Int J Clin Exp Med 2019;12(9):11684-11691
www.ijcem.com /ISSN:1940-5901/IJCEM0095897

Original Article

Combined aerosol inhalation of salbutamol and budesonide effectively improves neonatal bacterial pneumonia and reduces serum inflammatory factors in newborns

Xuemei Gao[1], Xiaohui Guo[2], Cui Kong[2], Qinghua Meng[1], Xiaojuan Jiang[3]

[1]Department of Pediatrics, Linyi Central Hospital, Linyi, Shandong Province, China; [2]Department of Pediatrics, The Third People's Hospital of Linyi, Linyi, Shandong Province, China; [3]Department of Gynecology and Obstetrics, Ji'nan Maternity and Child Care Hospital, Ji'nan, Shandong Province, China

Received April 23, 2019; Accepted July 4, 2019; Epub September 15, 2019; Published September 30, 2019

Abstract: Objective: The goal of this study was to analyze the clinical efficacy of combined aerosol inhalation of salbutamol and budesonide for neonatal bacterial pneumonia and the effect of serum inflammatory factors in children. Methods: Medical records of 108 neonates with pneumonia were reviewed. Sixty-two patients who received routine treatment and budesonide inhalation were classified as the control group, and 46 patients, who were given routine treatment combined with budesonide and salbutamol inhalation, as the observation group. The therapeutic effects were observed and compared between the two groups after two courses of treatment based on measurements including disappearance times of dyspnea, pulmonary rales, and cough, the duration of oxygen therapy, the time to normal body temperature and the length of stay. Changes in lung function indices and inflammatory cytokines from baseline to 1 week after treatment and 2 weeks after treatment were compared between the two groups respectively. Results: After 2 weeks of treatment, the overall effective rate in the observation group was higher than that in the control group ($P<0.05$). The disappearance times of dyspnea, pulmonary rales, and cough, the duration of oxygen therapy, the time to normal body temperature and the length of stay were all shorter in the observation group than in the control group (all $P<0.05$). At 1 week and 2 weeks after treatment respectively, the observation group was lower in respiratory rate (RR) and higher in peak expiratory flow (PEF) and functional residual capacity (FRC) as compared with those of the control group (all $P<0.05$). The RR, PEF and FRC within the two groups were substantially improved after treatment respectively. At 1 week and 2 weeks after treatment, The RR was lower than that before treatment in both groups respectively (all $P<0.05$); the PEF and FRC were higher than those before treatment in both groups respectively (all $P<0.05$). At 2 weeks after treatment, the RR was lower than that at 1 week after treatment in both groups, respectively (both $P<0.05$); the PEF and FRC was higher than those at 1 week after treatment in both groups, respectively (all $P<0.05$). At 1 week and 2 weeks after treatment respectively, the observation group was lower in the levels of tumor necrosis factor alpha (TNF-α), interleukin-4 (IL-4), interleukin-10 (IL-10) as compared with those of the control group (all $P<0.05$). The levels of TNF-α, IL-4, and IL-10 remarkably decreased in two groups after treatment. At 1 week and 2 weeks after treatment, the levels of TNF-α, IL-4, and IL-10 were lower than those before treatment in both groups respectively (all $P<0.05$). The levels of TNF-α, IL-4, and IL-10 were lower at 2 weeks after treatment than those at 1 week after treatment in both groups respectively (all $P<0.05$). Conclusion: Combined inhalation of salbutamol and budesonide is effective in neonatal bacterial pneumonia by substantially alleviating such symptoms as dyspnea and cough, shortening the time of treatment, and improving the inflammatory response in newborns. Therefore, this is an approach worthy of clinical promotion.

Keywords: Salbutamol, budesonide, neonatal bacterial pneumonia, atomization therapy, inflammatory cytokine

Introduction

Neonatal pneumonia consists of neonatal aspiration pneumonia and neonatal infectious pneumonia, of which neonatal bacterial pneumonia is the most common respiratory infection causing neonatal death in newborns. Characterized by rapid onset and progress, pneumonia results in over 2 million newborn deaths worldwide each year, accounting for

10% of all neonatal deaths, according to statistics, which gravely threatens the life and health of newborns [1, 2]. Advancement of medical technology and the widespread use of antibiotics have effectively improved the prognosis of neonates with pneumonia. However, the mortality rate of nearly 25% still spurs people to find more effective treatments. Approaches to improve the existing treatments is a current focus of research [3, 4].

Salbutamol and budesonide are commonly used in aerosol inhalation therapy for neonatal bacterial pneumonia [5, 6]. Salbutamol is a short-acting selective β2-adrenergic receptor agonist. By binding to the β2 receptor on smooth muscle cells, salbutamol can effectively inhibit the release of allergic substances such as histamine and relieve bronchial smooth muscle spasm [7]. Budesonide is a glucocorticoid with a high level of lung deposition. It can enhance cell membrane stability and improve immune response, and also plays a role in palliating bronchial smooth muscle spasm [8]. In recent years, there have been some reports on using salbutamol or budesonide in neonatal infectious pneumonia, which have both shown ideal therapeutic effects [9, 10]. It has been reported that budesonide can promote the transcription and translation of β2 receptor-related genes. The synthesis, while salbutamol can also activate the glucocorticoid receptors [11, 12]. This indicates that the combination of salbutamol and budesonide can be more effective in theory, but there are few reports on comparing the efficacy of the combined use of salbutamol and budesonide with the use of budesonide alone in neonatal infectious pneumonia, especially on the effect of the combination on the levels of related inflammatory cytokines in newborns.

Therefore, this study analyzed retrospective data for the effect of salbutamol and budesonide combination on neonatal infectious pneumonia and inflammatory cytokines, providing guidance for the clinical treatment of neonatal infectious pneumonia.

Materials and methods

Subjects

This study conducted a retrospective analysis with the medical records of 108 neonates with pneumonia from April 2018 through January 2019 in the Department of Pediatric of Linyi Central Hospital. Sixty-two of them who received routine treatment and budesonide inhalation were classified as the control group, and 46 of them, who were given routine treatment combined with budesonide and salbutamol inhalation, as the observation group.

Inclusion criteria: All patients met the diagnostic criteria of neonatal bacterial pneumonia in the Guidelines for Clinical Diagnosis and Treatment in Internal Medicine-Pediatrics by Chinese Medical Association, presented symptoms and signs of respiratory infection, were full-term neonates, and had no history of allergic diseases and drug allergy and respiratory diseases [13].

Exclusion criteria: Patients with severe pneumonia [13]; patients complicated with acute respiratory distress syndrome; patients complicated with liver or kidney dysfunction; patients complicated with congenital malformations; patients complicated with inherited metabolic diseases; patients complicated with endocrine diseases; patients treated with hormone medications; patients who were allergic to the study drug; patients who previously received β2-adrenergic receptor agonist or glucocorticoid therapy; patients who had abnormal bleeding or coagulopathy; patients complicated with cardiovascular or cerebrovascular diseases; patients complicated with digestive diseases; patients who were transferred to another hospital during the treatment; patients who were incapable of complying with the treatment due to their relatives; patients who had incomplete medical records; patients who had incomplete follow-up data.

This study was approved by the Ethics Committee of Linyi Central Hospital and it gained informed consent from all participants and their relatives before their entry into the study. See **Figure 1** for the flow diagram of the study.

Treatment

All newborns were given routine treatment, including clearance of respiratory tract secretions to ensure airway patency, maintenance of electrolytes and water balance, use of appropriate antibiotics according to the guidelines,

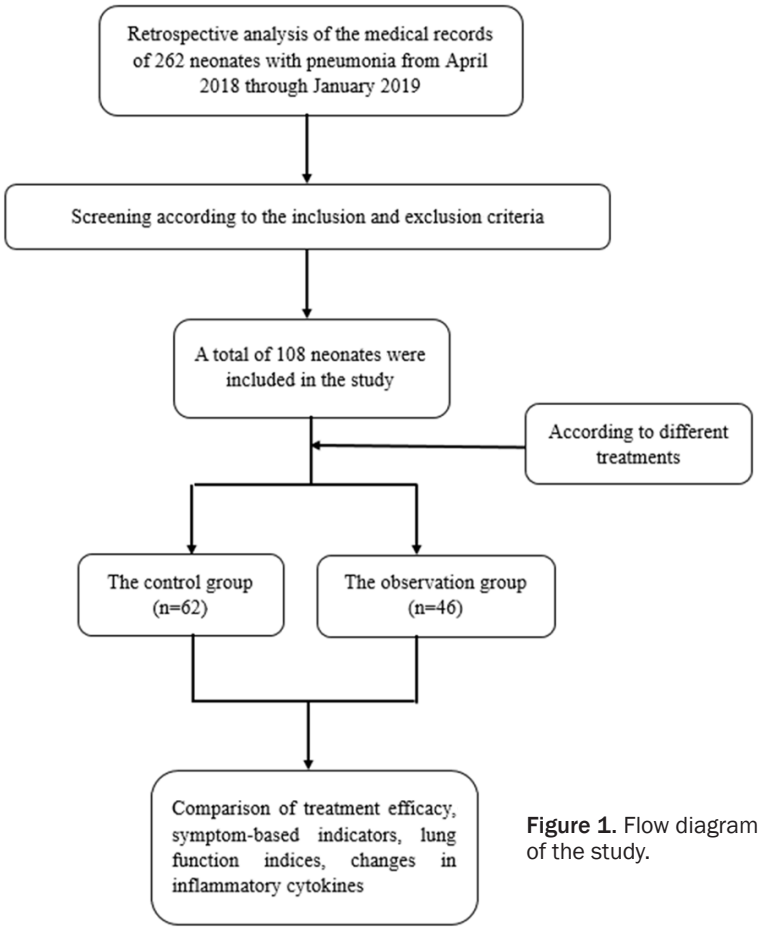

Figure 1. Flow diagram of the study.

and proactive efforts were applied to keep the patients warm. Upon receiving routine treatment, the control group was given budesonide aerosol inhalation (Shanghai Xinyi Bailuda Pharmaceutical Co., Ltd.) twice a day, with a dose of 1 mL budesonide + 1 mL 0.9% sodium chloride solution each time. While receiving routine treatment, the observation group was treated with aerosol inhalation of budesonide combined with salbutamol (Chongqing Kerui Pharmaceutical (Group) Co., Ltd.). The dose given was 1 mL budesonide + 0.2 mL salbutamol + 2 mL 0.9% sodium chloride solution at an oxygen flow rate of 6-8 L/min. The inhalation was performed on an empty stomach and 1 hour after the meal, once in the morning and afternoon respectively, with the time of each inhalation ranging between 15-20 minutes. The time interval between the drug administrations was not less than 6 hours. A course of treatment was defined as 7 days, and two courses of treatment were given to the two groups.

Measurements

The therapeutic effects were observed and compared between the two groups after two courses of treatment based on measurements including disappearance times of dyspnea, pulmonary rales, and cough, the duration of oxygen therapy, the time to normal body temperature and the length of stay. The lung function indices, including respiratory rate (RR), peak expiratory flow (PEF) and functional residual capacity (FRC) were compared between the two groups before treatment, 1 week after treatment and 2 weeks after treatment respectively. The SterScreen BabyBody spirometer was purchased from JEAGER, Germany. Changes in inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-4 (IL-4) and interleukin-10 (IL-10) were observed and compared between the two groups.

Criteria for efficacy assessments

The efficacy was divided into several levels, markedly effective, effective and ineffective. Markedly effective was defined as complete recovery of pneumonia with the elimination of cough, dyspnea and lung rales, normal body temperature, no complications and no pulmonary inflammation according to chest X-ray. Effective was defined as basic recovery of pneumonia with improvements in cough, dyspnea and lung rales, and substantial reduction of pulmonary inflammation according to chest X-ray. Ineffective was defined as the absence of improvements in cough, dyspnea and lung rales, or even deterioration of the disease. Overall effective rate = (cases of markedly effective + cases of effective)/total number of cases * 100%.

Enzyme-linked immunosorbent assay (ELISA)

TNF-α, IL-4, and IL-10 were detected by ELISA. Fasting venous blood was drawn from all the

Table 1. Baseline characteristics

	Control group (n=62)	Observation group (n=46)	t/χ^2	P
Gender (n, %)			0.449	0.503
Male	33 (53.23)	21 (45.65)		
Female	29 (46.77)	25 (54.35)		
Gestational age (weeks)	38.9±0.6	39.0±0.7	0.798	0.427
Age (days)	15.5±0.5	15.7±0.7	1.733	0.086
Body length (cm)	46.35±1.83	46.62±1.49	0.819	0.415
Weight (g)	3345.62±224.73	3386.29±213.16	0.950	0.344
Weight at admission (g)	3583.22±364.58	3524.21±401.15	0.797	0.427
Head circumference (cm)	34.04±0.83	34.09±0.86	0.305	0.761
Types of bacteria (n, %)			0.012	0.914
Gram-positive bacteria	29 (46.77)	22 (47.83)		
Gram-negative bacteria	33 (53.23)	24 (52.17)		
Mode of delivery (n, %)			0.097	0.756
Vaginal delivery	40 (64.52)	31 (67.39)		
Cesarean section	22 (35.48)	15 (32.61)		
Mother's Age (years)	28.82±4.63	29.57±4.84	0.817	0.416
Gravidity	2.13±1.09	2.19±1.04	0.288	0.774
Parity	1.25±0.49	1.27±0.51	0.206	0.837

patients in the morning and tested within one hour. The blood was centrifuged for serum to measure levels of inflammatory cytokines. Sample buffer and serum, 50 μL respectively, were added to each well of the plate and incubated at room temperature for 2 hours. After incubation, the plate was rinsed 5 times, then 100 μL of biotinylated antibody was added per well before the plate was sealed and incubated for an hour at room temperature. The plate was then rinsed again before adding 100 μL of horseradish peroxidase-labeled antibody per well. The plate was sealed and incubated in the dark at room temperature for 20 min. Followed incubation, 100 μL of chromogenic substrate, 3,3',5,5'-Tetramethylbenzidine, was added per well and the plate was incubated at room temperature for 20 minutes in the dark. Finally, 50 μL of stop solution was added per well and the maximum absorbance was measured within 15 minutes at a wavelength of 450 nm using CLARIOstar multi-mode microplate reader (BMG LabTech, Germany). ELISA kits for TNF-α, IL-4, and IL-10 detection were purchased from Shanghai Jingkang Biological Engineering Co., Ltd. (Item No.: JK-(a)-2161, JK-(a)-2152, JK-(a)-2145).

Statistical analysis

All the data were statistically processed using SPSS 19.0 software package. The enumeration data are expressed as cases/percentage (n, %), and were compared based on Chi-square test. The measurement data are expressed as mean ± standard deviation ($\bar{x}$ ± sd). Comparison between two groups was based on t-test. Comparison within the group at different time points was based on repeated measures analysis of variance. $P<0.05$ was considered statistically significant.

Results

Comparison of baseline characteristics

There were no statistical differences in baseline characteristics between the two groups, indicating that the two groups were comparable in this study. There were no significant differences in gender ratio and age between the two groups (both $P>0.05$). There were no statistical differences between the two groups in other baseline characteristics including body length, weight, head circumference, mode of delivery, and mother's age (all $P>0.05$) as shown in **Table 1**.

Comparison of treatment efficacy

After 2 weeks of treatment, the overall effective rate in the observation group was higher than that in the control group ($P<0.05$) as shown in **Table 2**.

Table 2. Efficacy assessments (n, %)

	Control group (n=62)	Observation group (n=46)	χ^2	P
Markedly effective	31 (50.00)	33 (71.74)		
Effective	17 (27.42)	10 (21.74)		
Ineffective	14 (22.58)	3 (6.52)		
Overall effective rate	48 (77.42)	43 (93.48)	5.135	0.023

Comparison of symptom-based indicators

The observation group was significantly shorter than the control group in the disappearance times of dyspnea, pulmonary rales, and cough, the duration of oxygen therapy, the time to normal body temperature and the length of stay (all P<0.05) as shown in **Table 3**.

Comparison of changes in lung function indices

The lung function testing showed that no significant differences were found between the observation group and the control group at baseline in RR, PEF and FRC (all P>0.05). At 1 week and 2 weeks after treatment respectively, the observation group was lower in RR and higher in PEF and FRC as compared with the control group (all P<0.05). The RR, PEF and FRC within the two groups were substantially improved after treatment respectively. At 1 week and 2 weeks after treatment, the RR was lower than that before treatment in both groups respectively (all P<0.05); the PEF and FRC were higher than those before treatment in both groups respectively (all P<0.05). At 2 weeks after treatment, the RR was lower than that at 1 week after treatment in both groups respectively (both P<0.05); the PEF and FRC were higher than those at 1 week after treatment in both groups respectively (all P<0.05) as shown in **Table 4**.

Comparison of changes in inflammatory cytokines

At baseline, there were no significant differences between two groups in TNF-α, IL-4, IL-10 (all P>0.05). At 1 week and 2 weeks after treatment respectively, the observation group was lower in the levels of TNF-α, IL-4, IL-10 as compared with the control group (all P<0.05). The levels of TNF-α, IL-4, and IL-10 remarkably decreased in two groups after treatment. At 1 week and 2 weeks after treatment, the levels of TNF-α, IL-4, and IL-10 were lower than those at baseline in both groups respectively (all P<0.05). The levels of TNF-α, IL-4, and IL-10 at 2 weeks after treatment were lower than those at 1 week after treatment in both groups respectively (all P<0.05) as shown in **Figure 2**.

Discussion

Owing to less-developed organs, relatively narrow bronchial lumen, unstable regulation of autoimmune response, fragile respiratory mucosa, newborns are prone to infectious pneumonia, which causes breathing difficulty in children. If not treated promptly, the infection will eventually impair organ function and even cause death [14, 15]. Currently, the major treatment for neonatal infectious pneumonia is aerosol inhalation therapy, which is characterized by relatively high local drug concentration and rapid action [16]. This study analyzed the clinical efficacy of combined inhalation of salbutamol and budesonide for neonatal bacterial pneumonia and its value for application.

The therapeutic effects of two treatments were first analyzed on neonatal bacterial pneumonia. The results of this study showed that the overall effective rate in the observation group was significantly higher than that in the control group. The measurements of lung function indices in both groups also showed that the improvements of RR, PEF and FRC in the observation group were significantly greater than those of the control group, indicating that salbutamol combined with budesonide has better therapeutic effect on neonatal bacterial pneumonia than budesonide alone. As a new medication of the corticosteroid type, budesonide is a glucocorticoid with a high level of lung deposition, which prolongs its therapeutic effect. It binds rapidly and effectively to the corresponding glucocorticoid receptor on the cell membrane to inhibit bronchial hyper-responsiveness and repair the airway [17]. In this study, the observation group was shorter than the control group in the disappearance times of dyspnea, pulmonary rales, and cough, the duration of oxygen therapy, the time to normal body temperature and the length of stay.

Studies have shown that salbutamol combined with budesonide can substantially improve lung function as compared with budesonide alone, as evidenced by significant improvements in the forced expiratory volume in the first second

Table 3. Assessments of symptom-based indicators

	Control group (n=62)	Observation group (n=46)	t	P
Disappearance time of dyspnea (days)	6.22±0.58	4.26±0.73	15.545	<0.001
Disappearance time of pulmonary rales (days)	7.23±1.22	5.21±1.25	8.420	<0.001
Disappearance time of cough (days)	7.12±1.34	4.83±1.13	9.376	<0.001
Duration of oxygen therapy (days)	5.44±2.32	3.61±1.34	4.787	<0.001
Time to normal body temperature (days)	3.98±0.32	2.51±0.61	16.220	<0.001
Length of stay (days)	12.13±1.62	7.25±1.38	16.469	<0.001

Table 4. Changes of lung function indices in two groups

		Control group (n=62)	Observation group (n=46)	t	P
RR (breaths/min)	Before treatment	58.64±10.33	57.27±10.56	0.675	0.501
	1 week after treatment	52.81±10.25*	48.67±10.38*	2.064	0.041
	2 weeks after treatment	46.76±10.14*,#	42.15±9.83*,#	2.367	0.020
PEF (mL/s)	Before treatment	49.54±4.83	49.37±4.62	0.184	0.854
	1 week after treatment	60.41±5.74*	70.25±6.43*	8.368	<0.001
	2 weeks after treatment	65.87±6.62*,#	75.02±6.85*,#	6.998	<0.001
FRC (%)	Before treatment	70.28±6.57	70.49±6.64	0.234	0.816
	1 week after treatment	81.43±6.58*	89.21±6.87*	5.963	<0.001
	2 weeks after treatment	88.36±7.02*,#	94.37±7.14*,#	4.364	<0.001

Note: Compared with the baseline, *P<0.05; compared with the levels at 1 week after treatment, #P<0.05; PEF: peak expiratory flow; FRC: functional residual capacity.

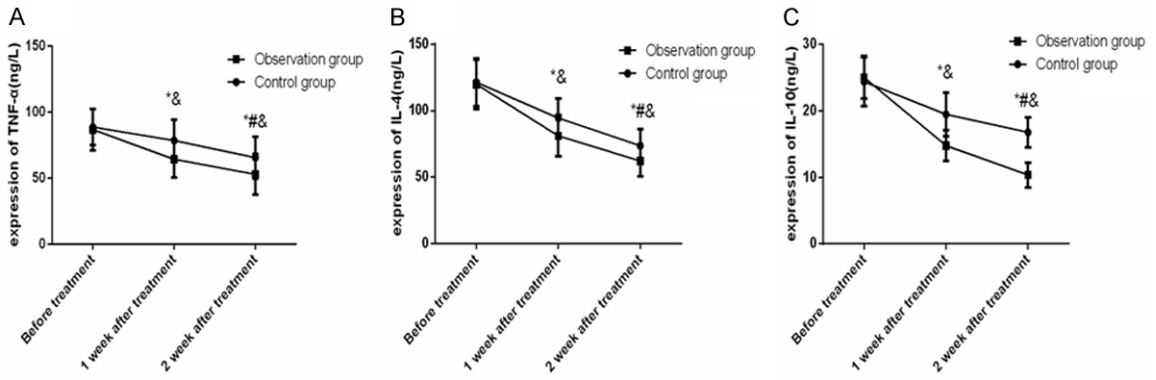

Figure 2. Analysis of inflammatory cytokines in two groups. A: Analysis of TNF-α levels in two groups; B: Analysis of IL-4 levels in two groups; C: Analysis of IL-10 levels in two groups. Compared with the baseline, *P<0.05; compared with the levels at 1 week after treatment, #P<0.05; compared with the control group at the time point, &P<0.05.

and the ratio of forced expiratory volume in one second over forced vital capacity [18]. This verifies the results of this study to some extent. The reason for such improvements is because salbutamol is a β2-adrenergic receptor agonist, which can effectively affect smooth muscle cells by binding to β2-adrenergic receptors with higher specificity than other β2-adrenergic receptor agonists, thereby alleviating bronchial spasm [19].

Three pro-inflammatory cytokines were examined that are closely related to inflammatory response, TNF-α, IL-4, and IL-10 [20-22]. The results showed that the levels of TNF-α, IL-4 and IL-10 decreased continuously after treatment than those before treatment in the two groups respectively, but the degree of reduction in the observation group was more obvious than that in the control group. This also shows that the effect of salbutamol combined with

budesonide on improving inflammatory response of neonates with pneumonia is greater than that of budesonide alone. Some studies have reported that salbutamol and budesonide can reduce inflammatory response. Budesonide and salbutamol can promote constriction of capillaries, thereby reducing the release of inflammatory cytokines, the edema, and the inflammatory cell infiltration. Budesonide can depress the expression of pro-inflammatory cytokines in epithelial and endothelial cells and inflammatory cell infiltration, while salbutamol can also play its anti-inflammatory role by activating β2-adrenergic receptors [23, 24]. Therefore, the combination of the two drugs has strong anti-inflammatory effects. But there are few reports on the treatment of neonatal bacterial pneumonia with salbutamol or budesonide, especially on salbutamol. The results of this study still require the verification of a large number of clinical trials. Another limitation of this study is that only short-term effect of salbutamol combined with budesonide in the treatment of neonatal bacterial pneumonia were analyzed, and the long-term effect remains to be verified by future studies.

In conclusion, salbutamol and budesonide combination has a good therapeutic effect in neonatal bacterial pneumonia. Its administration can effectively improve such symptoms as shortness of breath and cough, shorten the time of treatment, and reduce the inflammatory response in neonates. Therefore, it is worthy of future clinical study.

Disclosure of conflict of interest

None.

Address correspondence to: Xiaojuan Jiang, Department of Gynecology and Obstetrics, Ji'nan Maternity and Child Care Hospital, No. 2 Jianguoxiaojingsan Road, Ji'nan 250001, Shandong Province, China. Tel: +86-0531-82061448; E-mail: jiangxiaojuan57x@163.com

References

[1] Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, Cousens S, Mathers C and Black RE. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015; 385: 430-440.

[2] Yin XF and Lei XM. Effect of gamma globulin on serum immune index in neonatal pneumonia. Chinese Journal of Postgraduates of Medicine 2017; 40: 196-199.

[3] Sankar MJ, Natarajan CK, Das RR, Agarwal R, Chandrasekaran A and Paul VK. When do newborns die? A systematic review of timing of overall and cause-specific neonatal deaths in developing countries. J Perinatol 2016; 36 Suppl 1: S1-S11.

[4] Min LU and Tan JF. Clinical efficacy of ambroxol combined with budesonide aerosol inhalation in treating neonatal pneumonia. Chinese Journal of Biochemical and Pharmaceuticals 2017; 37: 237-239.

[5] Budesonide combined salbutamol aerosol inhalation observe specific effect for the treatment of neonatal pneumonia. Journal of North Pharmacy 2015; 12: 70-71.

[6] Luo HJ, Wang J, Xie HZ, Jia WT and Wang LZ. Effect of budesonide combined with ambroxol hydrochloride on newborns with aspiration pneumonia. Journal of Bengbu Medical College 2012; 37: 48-50.

[7] Lee W, Syed AA, Leow CY, Tan SC and Leow CH. Isolation and characterization of a novel anti-salbutamol chicken scFv for human doping urinalysis. Anal Biochem 2018; 555: 81-93.

[8] Virchow JC, Rodriguez-Roisin R, Papi A, Shah TP and Gopalan G. A randomized, double-blinded, double-dummy efficacy and safety study of budesonide-formoterol spiromax® compared to budesonide-formoterol Turbuhaler® in adults and adolescents with persistent asthma. BMC Pulm Med 2016; 16: 42.

[9] Yao HP. Clinical effect of budesonide combined with ambroxol in the treatment of neonatal aspiration pneumonia. Chinese Journal of Biochemical Pharmaceutics 2017; 5: 280-282.

[10] Cai HX. The effect analysis of children with asthmatic pneumonia for budesonide combined with salbutamol inhalation therapy. China Continuing Medical Education 2015; 7: 145-146.

[11] Omran A, Ali M, Saleh MH and Zekry O. Salivary C-reactive protein and mean platelet volume in diagnosis of late-onset neonatal pneumonia. Clin Respir J 2018; 12: 1644-1650.

[12] Zhong Q, Feng H, Lu Q, Liu X, Zhao Q, Du Y, Zhang XH and Wang JR. Recurrent wheezing in neonatal pneumonia is associated with combined infection with respiratory syncytial virus and staphylococcus aureusor klebsiella pneumoniae. Sci Rep 2018; 8: 995.

[13] Chinese medical association: clinical diagnosis and treatment guidelines for pediatric internal medicine. Edited by chinese medical association. Beijing, People's Health Publishing House 2005.

[14] Yang Z, Xiao X, Huang Y, He X, Lu Q, Chen S and Lin Z. Effects and mechanisms of ambroxol inhalation (mucosolvan®) in the treatment of neonatal pneumonia. Pharmazie 2017; 72: 604-607.

[15] Lucendo A, Miehlke S, Vieth M, Schlag C, Von Arnim U, Molina-Infante J, Hartmann D, Bredenoord AJ, De Los Ríos CC, Schubert S, Brückner S, Madisch A, Hayat JO, Tack JF, Attwood SE, Mueller R, Greinwald R, Schoepfer AM and Straumann A. Budesonide orodispersible tablets are highly effective for treatment of active eosinophilic esophagitis: results from a randomized, double-blind, placebo-controlled, pivotal multicenter trial (EOS-1). Gastroenterology 2017; 152: S207.

[16] Fan X and Ke H. Meta-analysis on the efficacy of nebulized budesonide and salbutamol in the treatment of asthma. Chongqing Medicine 2015; 3: 349-352.

[17] Rider CF, Miller-Larsson A, Giembycz M and Newton R. Long-acting β2-adrenoceptor agonists enhance glucocorticoid-inducible gene expression via a rapidly acting pathway without affecting glucocorticoid receptor expression or translocation. Am J Respir Crit Care Med 2015; A5026.

[18] Keränen T, Hömmö T, Hämäläinen M, Moilanen E and Korhonen R. Anti-inflammatory effects of β2-receptor agonists salbutamol and terbutaline are mediated by MKP-1. PLoS One 2016; 11: e0148144.

[19] Kang Q, Zhang X, Liu S and Huang F. Correlation between the vitamin D levels and asthma attacks in children: evaluation of the effects of combination therapy of atomization inhalation of budesonide, albuterol and vitamin D supplementation on asthmatic patients. Exp Ther Med 2018; 15: 727-732.

[20] Ju NY, Gao H, Huang W, Niu FF, Lan WX, Li F and Gao W. Therapeutic effect of inhaled budesonide (pulmicort® turbuhaler) on the inflammatory response to one-lung ventilation. Anaesthesia 2014; 69: 14-23.

[21] Uzkeser H, Cadirci E, Halici Z, Odabasoglu F, Polat B, Yuksel TN, Ozaltin S and Atalay F. Anti-inflammatory and antinociceptive effects of salbutamol on acute and chronic models of inflammation in rats: involvement of an antioxidant mechanism. Mediators Inflamm 2012; 2012: 438912.

[22] Hennessy E, Griffin ÉW and Cunningham C. Astrocytes are primed by chronic neurodegeneration to produce exaggerated chemokine and cell infiltration responses to acute stimulation with the cytokines IL-1β and TNF-α. J Neurosci 2015; 35: 8411-8422.

[23] Bal SM, Bernink JH, Nagasawa M, Groot J, Shikhagaie MM, Golebski K, van Drunen CM, Lutter R, Jonkers RE, Hombrink P, Bruchard M, Villaudy J, Munneke JM, Fokkens W, Erjefält JS, Spits H and Ros XR. IL-1β, IL-4 and IL-12 control the fate of group 2 innate lymphoid cells in human airway inflammation in the lungs. Nat Immunol 2016; 17: 636-645.

[24] Ip WKE, Hoshi N, Shouval DS, Snapper S, Medzhitov R. Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. Science 2017; 356: 513-519.