years. The two groups were similar in general information.

### Inclusion criteria

Patients in the following categories were included in the study: those who met relevant diagnostic criteria for acute laryngitis; patients with symptoms such as hoarseness, dyspnea, wheeze, and croup, and laryngeal obstruction on physical examination, and those with complete clinical data and good compliance with treatment. The study was approved by the Ethics Committee of The People's Hospital of Zhangqiu District (approval no. ZQH20180925). Undersigned informed consent has been obtained from the patients. This study was conducted in strict accordance with the protocol of Helsinki Declaration [6].

### Exclusion criteria

The following categories of patients were excluded: patients who had other severe organic diseases; those who were allergic to aerosol inhalation, patients who had laryngeal-tracheobronchial and throat congenital diseases,

and those whose conditions were complicated with severe coagulation dysfunction.

### Study design and treatments

The two groups received antipyretic, respiratory tract patency assurance, antibiotics, sputum elimination, and cough relief treatments after admission. In addition, anti-inflammatory treatment was given to patients based on their peripheral hemogram. The control group was given pulmicort respules (AstraZeneca Pty Ltd, SFDA approval No. H20140475; specification: 1 mg/2 mL). In essence, 2 mL of Pulmicort respules in 4 - 5 mL of 0.9 % sodium chloride was administered in oxygen-driven nebulization, once in the morning and once in the evening, each time for 15 - 20 min. In addition, the study group received epinephrine (Beijing Shuanghe Pharmaceutical Co. Ltd, SFDA approval no: H11021685, specification: 1 mg/mL). Epinephrine and 2 mL of pulmicort respules were added to 5 mL of 0.9 % sodium chloride and given as oxygen-driven aerosol inhalation, once in the morning and once in the evening, each time for 15 - 20 min. Children in the two groups received continuous treatment for 5 days.

### Evaluation of indicators/parameters

The times taken for the remission of dyspnea, wheeze, croup, and hoarseness were observed and recorded. Adverse reactions and hospitalization time were also noted and recorded.

### Clinical efficacy

Clinical efficacy was classified into three types.

**Markedly effective:** This applied to the disappearance of symptoms such as dyspnea, wheeze, croup, and hoarseness, as well as laryngeal obstruction within 24 h of treatment.

**Effective:** This applied to significant mitigation of clinical symptoms and laryngeal obstruction within 24 h of treatment.

**Ineffective:** Treatment was deemed ineffective if there were no reductions in the clinical symptoms and laryngeal obstruction within 24 h of treatment, or if these clinical symptoms rather became worse.

Total treatment effectiveness (%) was determined as the sum of *markedly effective* and *effective cases*, expressed as a percentage of total cases.

## Inflammatory factors

Two milliliters of fasting peripheral venous blood were collected before treatment, and 5 days after treatment. The samples were placed at 4 °C for 2 h before centrifuging at 3000 rpm for 15 min to obtain sera. Serum levels of IL-8, IL-6, TNF- $\alpha$ , and CRP were determined using immunofluorescence assay kits as per the instructions in the kit manuals.

## Statistical analysis

The SPSS 20.0 software was used for data analyses, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was employed for graphics plotting. Count data are expressed as numbers and percentages {n (%)} and analyzed using the chi-square test. Measurement data are expressed as mean  $\pm$  SD and analyzed using Student's *t*-test. Values of *p* < 0.05 indicated statistically significant differences.

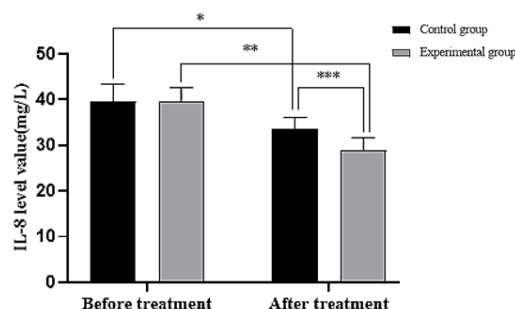
## RESULTS

### Remission time

Compared with the group given pulmicort respules alone, the combination treatment group had a shorter remission time for dyspnea, wheeze, croup, and hoarseness (*p* < 0.05, Table 1).

### Clinical efficacy

Pulmicort respules plus nebulized epinephrine inhalation treatment was associated with significantly higher treatment effectiveness (96 %) versus pulmicort respules alone (82 %, *p* < 0.05, Table 2).



**Figure 1:** Comparison of serum IL-8 levels between the two groups (mean  $\pm$  SD). \**P* = 0, comparison of IL-8 levels before and after treatment in the control group; \*\**p* = 0, IL-8 levels before vs IL-8 levels after treatment in the study group; \*\*\**p* = 0, comparison of IL-8 levels between the two groups after treatment

### Serum IL-8 levels

The two groups had no obvious difference in IL-8 levels before treatment (*p* > 0.05). Post-treatment, IL-8 level was decreased in both groups, with a markedly lower level in the group given combination treatment (*p* < 0.05) (Figure 1). The levels of IL-8 in the control group before and after treatment were 39.71  $\pm$  3.73 and 33.70  $\pm$  2.46 mg/L, respectively; IL-8 levels in the study group before and after treatment were 39.54  $\pm$  3.19 and 28.96  $\pm$  2.63 mg/L, respectively.

### Serum IL-6 levels

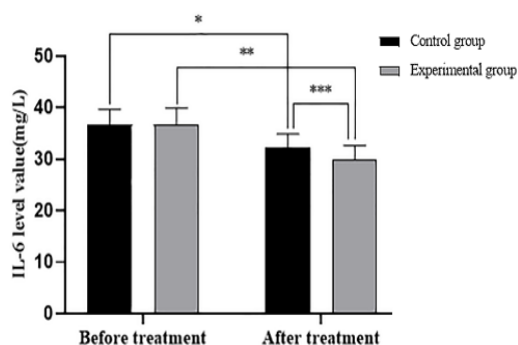
The two groups had similar IL-6 levels before treatment. After treatment, IL-6 levels increased significantly in both groups, with lower levels in the study group (*p* < 0.05) (Figure 2). The levels of IL-6 in the control group before and after treatment were 36.63  $\pm$  3.07 and 32.20  $\pm$  2.71 mg/L, respectively; IL-6 levels in the study group before and after treatment were 36.75  $\pm$  3.18 and 29.82  $\pm$  2.83 mg/L, respectively.

**Table 1:** Comparison of remission times for symptoms between the two groups (mean  $\pm$  SD, days, n = 50)

Group	Dyspnea	Wheeze	Croup	Hoarseness
Study	0.96 $\pm$ 0.35	1.81 $\pm$ 0.55	2.06 $\pm$ 0.54	2.92 $\pm$ 0.58
Control	1.62 $\pm$ 0.44	3.16 $\pm$ 0.73	3.27 $\pm$ 0.66	3.95 $\pm$ 0.72
<i>T</i>	8.301	10.444	10.033	7.878
<i>P</i> -value	<0.05	<0.05	<0.05	<0.05

**Table 2:** Treatment effectiveness in the two groups {n, mean  $\pm$  SD (%),}

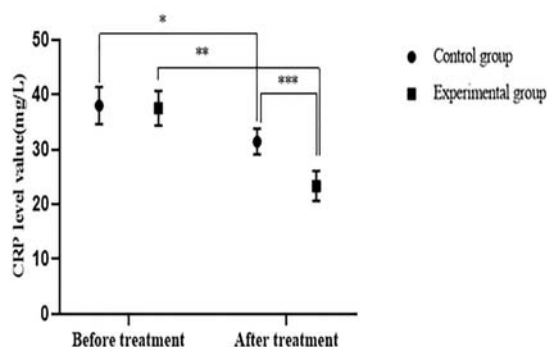
Group	Markedly effective	Effective	Ineffective	Total effectiveness
Study	22 (44.0)	26 (52.0)	2 (4.0)	2.92 $\pm$ 0.58
Control	13 (26.0)	28 (56.0)	9 (18.0)	3.95 $\pm$ 0.72
$\chi^2$				5.005
<i>P</i> -value				<0.05



**Figure 2:** Comparison of serum IL-6 levels between the two groups (mean  $\pm$  SD). \* $P = 0$ , IL-6 levels in the control group before and after treatment; \*\* $p = 0$ , comparison of IL-6 levels before and after treatment in the experimental group; \*\*\* $p = 0$ , comparison of IL-6 levels between the study group and the control group after treatment

### Serum CRP levels

The two groups showed similar CRP levels before treatment. After treatment, the CRP levels decreased in both groups, and the study group had significantly lower results ( $p < 0.05$ , Figure 3). The levels of CRP in the control group before and after treatment were  $38.03 \pm 3.37$  and  $31.45 \pm 2.36$  mg/mL, respectively; the levels of CRP in the study group before and after treatment were  $37.55 \pm 3.14$  and  $23.37 \pm 2.72$  mg/L, respectively.

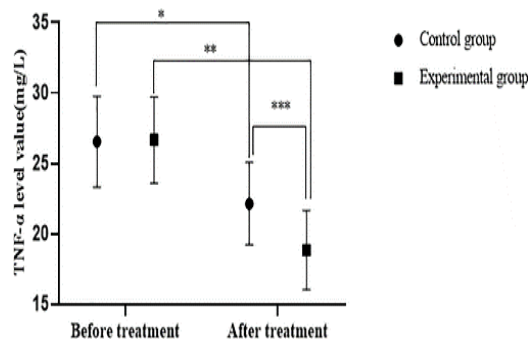


**Figure 3:** Serum CRP levels in the two groups (mean  $\pm$  SD). \* $P = 0$ , comparison of CRP levels in the control group before and after treatment; \*\* $p = 0$ , CRP levels in the study group before and after treatment; \*\*\* $p = 0$ , comparison of CRP levels between the study group and the control group after treatment

### Serum TNF- $\alpha$ levels

The two groups had similar pre-treatment TNF- $\alpha$  levels. TNF- $\alpha$  levels decreased in both groups after treatment, with lower levels in the study group ( $p < 0.05$ ) (Figure 4). The levels of TNF- $\alpha$  in the control group before and after treatment

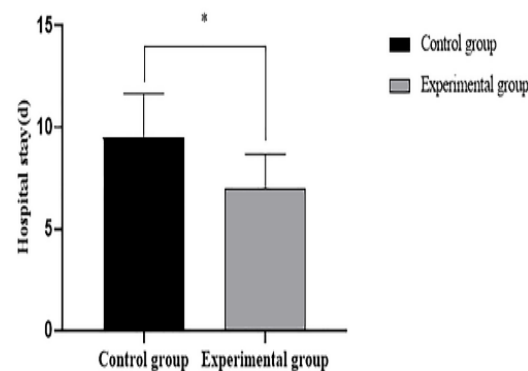
were  $26.55 \pm 3.22$  and  $22.15 \pm 2.93$  mg/L, respectively; the levels of TNF- $\alpha$  in the study group before and after treatment were  $26.67 \pm 3.06$  and  $18.84 \pm 2.82$  mg/L, respectively.



**Figure 4:** Serum TNF- $\alpha$  levels in the two groups. \* $P = 0$ , comparison of TNF- $\alpha$  before and after treatment in the control group; \*\* $p = 0$ , comparison of TNF- $\alpha$  before and after treatment in the study group; \*\*\* $p = 0$ , comparison of TNF- $\alpha$  after treatment between the study group and the control group

### Duration of hospital stay

Compared with patients given pulmicort respules only, those who received combination treatment had a significantly shorter hospital stay ( $p < 0.05$ ) (Figure 5). The hospitalization time of children in the control group was  $9.50 \pm 2.18$  days, while the hospitalization time of children in the experimental group was  $7.03 \pm 1.65$  days.



**Figure 5:** Comparison of duration of hospital stay between the two groups (mean  $\pm$  SD). \* $P = 0$ , comparison of hospital stay between the 2 groups

### Adverse reactions

Patients receiving pulmicort respules plus nebulized epinephrine inhalation treatment had a lower incidence of adverse reactions (4 %) versus those given pulmicort respules alone (8 %;  $p > 0.05$ ).

**Table 3:** Comparison of incidence of adverse reactions between the two groups {n (%)}

Group	Flush	Edema	Elevated blood pressure	Incidence of adverse reactions
Experimental	1 (2.0)	1 (2.0)	2 (4.0)	2 (4.0)
Control	2 (4.0)	1 (2.0)	1 (2.0)	4 (8.0)
$\chi^2$				0.709
P-value				>0.05

## DISCUSSION

Recent years have witnessed an increasing incidence of acute laryngitis, especially amongst children of younger age, a situation which may hobble the growth and development of children [7]. Given that a young child has tender respiratory mucosa, narrow pharyngeal cavity, rich lymph nodes, high number of blood vessels, thyroid cartilage hypoplasia, and loose subcutaneous tissue, the incidence of acute laryngitis could give rise to respiratory tract spasm, edema, and pharyngeal mucosal congestion [8]. At present, clinical treatment of acute laryngitis is aimed at eliminating airway inflammation and maintaining smooth breathing [9].

Pulmicort is a glucocorticoid that has been widely applied in clinics for its reliable water solubility, strong binding to glucocorticoid receptors, and anti-inflammatory potential. It relieves microvascular contraction, mitigates edema and capillary dilatation, and inhibits inflammatory reactions. It is suitable for local treatment of airway inflammation, and it directly stems from respiratory inflammation [10]. Epinephrine relaxes the  $\beta$ -receptor of bronchial smooth muscle, prevents partial mast cells from releasing histamine, promotes contraction of mucosal blood vessels, improves the permeability of blood vessels in children, and eliminates mucosal edema caused by bronchi [11]. Studies have reported that the use of nebulized epinephrine inhalation in conjunction with pulmicort respules produced beneficial effects in the treatment of emergency pediatric laryngitis, and it was conducive to the relaxation of the airway in children [12-14].

Herein, pulmicort respules plus nebulized epinephrine inhalation treatment resulted in a shorter remission time for dyspnea, wheeze, croup, and hoarseness, and higher total treatment effectiveness versus pulmicort respules. These findings are consistent with the results of Tsentsevitsky *et al* [15]. It suggests that the combination of epinephrine and pulmicort respules potentiate the treatment efficiency of laryngitis. Moreover, pulmicort respules plus nebulized epinephrine inhalation treatment resulted in significantly lower serum levels of IL-

8, IL-6, CRP, TNF- $\alpha$  versus pulmicort respules. A study by Lubberding *et al* [16] demonstrated that the application of epinephrine in combination with pulmicort respules in the treatment of pediatric laryngitis led to an increased degree of inflammatory reactions. In the present study, patients who received combination treatment enjoyed a significantly shorter hospitalization time and a lower incidence of adverse reaction, when compared to the group that received pulmicort respules only. Given the mild symptoms of adverse reactions, the combined treatment can be considered safe. This is in conformity with previous studies, and it indicates the high safety of nebulized epinephrine in combination with pulmicort respules in treating pediatric laryngitis [17].

## CONCLUSION

Nebulized epinephrine inhalation plus pulmicort respules alleviates clinical symptoms of patients with emergency pediatric laryngitis, reduce inflammatory response, and shortens hospital stay with a high safety profile. It may therefore be considered for clinical application in the management of emergency pediatric laryngitis after further clinical trials.

## DECLARATIONS

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

The authors 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 them.

### *Open Access*

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/rea>)

d), which permit unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

## REFERENCES

1. Sigal AP, Sandel KM, Buckler DG, Wasser T, Abella BS. Impact of adrenaline dose and timing on out-of-hospital cardiac arrest survival and neurological outcomes. *Resuscitation* 2019; 139: 182-188.
2. Perkins GD, Kenna C, Ji C, Deakin CD, Nolan JP, Quinn T, Fothergill R, Gunson I, Pocock H, Rees N, et al. The effects of adrenaline in out of hospital cardiac arrest with shockable and non-shockable rhythms: Findings from the PACA and PARAMEDIC-2 randomised controlled trials. *Resuscitation* 2019; 140: 55-63.
3. Biswas S, Naskar H, Pradhan S, Wang Y, Bandyopadhyay R, Pramanik P. Simultaneous voltammetric determination of Adrenaline and Tyrosine in real samples by neodymium oxide nanoparticles grafted graphene. *Talanta* 2020; 206: 120176.
4. Kodandaraman G, Bankoglu EE, Stopper H. Overlapping mechanism of the induction of genomic damage by insulin and adrenaline in human promyelocytic HL-60 cells. *Toxicol In Vitro* 2020; 66: 104867.
5. Aloua R, Kerdoud O, Kaouani A, Belem O, Konsem T, Slimani F. Locoregional anesthesia for removal osteosynthesis hardware from healed corpus mandibularis fractures: A descriptive study of a series of 40 cases. *Ann Med Surg (Lond)* 2021; 68: 102619.
6. Associazione Medica Mondiale (AMM) dichiarazione di Helsinki. Principi etici per la ricerca medica che coinvolge soggetti umani {World Medical Association (AMM). Helsinki Declaration. Ethical principles for medical research involving human subjects}. *Assist Inferm Ric* 2001; 20(2): 104-107.
7. Farkash U, Herman A, Kalimian T, Segal O, Cohen A, Laish-Farkash A. Keeping the Finger on the Pulse: Cardiac Arrhythmias in Hand Surgery Using Local Anesthesia with Adrenaline. *Plast Reconstr Surg* 2020; 146(1): 54e-60e.
8. Gomes A, Soares R, Costa R, Marino F, Cosentino M, Malagon MM, Ribeiro L. High-fat diet promotes adrenaline production by visceral adipocytes. *Eur J Nutr* 2020; 59(3): 1105-1114.
9. Sirota TV. Deĭstvie serosoderzhashchikh soedinenĭi na khinoidnyĭ protsess avtookisleniia adrenalina; potentsial'nye neĭroprotektory {Effect of the sulfur-containing compounds on the quinoid process of adrenaline autoxidation; potential neuroprotectors}. *Biomed Khim* 2019; 65(4): 316-323.
10. Elvebakk O, Tronstad C, Birkeland KI, Jenssen TG, Bjørngaas MR, Frøslie KF, Godang K, Kalvøy H, Martinsen ØG, Gulseth HL. Evaluation of Hypoglycaemia with Non-Invasive Sensors in People with Type 1 Diabetes and Impaired Awareness of Hypoglycaemia. *Sci Rep* 2018; 8(1): 14722.
11. Julian MM, Rosenblum KL, Doom JR, Leung CYY, Lumeng JC, Cruz MG, Vazquez DM, Miller AL. Oxytocin and parenting behavior among impoverished mothers with low vs. high early life stress. *Arch Womens Ment Health* 2018; 21(3): 375-382.
12. Stepanikova I, Baker E, Oates G, Acharya S, Uddin J, Thon V, Svancara J, Kukla L. Perinatal Maternal Stress and Susceptibility to Infectious Diseases in Later Childhood: An Early Life Programming Perspective. *J Psychol* 2019; 153(1): 67-88.
13. Schweiger C, Manica D, Lubianca Neto JF, Sekine L, Krumenauer R, Caixeta JA, Maunsell R, Gomes Avelino M. Determinants of successful tracheostomy decannulation in children: a multicentric cohort study. *J Laryngol Otol* 2020; 134(1): 63-67.
14. Adenekan AT, Aderounmu AA, Wuraola FO, Owojuyigbe AM, Adetoye AO, Nepogodiev D, Magill L, Bhangu A, Adisa AO. Feasibility study for a randomized clinical trial of bupivacaine, lidocaine with adrenaline, or placebo wound infiltration to reduce postoperative pain after laparoscopic cholecystectomy. *BJS Open* 2019; 3(4): 453-460.
15. Tsentsevitsky AN, Kovyazina IV, Bukharaeva EA. Diverse Effects of Noradrenaline and Adrenaline on the Quantal Secretion of Acetylcholine at the Mouse Neuromuscular Junction. *Neurosci* 2019; 423: 162-171.
16. Lubberding AF, Thomsen MB. Low-Dose Adrenaline Reduces Blood Pressure Acutely in Anesthetized Pigs Through a  $\beta$ 2-Adrenergic Pathway. *J Cardiovasc Pharmacol* 2019; 74(1): 38-43.
17. Okamoto Y, Fujieda S, Okano M, Hida H, Kakudo S, Masuyama K. Efficacy of house dust mite sublingual tablet in the treatment of allergic rhinoconjunctivitis: A randomized trial in a pediatric population. *Pediatr Allergy Immunol* 2019; 30(1): 66-73.