Clinical Trial/Experimental Study

Medicine

OPEN

The effect of high-frequency oscillatory ventilator combined with pulmonary surfactant in the treatment of neonatal respiratory distress syndrome

Tie-Yan Wang, MB[a], Ying Zhu, MM[a], Jia-Lin Yin, MB[a], Li-Yan Zhao, MB[b], Hai-Jun Wang, MM[c,*], Chun-Wang Xiao, MD[d], Li-Yan Wu, MB[c]

Abstract

Objective: To investigate the efficacy of high-frequency oscillatory ventilation (HFOV) combined with pulmonary surfactant (PS) in the treatment of neonatal respiratory distress syndrome (NRDS).

Methods: This study is a retrospective clinical study. Seventy-two NRDS neonates were selected as the subjects from November 2019 to November 2020, and divided into observation group (40 cases, HFOV treatment) and control group (32 cases, conventional mechanical ventilation treatment). All cases were treated with PS and comprehensive treatment. The therapeutic effect, arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), Percentage of inhaled oxygen concentration (FiO_2), mean arterialpressure, oxygenation index (OI), and complications were compared in the 2 groups.

Results: The total effective rate of the observation group was 90.0%, significantly higher than that of the control group. After treatment, the observation group has higher PaO_2 levels and lower levels of $PaCO_2$, mean arterial pressure, FiO_2, and OI than the control group. There was no significant difference in the incidence of complications between the 2 groups.

Conclusion: HFOV combined with PS has a significant effect on NRDS, which can improve the arterial blood gas index without increasing the incidence of complications.

Abbreviation: CMV = conventional mechanical ventilation, FiO_2 = Percentage of inhaled oxygen concentration, HFOV = high-frequency oscillatory ventilation, MAP = mean arterialpressure, NICU = neonatal intensivecare unit, NRDS = neonatal respiratory distress syndrome, OI = oxygenation index, $PaCO_2$ = arterial partial pressure of carbon dioxide, PaO_2 = arterial partial pressure of oxygen, PS = pulmonary surfactant.

Key Words: arterial blood gas index, high-frequency oscillatory ventilator, neonatal respiratory distress syndrome, pulmonary surfactant

1. Introduction

Neonatal respiratory distress syndrome (RDS) is a disease that is unique to newborn infants. It is caused by a deficiency of pulmonary surfactant (PS), which is usually ready to be activated around the perinatal period. NRDS is a leading cause of morbidity in premature newborns and is a common reason for admission to the neonatal intensive care unit (NICU).[1] The etiology of NRDS is complex, and the main cause is the lack of pulmonary surfactant (PS).[2] According to some reports, pulmonary surfactants can increase lung compliance, reduce inspiratory resistance, and maintain stable alveolar volume in NRDS, but the efficacy was difficult was not satisfactory.[3] Some studies have shown that it is difficult to achieve the ideal effect by using a single treatment method in NRDS, and PS combined with respiratory support is often used in clinical treatment.[4]

High-frequency oscillatory ventilation (HFOV) is a new type of ventilation, and noninvasive HFOV has been developed into a common way of high-frequency ventilation in neonates.[5,6] HFOV has the characteristics of high ventilation frequency, low tidal volume and low ventilation pressure, and can increase convection and diffusion with the help of high-speed gas, correct arterial blood gas, avoid lung injury, and reduce the rate of oxygen poisoning.[7,8] High-tidal volume is one of the main causes of lung injury. Compared with conventional mechanical

All authors agreed the submission and the policy of the journal and copyright.

The authors have no funding and conflicts of interest to disclose.

All data in this study can be obtained by proper request from the authors.

The present study was approved by the ethic committee of The First Affiliated Hospital of Qiqihar Medical University of Science and Technology.

[a] Department of Paediatrics, The Second Affiliated Hospital of Qiqihar Medical University, Heilongjiang, China, [b] Department of Neonatology, Qiqihar Traditional Chinese Medicine Hospital, Heilongjiang, China, [c] Department of Pediatrics, The First Affiliated Hospital of Qiqihar Medical University, Heilongjiang, China, and [d] Department of Sarcomaand Nano-oncology Group, Adult Cancer Program, Lowy Cancer Research Centre, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia.

** Correspondence: Hai-Jun Wang, MM, Department of Pediatrics, The First Affiliated Hospital of Qiqihar Medical University, Qiqihar, 37 Zhonghua West Road, Jianhua District, Heilongjiang 161002, China (e-mail: haijunw@126-web.net).*

How to cite this article: Wang T-Y, Zhu Y, Yin J-L, Zhao L-Y, Wang H-J, Xiao C-W, Wu L-Y. The effect of high-frequency oscillatory ventilator combined with pulmonary surfactant in the treatment of neonatal respiratory distress syndrome. Medicine 2022;101:32(e29940).

Received: 24 May 2021 / Received in final form: 24 May 2022 / Accepted: 16 June 2022

http://dx.doi.org/10.1097/MD.0000000000029940

ventilation (CMV), HFOV has the advantages of low tidal volume and high ventilation frequency, which is one of the main reasons that HFOV can effectively reduce the incidence of lung injury and oxygen poisoning in the process of treatment.[9,10] This study aimed to investigate the clinical efficacy and safety of HFOV combined with PS in the treatment of NRDS.

2. Material and Methods

2.1. General data

From November 2019 to November 2020, 72 cases of NRDS neonates in our hospital were selected and divided into observation group (n = 40, HFOV combined with PS) and control group (n = 32, CMV combined with PS) according to the treatment methods. Research flowchart was shown in Figure 1. There were 21 males and 19 females in the observation group; the gestational age was 29 to 34 weeks, with an average of 31.15 ± 1.55 weeks; 1 minute after birth, Apgar score was 4 to 5, with an average of (4.49 ± 0.31). There were 17 males and 15 females in the control group; gestational age was 28 to 34 weeks, with an average of 31.5 ± 1.40 weeks; Apgar score was 4 to 5 at 1 minute after birth, with an average of (4.53 ± 0.29). There was no significant difference in general data between the 2 groups (Table 1).

2.2. Inclusion and exclusion criteria

According to the NRDS diagnostic criteria in the European consensus guidelines for the prevention and treatment of NRDS,[11] the inclusion criteria as follows:(1) acute onset, shortly after birth, respiratory distress occurs, manifested as shortness of breath, cyanosis, nose fan, inhale three concave sign, and so on, oxygen ineffective, need auxiliary ventilation; (2) respiratory distress is progressive aggravate; (3) chest X-ray film showed a general decrease in translucency of both lungs, reticular, granular shadows, bronchial bronchograms, and severe cases were "white lungs." Exclusion criteria: (1) dyspnea caused by other congenital malformations, such as heart and respiratory tract, intrauterine infectious pneumonia, and meconium aspiration syndrome. This study was approved by ethics committee of second affiliated hospital of Qiqihar Medical University.

2.3. Treatment

The neonates in both groups were injected with 80 to 100 mg of PS (Curosurf, Chiesi Farmaceutici S.p.A) through endotracheal intubation before operation. Meanwhile, they were given conventional treatment such as keeping warm, maintaining water-electrolyte balance, improving microcirculation, intravenous nutrition, using antibiotics and so on. The control group was given CMV treatment. Using Germany Siemens MAQUET ventilator, parameter set as follows: peak inspiratory pressure (15–25 cmH_2O), positive end-expiratory pressure (4–6 cmH_2O), expiratory frequency (40–60 beats/min), percentage of inhaled oxygen concentration (FiO2, 50%–80%, adjusted according to blood oxygen detection), respiratory ratio (1: [1.0–1.5]), which were adjusted by comprehensive blood gas analysis, clinical symptoms, and ECG monitoring index.

The observation group was given HFOV treatment. Using the high-frequency oscillatory ventilator (Stephanie, SERVO-1), the parameters set as follows: frequency (12–15 Hz), average airway pressure (10–15 cmH_2O), pressure amplitude (30–45 cmH_2O), inspiratory time percentage (33%), FiO_2 (40%–60%), which were adjusted by comprehensive blood gas analysis, clinical symptoms, and ECG monitoring index.

2.4. Main outcome measures

We judged the infant's condition according to the "2019 European guidelines for the management of respiratory distress syndrome."[11]

(1) The therapeutic effects of the 2 groups were compared. After 12 hours of treatment, the child's breathing was stable, X-ray showed that the bilateral lung permeability was significantly improved, lung expansion was good, SaO_2 was more than 85%, and cyanosis, dyspnea, groan, and other symptoms disappeared completely, which was judged as a significant effect. After 12 hours of treatment, SaO_2 was maintained at 70%–80%, cyanosis, dyspnea, groan, and other symptoms were alleviated, and X-ray showed that the patient's breathing was stable, which was judged as an effect. After 12 hours of treatment, SaO_2 < 75%, cyanosis, dyspnea, groan, and other symptoms did not improve, chest X-ray showed that the pulmonary ground-glass shadow did not reduce or even aggravate, it was judged as invalid. Total effective rate = (markedly effective cases + effective cases)/total cases × 100%.
(2) The changes of arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), FiO_2, mean arterial pressure, and oxygenation index (OI = 100 × mean arterial pressure × FiO_2/PaO_2) were compared between the 2 groups before treatment, 12 hours after operation and 24 hours after operation.
(3) Complications including pneumothorax, pulmonary hemorrhage, and pneumonia were recorded.

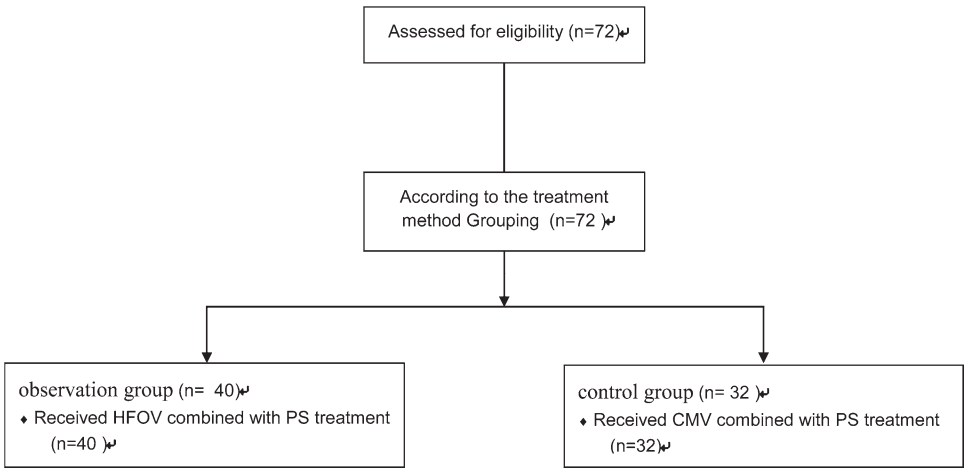

Figure 1. Research flowchart.

Table 1

General clinical data of the 2 groups.

Variables	Control (n = 32)	Observation (n = 40)	95% CI	P
Gestational age (week)	31.50 ± 1.40	31.15 ± 1.55	–1.049 to 0.358	.331
Sex male (%)	17 (53.13)	21 (52.50)	0.589 to 1.787	.929
1 min Apgar	4.53 ± 0.29	4.49 ± 0.31	–0.173 to 0.109	.658
Steroid hormone therapy, n (%)	3 (9.38)	3 (7.5)	0.468 to 0.348	.633

2.5. Statistical analysis

SPSS 25.0 software and Graphpad prism 6.0 were used to analyze data. The measurement data were expressed as (mean ± SD), and the Student *t* test was used for comparison between 2 groups. The rates were compared by Chi-square test. $P < .05$ was considered as statistically different.

3. Results

3.1. Comparison of therapeutic effect between the 2 groups

The total effective rate of the observation group (90.0%) was higher than that of the control group (71.87%), the difference was statistically significant ($P < .05$, Table 2).

3.2. Comparison of mechanical ventilation time, hospital stay, and survival rate between the 2 groups

The mechanical ventilation time and a hospital stay of the observation group were shorter than those of the control group ($P < .05$), and there was no significant difference in survival rate between the 2 groups ($P > .05$, Table 3).

3.3. Comparison of blood gas indexes between the 2 groups after treatment

Before treatment, there was no significant difference in arterial blood gas indexes between the 2 groups (the data was not shown). After treatment, compared with the control group, the blood gas analysis of the observation group was significantly better than that of the control group after 12 hours and 24 hours of treatment, and the FiO_2 and OI were significantly lower ($P < .05$, Table 4).

Table 2

Comparison of therapeutic effect between the 2 groups.

Variables	Control (n = 32)	Observation (n = 40)	95% CI*	P
Efficacy, n (%)				
Significantly effective	16 (50.0%)	24 (60.00%)		
Effective	7 (21.87%)	12 (30.00%)	0.004 to 0.006	.005
Invalid	9 (28.13%)	4 (10.00%)		

CI = confidence intervals.

Table 3

Comparison of mechanical ventilation time, hospital stay and survival rate between the 2 groups.

Variables	Control (n = 32)	Observation (n = 40)	95% CI	P
Mechanical ventilation time (h)	92.40 ± 6.90	84.41 ± 5.00	–10.798 to –5.194	<.001
Hospital duration (d)	34.41 ± 2.46	27.95 ± 1.88	–10.912 to –5.080	<.001
Survival rate, n (%)	27 (84.37)	36 (90.00)	0.257 to 1.400	.234

CI = confidence intervals.

3.4. Complications of the 2 groups

There was no significant difference in the incidence of pneumonia, pneumothorax, and pulmonary hemorrhage between the 2 groups ($P > .05$, Table 5).

4. Discussion

PS is a complex of lipids and proteins, which is aggregated and secreted by alveolar epithelial cells into a thin layer of fluid covering the respiratory surface of the lung, where the surfactant forms a surface film at the air-water interface. PS can significantly reduce the surface tension, thereby stabilizing the interface exposed to air and preventing alveolar collapse from respiratory mechanics.[12] With the progress of medical technology and the wide clinical application of PS, the cure rate of NRDS neonates has improved, but some neonates with severe illness still cannot achieve satisfactory curative effect,[13] especially CMV cannot achieve ideal ventilation and oxygenation effect under low oxygen concentration and pressure.[14] HFOV is a lung protection high-frequency ventilation strategy, and it is also the most frequent one among all high-frequency ventilation at present. It can improve oxygenation and reduce PaO_2 by enhancing gas exchange through convection and diffusion.[15]

This study observed the effect of PS combined with HFOV in the treatment of NRDS children. The results showed that

Table 4

Comparison of blood gas indexes of the 2 groups after 12 and 24 hours of treatment.

Variables		Control (n = 32)	Observation (n = 40)	95% CI	P
PaO_2 (mm Hg)	12 h	66.31 ± 6.48	70.56 ± 7.08	1.024 to 7.476	.011
	24 h	76.14 ± 8.33	82.54 ± 10.75	1.787 to 11.010	.007
$PaCO_2$ (mm Hg)	12 h	49.58 ± 4.58	44.46 ± 3.15	–6.941 to –3.299	<.001
	24 h	47.75 ± 3.52	38.61 ± 2.38	–10.530 to –7.749	<.001
MAP (cmH_2O)	12 h	10.37 ± 2.81	9.24 ± 1.41	–2.14% to –0.115	.029
	24 h	9.67 ± 2.16	8.05 ± 1.47	–2.475 to –0.764	<.001
FiO_2 (%)	12 h	0.72 ± 0.09	0.68 ± 0.07	–0.077 to –0.002	.037
	24 h	0.64 ± 0.08	0.55 ± 0.06	0.122 to –0.057	<.001
OI	12 h	21.96 ± 2.67	18.52 ± 2.26	–4.599 to –2.281	<.001
	24 h	15.31 ± 1.68	12.37 ± 1.54	–3.698 to –2.182	<.001

CI = confidence intervals, FiO_2 = percentage of inhaled oxygen concentration, MAP = mean arterial pressure, OI = oxygenation index, $PaCO_2$ = arterial partial pressure of carbon dioxide, PaO_2 = arterial partial pressure of oxygen.

Table 5

Comparison of complications in 2 groups.

Variables	Control (n = 32)	Observation (n = 40)	95% CI*	P
Complications, n (%)	14 (43.75)	17 (42.5)		
Pneumonia	8 (25.00)	8 (20.00)		
Pneumothorax	3 (9.38)	4 (10.00)	0.503 to 0.523	.513
Pulmonary hemorrhage	3 (9.38)	5 (12.50)		

*95% CI of this Chi-square test was calculated by Monte Carlo test.
CI = confidence intervals.

the effective rate of the observation group was 90.00%, which was significantly higher than that of the control group (71.87%). The mechanical ventilation time and a hospital stay of the observation group were shorter than those of the control group, but there was no significant difference in the survival rate between the 2 groups, which indicated that the effect of PS combined with HFOV in the treatment of NRDS children was better than that of CMV combined with PS. PS combined with HFOV can significantly shorten the hospitalization time, tracheal intubation time, mechanical ventilation time, and reduce the medical burden, which is similar to previous reports.[16,17] Moreover, after 12 and 24 hours of treatment, the PaO_2 value of the observation group was significantly higher than that of the control group. While the $PaCO_2$, FiO_2 and OI of the observation group were significantly lower than those of the control group, indicating that the combination of PS and HFOV in the treatment of NRDS can better improve the blood gas index of children. Finally, the oxygen concentration and oxygenation index decreased faster, which is conducive to protecting the lung tissue of neonates, and avoiding oxygen poisoning caused by high oxygen concentration and high blood oxygen partial pressure. These data were consistent with the conclusion of previous studies[18,19] that HFOV can improve abnormal blood gas analysis and lower oxygen concentration more quickly. Compared with CMV, HFOV can rapidly increase gas convection and dispersion through high-speed gas flow, and has a higher removal rate of carbon dioxide, which can significantly improve the state of hypoxia and reduce the body damage caused by high respiratory parameters. At the same time, HFOV can reduce the pressure fluctuation in the airway, maintain the optimal lung volume, and promote the rapid and effective gas exchange in lung tissue, which is beneficial to correct carbon dioxide retention and low blood oxygen. Combined with PS treatment, it can reduce the lung surface tension, improve the lung tissue compliance and oxygenation function, reduce the oxygen concentration, and keep the alveolar tissue stable in the low lung volume state.[20,21] Therefore, the improvement effect of arterial blood gas index in the observation group is better than that in the control group.

In addition, this study found that pneumothorax, pulmonary hemorrhage and pneumonia complications occurred in both groups, suggesting that the above risks exist in both mechanical ventilation methods. We speculated that the reason may be that after the use of mechanical ventilation and PS treatment, the lung compliance is improved, the lung ventilation and ventilation are improved, the pulmonary vessels are expanded, a large amount of blood quickly enters the lung tissue, causing congestion and edema, causing pulmonary hemorrhage and other pulmonary complications. Therefore, during mechanical ventilation, we should actively prevent these complications, maintain the blood oxygen saturation at 88% to 90%. If necessary, take chest film to evaluate the degree of lung expansion, and timely adjust the parameters of the ventilator according to the results of arterial blood gas analysis and chest film examination, to maintain the best lung volume and avoid excessive lung expansion. Wang et al have reported that compared with CMV combined with PS treatment, the complication rate of HFOV combined with PS treatment was lower.[22]In this study, there was no significant difference in the incidence of complications between the 2 groups, which was consistent with the results reported by Huang et al.[23]

Our study has several limitations: First, the sample size of the study is small. Second, the 2 groups of infants were not evaluated in terms of receiving other drug treatments (such as vitamin A compounds, corticosteroids). Third, the times of PS treatment and infant side effects were not counted.

In conclusion, the efficacy of PS combined with HFOV in the treatment of NRDS is significantly higher than that of PS combined with CMV. The blood gas index of the former is better improved, and there is no significant increase in complications, which is worthy of clinical promotion and practice.

Author contributions

TYW conducted most of the experiments and wrote the manuscript; YZ, JLY,LYZ and CWX conducted the experiments and analyzed the data, LYW designed the study and revised the manuscript. All authors have read and approved the manuscript.

References

[1] Liu J, Cao HY, Wang HW, et al. The role of lung ultrasound in diagnosis of respiratory distress syndrome in newborn infants. Iran J Pediatr. 2015;25:e323.

[2] Sardesai S, Biniwale M, Wertheimer F, et al. Evolution of surfactant therapy for respiratory distress syndrome: past, present, and future. Pediatr Res. 2017;81:240–8.

[3] Zhang L, Cao H, Zhao S, et al. Effect of exogenous pulmonary surfactants on mortality rate in neonatal respiratory distress syndrome: a network meta-analysis of randomized controlled trials. Pulm Pharmacol Ther. 2015;34:46–54.

[4] Wang L, Mao Q, Yang L. Effect of pulmonary surfactant combined with mechanical ventilation on oxygenation functions and expressions of serum transforming growth factor-beta1 (TGF-β1) and bone morphogenetic protein 7 (BMP-7) of neonatal respiratory distress syndrome. Eur Rev Med Pharmacol Sci. 2017;21:4357–61.

[5] Erdeve O, Okulu E, Tunc G, et al. An observational, prospective, multicenter study on rescue high-frequency oscillatory ventilation in neonates failing with conventional ventilation. PLoS One. 2019;14:e0217768.

[6] Gaertner V, Waldmann A, Davis P, et al. Transmission of oscillatory volumes into the preterm lung during noninvasive high-frequency ventilation. Am J Respir Crit Care Med. 2020.

[7] Schäfer C, Schumann S, Fuchs H, et al. Carbon dioxide diffusion coefficient in noninvasive high-frequency oscillatory ventilation. Pediatr Pulmonol. 2019;54:759–64.

[8] Wong R, Deakers T, Hotz J, et al. Volume and pressure delivery during pediatric high-frequency oscillatory ventilation. Pediatr Crit Care Med. 2017;18:e189–94.

[9] Snoek KG, Capolupo I, van Rosmalen J, et al. Conventional mechanical ventilation versus high-frequency oscillatory ventilation for congenital diaphragmatic hernia: a randomized clinical trial (The VICI-trial). Ann Surg. 2016;263:867–74.

[10] Bauer K, Nof E, Sznitman J. Revisiting high-frequency oscillatory ventilation in vitro and in silico in neonatal conductive airways. Clin Biomech (Bristol, Avon). 2019;66:50–9.

[11] Sweet D, Carnielli V, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome - 2019 update. Neonatology. 2019;115:432–50.

[12] Echaide M, Autilio C, Arroyo R, et al. Restoring pulmonary surfactant membranes and films at the respiratory surface. Biochim Biophys Acta Biomembr. 2017;1859(9 Pt B):1725–39.

[13] Pan S, Zhang Z. Less invasive surfactant administration combined with nasal high frequency oscillatory ventilation for an extremely low birth weight infant with severe hypercapnia: a case report. Medicine. 2020;99:e22796.

[14] Solberg MT, Solevåg AL, Clarke S. Optimal conventional mechanical ventilation in full-term newborns: a systematic review. Adv Neonatal Care. 2018;18:451–61.

[15] Li Y, Wei Q, Zhao D, et al. Non-invasive high-frequency oscillatory ventilation in preterm infants after extubation: a randomized, controlled trial. J Int Med Res. 2021;49:300060520984915.

[16] Chen D, Huang XL, Li XP. Clinical application of high-frequency oscillatory ventilation for the treatment of neonatal pneumothorax. Zhongguo Dang Dai Er Ke Za Zhi. 2012;14:499–501.

[17] Qiao JY, Li YZ, Wang HY, et al. A meta analysis of the efficacy of high-frequency oscillatory ventilation versus conventional mechanical ventilation for treating pediatric acute respiratory distress syndrome. Zhongguo Dang Dai Er Ke Za Zhi. 2017;19:430–5.

[18] Chattopadhyay A, Gupta S, Sankar J, et al. Outcomes of severe PARDS on high-frequency oscillatory ventilation - a single centre experience. Indian J Pediatr. 2020;87:185–91.
[19] Zhou B, Zhai J, Wu J, et al. Different ventilation modes combined with ambroxol in the treatment of respiratory distress syndrome in premature infants. Exp Thera Med. 2017;13:629–33.
[20] Meyers M, Rodrigues N, Ari A. High-frequency oscillatory ventilation: a narrative review. Can J Respir Ther. 2019;55:40–6.
[21] Taki K, Huang DT. High-frequency oscillation in early adult respiratory distress syndrome. Crit Care. 2014;18:310.
[22] Wang S, Zhang C, Wang X, et al; Pediatrics DO, Hospital DP. Effect of high frequency oscillatory ventilation combined with pulmonary surfactant on neonatal acute respiratory distress syndrome. China Health Std Manag. 2017.
[23] Huang F, Chen X, Rao H; Pediatrics DO. High frequency oscillatory ventilation combined with pulmonary surfactant in treatment of neonatal respiratory distress syndrome. J North Sichuan Med Coll. 2017.