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ORIGINAL ARTICLE

Observational Study

Effects of pulmonary surfactant combined with noninvasive positive pressure ventilation in neonates with respiratory distress syndrome

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Abstract

BACKGROUND

Neonatal respiratory distress syndrome (NRDS) is one of the most common diseases in neonatal intensive care units, with an incidence rate of about 7% among infants. Additionally, it is a leading cause of neonatal death in hospitals in China. The main mechanism of the disease is hypoxemia and hypercapnia caused by lack of surfactant

AIM

To explore the effect of pulmonary surfactant (PS) combined with noninvasive positive pressure ventilation on keratin-14 (KRT-14) and endothelin-1 (ET-1) levels in peripheral blood and the effectiveness in treating NRDS.

METHODS

Altogether 137 neonates with respiratory distress syndrome treated in our hospital from April 2019 to July 2021 were included. Of these, 64 control cases were treated with noninvasive positive pressure ventilation and 73 observation cases were treated with PS combined with noninvasive positive pressure ventilation. The expression of KRT-14 and ET-1 in the two groups was compared. The deaths, complications, and PaO_2, $PaCO_2$, and PaO_2/FiO_2 blood gas indexes in the two groups were compared. Receiver operating characteristic curve (ROC) analysis was used to determine the diagnostic value of KRT-14 and ET-1 in the treatment of NRDS.

RESULTS

The observation group had a significantly higher effectiveness rate than the control group. There was no significant difference between the two groups in terms of neonatal mortality and adverse reactions, such as bronchial dysplasia, cyanosis, and shortness of breath. After treatment, the levels of PaO_2 and PaO_2/FiO_2 in both groups were significantly higher than before treatment, while the level of $PaCO_2$ was significantly lower. After treatment, the observation group had significantly higher levels of PaO_2 and PaO_2/FiO_2 than the control group, while $PaCO_2$ was notably lower in the observation group. After treatment, the KRT-14 and ET-1 levels in both groups were significantly decreased compared with the pre-treatment levels. The observation group had a reduction of KRT-14 and ET-1 levels than the control group. ROC curve analysis showed that the area under the curve (AUC) of KRT-14 was 0.791, and the AUC of ET-1 was 0.816.

CONCLUSION

Combining PS with noninvasive positive pressure ventilation significantly improved the effectiveness of NRDS therapy. KRT-14 and ET-1 levels may have potential as therapeutic and diagnostic indicators.

Key Words: Pulmonary surfactant; Non-invasive positive pressure ventilation; Neonatal respiratory distress syndrome; Keratin-14; Endothelin-1

Core Tip: The purpose of this study was to explore the effect of pulmonary surfactant (PS) combined with noninvasive positive pressure ventilation on the levels of keratin-14 (KRT-14) and endothelin-1 (ET-1) in peripheral blood and the effectiveness for treating neonatal respiratory distress syndrome (NRDS). KRT-14 and ET-1 expression in the two groups was compared. The therapeutic effectiveness, occurrence of death and complications, and the blood gas indexes PaO_2, $PaCO_2$ and PaO_2/FiO_2 in the two groups were compared. Receiver operating characteristic curve analysis was used to determine the diagnostic value of KRT-14 and ET-1 for the effectiveness of NRDS therapy. PS combined with noninvasive positive pressure ventilation significantly improved the effectiveness of NRDS therapy. KRT-14 and ET-1 levels may have potential as diagnostic indicators of therapy.

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INTRODUCTION

Neonatal respiratory distress syndrome (NRDS) is one of the most common conditions in neonatal intensive care units. The incidence is about 7% and it is one of the main causes of neonatal death in hospitals in China[1,2]. The main mechanism of the disease is hypoxemia and hypercapnia caused by lack of surfactant. The diffusion efficiency of oxygen through the alveolar-capillary exchange barrier is disturbed owing to various factors, and lung injury in neonates leads to asthma, septicemia, pneumonia, and other complex symptoms[3]. Premature delivery of pregnant women and pregnancy disease may lead to morbidity. Only early diagnosis and treatment can improve the quality of life of neonates[4,5].

As the pathogenesis of NRDS is the lack of pulmonary surfactant, exogenous pulmonary surfactant (PS) replacement therapy has been found to be an effective treatment[6]. When neonates suffer from respiratory failure, respiratory support can also improve their condition. However, invasive ventilation tends to cause a series of complications such as lung infection, ventilator-associated lung injury, *etc* that draws attention to its widespread use[7]. It has been found in many studies that noninvasive positive pressure ventilation significantly improves NRDS neonates and has good safety[8,9]. At the same time, some studies have found that PS combined with non-invasive positive pressure ventilation can further improve clinical efficacy[10].

Keratin-14 (KRT-14) is a cytoskeleton protein that has good diagnostic value for lung tissue injury[11]. A study by Confalonieri[12] reported that KRT-14 was a viable biomarker for activation and repair/regeneration of lung cells. It is involved in the repair and regeneration of alveoli when the alveoli collapse, and lung cells are severely damaged in neonates with NRDS. Therefore, KRT14 may be used as an indicator of the improvement of the condition of neonates with RDS. Endothelin-1 (ET-1) is a vasoactive substance, which is mainly produced in lung tissue. It promotes the gradual change of pulmonary vascular reactivity through angiogenesis. It participates in vascular regulation, bronchoconstriction, and inflammatory reactions in the respiratory system. Endothelial and epithelial dysfunction in RDS patients can be induced of pro-inflammatory mechanisms. The use of endothelin receptor antagonists can regulate lung injury[13,14]. El Shemi *et al* team[15] examined the plasma ET-1 concentration of 69 premature neonates from 28 to 34 wk of age and diagnosed with NRDS. They found that the ET-1 concentration increased significantly 3 d after birth, and was predictive of the development of bronchopulmonary dysplasia. At present, there are few study results on the correlation of KRT-14

and ET-1 with the curative effect of NRDS neonates. Therefore, this study aimed to provide a basis and direction for clinical research on PS combined with noninvasive positive pressure ventilation to treat NRDS in neonates and observe the KRT-14 and ET-1 levels in peripheral blood.

MATERIALS AND METHODS

Study population

A total of 137 neonates with NRDS were treated in our hospital between April 2019 and July 2021 and were included in the study. The neonates had been admitted to the hospital and received basic treatment to ensure smooth breathing, protect against infection, and maintain water and electrolyte balance. Sixty-four infants, 37 males and 27 females, were included in a control group that received noninvasive positive pressure ventilation and basic treatment. The other 73 infants, 38 males and 35 females, were included in an observation group treated with PS combined with noninvasive positive pressure ventilation in addition to basic treatment. The study was approved by the Medical Ethics Committee, and the parents of all infants signed an informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: All neonates included in the study had complete clinical data, were diagnosed NRDS by imaging using the diagnostic criteria established by the 2016 update of the European Consensus Guidelines on the management of respiratory distress syndrome[16]. All families agreed with the treatment and follow-up. Exclusion criteria: Neonates with congenital immune defects, status complicated by other respiratory diseases, acute infectious disease, liver and kidney insufficiency, or allergic to therapeutic drugs or methods were excluded.

Therapies

After admission, the two groups of neonates were treated with 21%-80% oxygen at a 6-8 L/min gas flow rate, and 4-7 cmH_2O pressure. If the continuous positive airway pressure decreased to 2-3 cmH_2O and the oxygen concentration decreased to 25%, and dyspnea was significantly relieved or had disappeared, the treatment was terminated. If the oxygen concentration was > 80%, the pressure was > 6-7 cmH_2O, and the oxygen saturation was < 85% after 6-8 h of treatment, or if type II respiratory failure occurred, the treatment was changed to mechanical ventilation. Based on the above, neonates in the observation group were given exogenous PS[17] by tracheal administration as soon as possible.

Sample collection and ELISA detection

After hospital admission and at 7:00 am the morning after treatment began, 5 mL of sterile venous blood was collected into a coagulation tube, serum was separated by centrifugation at 3000 *g* at 4 °C for 10 min and stored −80 °C. KRT-14 and ET-1 levels were determined by ELISA. The assay wells included a blank with 0 μL standard; a standard with 50 μL of standard substance at different concentrations, and a sample-to-be tested with 10 μL of sample and 40 μL diluent. Nothing was added to the blank well. In addition to the blank wells, 100 μL of horseradish peroxidase-labeled detection antibody was added to each of the standard wells and the sample wells. The reaction wells were sealed and incubated in a water bath at 37 °C for 65 min. The liquid was discarded, and the absorbent paper was patted dry. Each well was filled with washing liquid and allowed to stand for 2 min. The washing liquid was discarded, and the absorbent paper was patted dry. This procedure was repeated six times before 50 μL of substrate A and B solution was added to each well and incubated at 37 °C in the dark for 10 min. The optical density (OD) of each well was measured at 450 nm within 15 min after adding 50 μL of stop solution to each well, and the concentration was calculated.

Efficacy evaluation

After effective treatment, clinical symptoms resolved or improved, abnormal shadows in the lungs disappeared or improved on X-ray films, and blood gas indexes normalized or improved. After Ineffective treatment, the clinical symptoms worsened or did not improve, or the neonate died, X-ray films showed enlarged shadow areas or lack of improvement. Blood gas indexes worsened or did not improve.

Outcome measures

Main the outcome measures were KRT-14 and ET-1 expression in the observation and control groups. The therapeutic effect, death, and complications in the two groups were compared. The secondary outcomes were the clinical data of the two groups of neonates The blood gas indexes PaO_2, PaO_2, and PaO_2/FiO_2 of the two groups of neonates were compared and the value of KRT-14 and ET-1 for predicting the therapeutic effect in NRDS neonates was evaluated by ROC curve analysis.

Statistical analysis

SPSS 20.0 (IBM Corp., Armonk, NY, United States) was used to perform the statistical analysis. GraphPad Prism 7 (GraphPad, La Jolla, CA, United States) was used to graph the collected data. Enumeration data were reported as numbers and percentages (%), and compared by chi-square tests. Measurement data were reported as means ± SD and independent sample *t*-tests were used to compare measurement data that were normally distributed. ROC was used to evaluate the diagnostic value of KRT-14 and ET-1 in the therapeutic effect of NRDS neonates. $P < 0.05$ was regarded as statistically significant.

Table 1 Clinical data

Parameter	Observation group, *n* = 73	Control group, *n* = 64	X^2/t	*P* value
Sex			0.456	0.499
Male	38 (52.05)	37 (57.81)		
Female	35 (47.95)	27 (42.19)		
Gestational age in wk	33.37 ± 2.12	32.87 ± 2.05	1.399	0.164
Body mass in kg	2.82 ± 0.69	2.71 ± 0.58	1.002	0.318
Apgar score	8.47 ± 1.31	8.28 ± 1.26	0.862	0.390
Age of pregnant woman in yr	27.3 ± 4.8	26.5 ± 4.1	1.041	0.230
Hypertension of Pregnant Women	9 (12.33)	5 (7.81)	0.758	0.384
Diabetes of pregnant women	11 (15.07)	7 (10.94)	0.510	0.475
Premature rupture of membranes	9 (12.33)	10 (15.63)	0.310	0.578
Delivery mode				
Eutocia	41 (56.16)	40 (62.50)	0.566	0.452
Cesarean section	32 (43.84)	24 (37.50)		
Premature delivery				
Yes	52 (71.23)	41 (64.06)	0.804	0.370
No	21 (28.77)	23 (35.94)		
Delivery history			0.027	0.870
Primiparity	50 (68.49)	43 (67.19)		
Multiparity	23 (31.51)	21 (32.81)		

RESULTS

Clinical data

Comparison of the clinical data (Table 1) found no significant differences between the two groups in sex, gestational age, body mass, Apgar score, age at pregnancy, hypertension during pregnancy, maternal diabetes, premature rupture of membranes, delivery mode, premature delivery, and delivery history.

Comparison of therapeutic effect and adverse reactions between the two groups

We observed and compared the therapeutic effects of the two groups of neonates after treatment. The effectiveness of treatment was significantly better in the observation group than in the control group. As shown in Table 2 between-group differences in death, bronchial dysplasia, cyanosis, and shortness of breath were not significant.

Blood gas indexes in the study groups

Comparing the blood gas indexes PaO_2, $PaCO_2$, and PaO_2/FiO_2 before and after treatment, found no significant difference between the control and observation groups before treatment. After treatment, PaO_2, and PaO_2/FiO_2 in both groups were significantly higher than before treatment, and $PaCO_2$ was notably lower than before treatment. The levels of PaO_2, PaO_2/FiO_2 in the observation group were considerably higher than the control group, while $PaCO_2$ was considerably lower than the control group, as shown in Figure 1.

Levels of KRT-14 and ET-1 before and after treatment in the two groups

A comparison of the levels of KRT-14 and ET-1 before and after treatment in the two groups revealed that there is no difference between the two groups before the treatment. After treatment, the levels of KRT-14 and ET-1 were significantly reduced in both groups when compared to their pre-treatment levels. Moreover, the levels in the observation group were significantly lower than those in the control group, as shown in Figure 2.

Diagnostic value of therapeutic effects of KRT-14 and ET-1

After comparing the levels of KRT-14 and ET-1 in neonates with effective and ineffective curative effects, we found that neonates with ineffective curative effects had significantly higher levels of KRT-14 and ET-1 than neonates with effective curative effects ($P < 0.05$). ROC curve analysis of the diagnostic value of KRT-14 and ET-1 in the curative effectiveness of NRDS neonates found that the area under the curve (AUC) of KRT-14 was 0.791, and the AUC of ET-1 was 0.816, as shown in Table 3 and Figure 3.

Table 2 Effective therapy and adverse reactions

Outcome	Observation group, *n* = 73	Control group, *n* = 64	*t*	*P* value
Effective curative effect	67 (91.78)	51 (79.69)	4.175	0.041
Ineffective curative effect	6 (8.22)	13 (20.31)		
Death	3 (4.11)	6 (9.38)	1.540	0.215
Bronchial dysplasia	6 (8.22)	11 (17.19)	2.514	0.112
Cyanopathy	8 (10.96)	10 (15.63)	0.651	0.420
Shortness of breath	9 (12.33)	14 (21.88)	2.225	0.136

Table 3 Receiver operating characteristic curve analysis

Index	AUC	95%CI	Specificity, %	Sensitivity, %	Youden index, %	Cut-off
KRT-14	0.791	0.665-0.917	85.47	60.00	45.47	> 3.645
ET-1	0.816	0.726-0.907	76.07	70.00	46.07	> 40.060

AUC: Area under the curve; ET-1: Endothelin-1; KRT-14: Keratin-14.

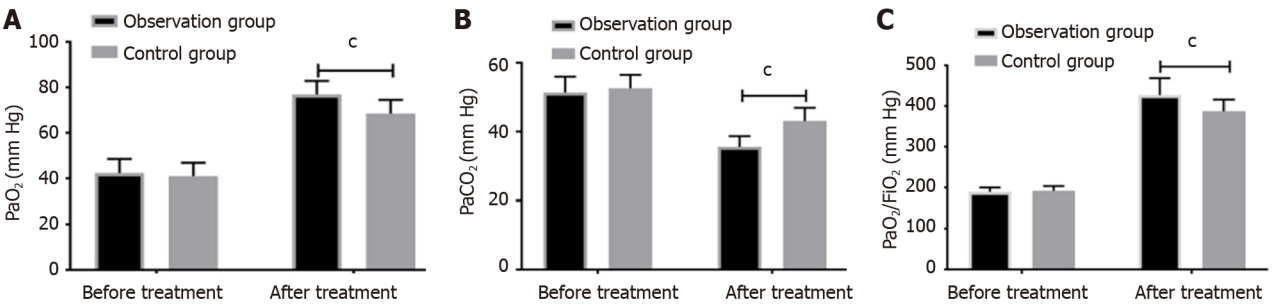

Figure 1 Changes in blood gas indexes before and after treatment. A: There was no significant difference in the PaO_2 in the observation group (42.39 ± 6.14) and in the control group (41.01 ± 5.89) (t = 1.338, P = 0.183). The PaO_2 in both groups was significantly increased after treatment (P < 0.05), and it was significantly higher than the control group (68.54 ± 5.96) than in the observation group (76.92 ± 5.94), (t = 8.226, P < 0.001); B: There was no significant difference in the $PaCO_2$ in the observation group (51.38 ± 4.57) and the control group (52.64 ± 3.89) (t = 1.725, P = 0.087). The $PaCO_2$ in both groups was significantly decreased after treatment (P < 0.05), and in the observation group (35.58 ± 3.10) it was significantly lower than the control group (43.08 ± 3.83) (t = 12.659, P < 0.001); C: There was no significant difference in the PaO_2/FiO_2 of the observation group (189.19 ± 10.95) and in the control group (192.05 ± 11.55) (t = 1.487, P = 0.139). The PaO2/FiO2 was significantly increased in both groups after treatment (P < 0.05), and in the observation group (426.97 ± 41.39), it was significantly higher than the control group (387.18 ± 28.86) (t = 6.115, P < 0.001). °P < 0.001.

DISCUSSION

The pathogenesis of NRDS involves acute diffuse alveolar-capillary injury, which leads to increased pulmonary capillary permeability, and alveolar and interstitial edema, and ultimately gives rise to type II alveolar cell damage. This kind of damage reduces PS, leading to an increase in alveolar surface tension, contraction of alveolar groups, and abnormal pulmonary ventilation/blood flow ratio, eventually triggering severe hypoxemia[18,19]. Noninvasive positive pressure ventilation can relax the alveoli of neonates, improve the compliance of neonate lungs, maintain the pressure in alveoli, and maintain smooth breathing. Exogenous PS can supplement the lack of PS in neonates, thus reducing the tension of alveoli in neonates, preventing alveoli atrophy, improving lung respiratory function and lung compliance, and increasing blood oxygen saturation in NRDS, thus reducing the mechanical ventilation time of neonates[20,21].

We compared the therapeutic effect and adverse reactions of the two groups after treatment and found that the combination of PS and noninvasive positive pressure ventilation had a significantly better therapeutic effect than noninvasive positive pressure ventilation alone. However, the difference of the mortality rates in the two groups was not significant. We also compared the blood gas indexes PaO_2, PaO_2, and PaO_2/FiO_2 of the two groups before and after treatment. After treatment, PaO_2, PaO_2/FiO_2 increased in both groups, and $PaCO_2$ decreased significantly. After treatment, the PaO_2, and PaO_2/FiO_2 levels were significantly higher and PaO2 was significantly lower in the observation group than in the control group. The blood gas levels of neonates with NRDS are significantly worse than those of healthy newborns as a result of differences in lung oxygenation and respiratory function. After the symptoms are controlled and pulmonary function improves, the blood gas index of the neonates returns to normal[22]. The study

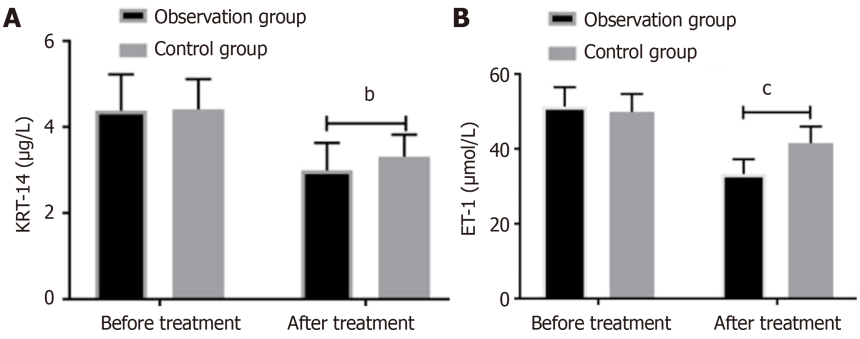

Figure 2 Levels of keratin-14 and endothelin-1 before and after treatment. A: There was no significant difference in keratin-14 (KRT-14) in the observation group (4.38 ± 0.84) and in the control group (4.41 ± 0.70) (t = 0.822, P = 0.225). KRT-14 was significantly decreased in both groups after treatment (P < 0.05), and in the observation group (2.99 ± 0.64), the decrease was significantly lower than the control group (3.31 ± 0.51) (t = 3.206, P < 0.002); B: There was no significant difference in endothelin-1 (ET-1) between the observation group (51.34 ± 5.13) and the control group (49.90 ± 4.75) (t = 1.697, P = 0.092). ET-1 was significantly decreased in both groups after treatment (P < 0.05), and it was significantly lower in the observation group (33.29 ± 3.93), than in the control group (41.51 ± 4.48) (t = 11.441, P < 0.001). ^{b}P < 0.01, ^{c}P < 0.001.

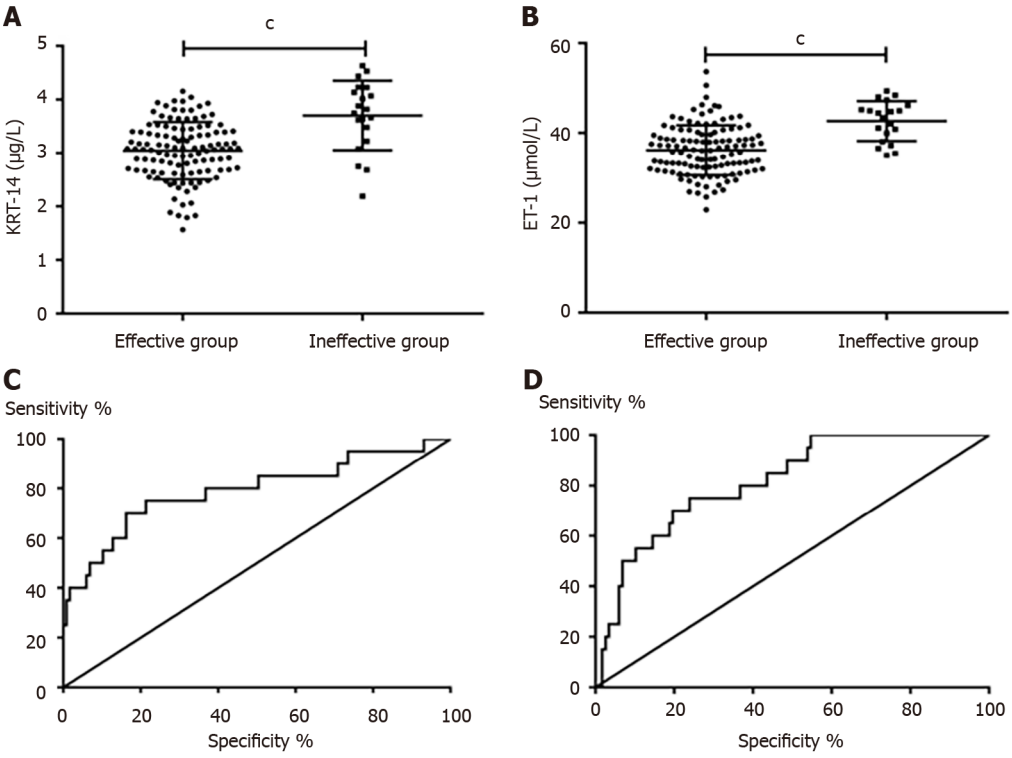

Figure 3 Diagnostic value of the curative effectiveness of keratin-14 and endothelin-1. A: Keratin-14 was significantly lower in neonates with effective therapy (2.94 ± 0.56) than in neonates with ineffective therapy (3.70 ± 0.65) (t = 5.472, P < 0.001); B: Endothelin-1 (ET-1) was significantly lower in neonates with effective therapy (33.80 ± 5.36) than that in neonates with ineffective therapy (42.68 ± 4.48) (t = 6.997, P < 0.001); C: Receiver operating characteristic (ROC) curves of keratin-14 in the diagnosis of effective therapy; D: ROC of ET-1 in diagnosis of therapeutic effect after treatment.

results shows that the combined treatment was more effective.

We measured the levels of KRT-14 and ET-1 in both groups of neonates. KRT-14 and ET-1 are lung tissue factors[23,24] and KRT14 increases rapidly in response to lung injury. Previous studies reported a negative correlation between KRT14 and PaO2/FiO2, and KRT14 is elevated in RDS. We found that KRT-14 and ET-1 levels in both were significantly lower after treatment than they were before treatment, and they were significantly lower in the observation group than in the control group after treatment. Additionally, our findings indicate that KRT-14 and ET-1 levels were significantly elevated in neonates who did not respond effectively to therapy compared with those who did. This suggests that KRT-14 and ET-1 could potentially be valuable diagnostic indicators for neonates with NRDS who are undergoing treatment. Therefore, we the value of KRT-14 and ET-1 for diagnosing therapeutic effectiveness by ROC curve analysis, and the AUC of each factor indicated that both were specific and sensitive. Both factors have diagnostic value in assessing the effectiveness of NRDS treatment in neonates and could potentially serve as diagnostic indices of effective treatment. Thus, KRT-14 can serve as an indicator of improvement in RDS patients, decreasing as their condition improves.

The study has some weaknesses. The subjects included in our study were all sick neonates and healthy newborns were not included for comparison. We did not explore differences between the measures tested in this study and the indexes measured in healthy newborns. Secondly, various types of PS are available for treatment[25], and therefore it is expected that further research can be conducted to assess the differences of the therapeutic effectiveness of different PS preparations. Finally, we found that some complications occurred during the treatment of the neonates, but we did not explore the risk factors of these complications. We hope to add to this discussion after completing our follow-up study.

CONCLUSION

In conclusion, PS combined with noninvasive positive pressure ventilation significantly improved the effectiveness of NRDS therapy. KRT-14 and ET-1 levels are potential therapeutic diagnostic indicators.

FOOTNOTES

Author contributions: Shi ZN, Zhang X, and Du CY were the guarantors of the integrity of the entire study; Zhang X and Zhao B performed the study concept and design; Shi ZN and Liu SG performed the literature study; Shi ZN and Zhang Xin pro conducted the study; Shi ZN and Zhang X conducted the statistical analysis; Shi ZN and Zhang X wrote the manuscript; All authors have access to the data and played a role in writing this manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of the Hospital affiliated to the Military Medical University (Approval No. 2024007).

Informed consent statement: As this study was retrospective, informed consent of patients was not required.

Conflict-of-interest statement: All authors have no conflicts of interest to disclose.

Data sharing statement: Data for this study were obtained from the corresponding authors.

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