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Differences in Clinical Characteristics and Therapy of Neonatal Acute Respiratory Distress Syndrome (ARDS) and Respiratory Distress Syndrome (RDS): A Retrospective Analysis of 925 Cases

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Background: This study assessed the clinical characteristics of neonatal acute respiratory distress syndrome (ARDS) and differences in therapy in comparison to RDS.

Material/Methods: The clinical data of 925 preterm infants with respiratory distress were collected and divided into 4 groups. Group A and B both met the diagnosis of neonatal RDS, whereas infants in group B also showed inflammatory response. Group C met the Montreux definition of neonatal ARDS and group D was the control.

Results: We found that 73.50% of the 925 preterm infants were diagnosed with RDS, of which RDS with inflammatory response accounted for 42.05%. ARDS accounted for 5.29% and control group accounted for 21.19%. Group C infants were the heaviest (2168.16±654.43 g) and had the oldest gestational age. The pregnancy-induced hypertension was highest (30.07%) in group B and lowest in group D (13.26%). Group C had higher iNO and longer invasive ventilator times, but had less frequent surfactant treatment, as well as shorter oxygen time and hospital stay. Group B had significantly longer invasive ventilator use than in Group A. In group A, PDA, ROP, and PPHN were the most common complications, with morbidity rates at 78.35%, 8.4%, and 25.77%, respectively, while group C had higher incidence of PDA (71.42%) and coagulation disorders (38.77%).

Conclusions: ARDS mainly occurs in late preterm infants. Its treatment is dependent on iNO and invasive ventilator-assisted therapy, and the surfactant treatment rate was relatively lower in comparison to RDS. RDS accompanied with inflammatory response is also dependent on prolonged use of an invasive ventilator.

MeSH Keywords: Respiratory Distress Syndrome, Adult • Respiratory Distress Syndrome, Newborn • Systemic Inflammatory Response Syndrome • Therapeutics

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Background

Respiratory distress is a common disease in infants, with an incidence rate of 7% [1], and preterm infants have higher incidences of respiratory distress [1,2]. Clinical manifestations include apnea, cyanosis, wheezing-like breathing, nasal incontinence, feeding intolerance, shortness of breath or apnea, and inspiratory depression. The most common cause of respiratory distress in preterm infants is neonate respiratory distress syndrome (RDS). Speer [3] considers RDS an inflammatory disease. Intrauterine "low" inflammatory stimuli can possibly promote the maturation of the fetal pulmonary surfactant system and protect premature infants from developing moderate to severe RDS. However, if the inflammatory damage to the alveolar-capillary units is too severe, subsequent injury to the "first hit" in the uterus, such as mechanical ventilation or oxygen toxicity, may lead to development of more severe RDS in preterm infants and poor response to surrogate surfactant. Therefore, this study was divided into 2 groups – RDS and RDS accompanied with inflammatory response – to compare their clinical characteristics and treatment.

ARDS is another common cause of respiratory distress, and is often defined according to the criteria of adult ARDS [4]. Although the Pediatric ALI Consensus Conference 2015 (PALICC) [5] developed specific diagnostic criteria for ARDS in children (pARDS) ranging from infants to teenagers, it still excluded preterm newborn with lung disease and perinatal lung injury. In 2017, De Luca et al. [6] proposed the Montreux standard for neonatal ARDS on the basis of pARDS. To better characterize the criteria of neonatal RDS and ARDS, we divided preterm infants into groups based on gestational age, weight, perinatal risk factors, clinical complications, and treatment.

Material and Methods

Grouping

A total of 925 cases of mechanically ventilated preterm infants were collected at BaYi Children's Hospital, Seventh Medical Center of PLA General Hospital, Southern Medical University for Children from January 1, 2014 to July 30, 2017, and divided them into 4 groups: group A was compliance with RDS diagnostic criteria, but no inflammatory response; group B was compliance with RDS diagnostic criteria [7] accompanied with inflammatory response such as ischemia, hypoxia, infection (premature rupture of membranes, amniotic fluid abnormalities, prenatal fever), inhalation, ventilator injury, trauma, poisoning, allergies, circulatory disorders, and others; group C was in line with Montreux definition of neonatal ARDS; and group D was infants with respiratory distress that do not meet the appeal criteria such as temporary respiratory distress in newborns.

Exclusion criteria were: 1) incomplete records; 2) gestational age at birth ≥37 weeks; 3) genetic diseases and other congenital heart disease or primary pulmonary hypertension; 4) treatment abandoned within 72 h after birth due to personal reasons; and 5) other congenital abnormalities such as congenital diaphragmatic hernia or alveolar-capillary dysplasia. This study was approved by the Ethics Committee of the PLA Army General Hospital (series 2017-77).

Diagnostic criteria for the following complications were according to the references: Bronchopulmonary dysplasia (BPD) [8], Retinopathy of prematurity (ROP) [9], Hypoxic-ischemic encephalopathy [10], Persistent pulmonary hypertension of the newborn (PPHN) [11], Necrotizing enterocolitis (NEC) [12], IVH [13], and PDA based on sonography. The criteria for abnormal coagulopathy were: 1) PT reference range (9.8–12.8 s); PT extension for more than 3 s is abnormal; 2) APTT reference range (25.1–36.5 s), APTT extension for 10 s is abnormal; 3) FIB was abnormal outside 2.0–4.0g/L, 4. DD>0.3 mg/L; 5) FDP ≥5 ug/ml; and 6) PLT $<100\times10^9$/L.

A retrospective case-control study was conducted to collect and analyze the following data of children in each group: 1) birth weight, sex, and perinatal status of the mother (pregnancy-induced hypertension, diabetes, multiple pregnancy, placenta, prenatal corticosteroids, Amniotic fluid, thyroid function with or without abnormalities, with or without prenatal fever, stillbirth or spontaneous abortion history); 2) the infant's perinatal status (history of intrauterine asphyxia, Apgar score, mode of delivery), and their blood analysis, including arterial blood PH, partial pressure of oxygen and inhaled oxygen concentration ratio (PaO2/FiO2), at 12 h, 24 h, 48 h, and 72 h after admission, 3) surfactant treatment after birth, 12 h, 24 h, 48 h, and 72 h of assisted ventilation, NO usage, length of stay, and total duration of oxygen use; 4) clinical examinations such as chest radiography, color Doppler, blood tests and other results; 5) complications (including BPD, ROP, HIE, PPHN, IVH, infection, Sepsis, DIC, NEC).

Statistical analysis

Data analysis was performed using SPSS20.0 statistical software. The measured data with normal distribution were recorded as mean ± standard deviation. The *t* test was used for comparisons between 2 groups, and comparison between multiple groups was performed using ANOVA, with SNK test used for each 2-group comparisons. Dataset with non-normal distribution were recorded as the median (interquartile range at [M (P25, P75)]), and the comparison between the 2 groups was done using the rank sum test. Comparison between groups used the chi-square test, and the level of statistical significance was set at $P<0.05$.

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Table 1. General situation of 925 premature infants with respiratory distress.

	Group A (291)	Group B (389)	Group C (49)	Group D (196)	F/χ^2	p	p_1	p_2	p_3
Birthweight	1717.69±649.86	1790.26±624.24	2168.16±654.43	1861.27±562.11	8.09	0.000	0.142	0.000	0.000
Male infant	174 (59.79)	237 (60.92)	28 (57.14)	119 (60.71)	0.31	0.958	0.765	0.727	0.610
Gestational age									
<28	32 (10.99)	23 (5.91)	0 (0)	7 (3.57)	22.77	0.001	0.052	0.015	0.030
28~32	194 (66.66)	279 (71.72)	29 (59.18)	128 (65.30)					
32~36^{+6}	65 (22.33)	87 (22.36)	20 (40.81)	61 (31.12)					

p_1 – P-values between group A (RDS) and group B(with inflammatory factors RDS); p_2 – P-values between group A (RDS) and group C (ARDS); p_3 – P-values between B group (with inflammatory factor RDS) and group C (ARDS).

Results

General information comparison

There were 1220 cases of premature infants with ventilator-assisted breathing in our hospital from January 2014 to December 2017. We excluded 225 cases with incomplete records, 33 cases with treatment abandoned within 72 h after birth due to personal reasons, 6 cases of metabolic genetic disease, and 1 case with esophageal atresia. Thus, a total of 925 cases were included in the study. We found that 73.5% of the cases met RDS diagnosis criteria, of which RDS accounted for 31.45% (group A), RDS with inflammatory factors accounted for 42.05% (group B), 5.29% (group C) met the ARDS diagnosis criteria, and 21.19% (group D) were in the control group. There were 588 males and 337 females in the study, including 63 cases (6.81%) at 28 weeks, 630 cases (68.1%) at 28–32 weeks, and 232 cases (25.08%) at 32–36 weeks. The mean birth weights of groups A to D were 1717.69±649.86 g, 1790.26±624.24 g, 2168.16±654.43 g, and 1861.27±562.11 g, respectively. There was a significant difference in birth weight and gestational age between the 4 groups (P<0.01), and ARDS group was the highest of all. The proportion of males was all high in all 4 groups, and there were no significant differences between the groups (P=0.31) (Table 1).

Perinatal factors comparison

There were no significant differences among the 4 groups in terms of multiple pregnancy, gestational diabetes, placental abruption, prenatal glucocorticoid, thyroid dysfunction, vaginitis, history of stillbirth or spontaneous abortion, intrauterine distress, gestational age, and other factors. The incidence of pregnancy-induced hypertension was the highest in group B (30.07%), followed by group A (21.30%), and was the lowest in group D (13.26%), and the difference was statistically significant (p<0.01). There were significant differences in the incidence of asphyxia when comparing group A against groups B and C, but there was no significant difference between group B and group C (Table 2).

Comparison of treatment

The NO application rate and invasive ventilator use were highest in group C, but PS and oxygen use, as well as duration of hospital stay, were shorter (P<0.05). Invasive ventilator use was significantly longer in group B than in group A (P<0.05), but there were no significant differences in the rate of surfactant treatment and NO use (Table 3).

Comparison of complications

When comparing groups A and B to the control group, IVH, PDA, BPD, ROP, and PPHN complications were significantly higher (P<0.05). PDA, ROP, and PPHN were the most common complications in group A, and the morbidity rates were 78.35%, 8.4%, and 25.77% respectively. The incidences of PDA (71.42%) and coagulation dysfunction (38.77%) were higher in group C. The incidence of air leaks in each group was low, and there was no significant difference between groups. Pulmonary hemorrhage, air leak, gastrointestinal bleeding, and other complications were not significantly different among the 4 groups. However, the peripheral blood leucocytes in group B were higher than in group A (P<0.05), and CRP and PCT infection indexes were higher in group C than in the other groups (P<0.05) (Table 4).

Discussion

Respiratory distress is common in newborns. Premature birth, meconium aspiration (MSAF), cesarean section, gestational diabetes, maternal chorioamnionitis, septicemia, pneumothorax, persistent pulmonary hypertension, and congenital malformations all can lead to respiratory distress. Respiratory distress syndrome in preterm infants is often due to young gestational age, immature type II alveolar cells, and lack of

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Table 2. Comparison of perinatal factors (n=925).

Perinatal factors	Group A (291)	Group B (389)	Group C (49)	Group D (196)	F/χ^2	p	p_1	p_2	p_3
Multiple births	67 (23.02)	74 (24.93)	10 (20.40)	43 (21.93)	1.75	0.626	0.203	0.686	0.816
Gestational hypertension	62 (21.30)	117 (30.07)	8 (16.32)	26 (13.26)	41.25	0.000	0.000	0.060	0.000
Gestational diabetes	84 (28.86)	97 (24.93)	10 (20.40)	49 (25)	2.37	0.499	0.251	0.221	0.487
Placental abruption	21 (7.21)	44 (11.31)	6 (12.24)	20 (10.20)	3.56	0.314	0.072	0.251	0.846
Prenatal glucocorticoid	149 (51.20)	214 (55.01)	18 (36.73)	93 (47.44)	8.33	0.215	0.447	0.150	0.053
Thyroid dysfunction	17 (5.84)	33 (8.48)	1 (2.04)	16 (8.16)	3.96	0.266	0.192	0.488	0.155
Vaginitis	9 (3.09)	21 (5.39)	3 (6.12)	5 (2.55)	4.12	0.249	0.147	0.391	0.742
Abortion history	23 (7.90)	42 (10.79)	6 (12.24)	17 (8.67)	2.21	0.531	0.204	0.281	0.760
Intrauterine distress	28 (9.62)	49 (12.59)	3 (6.12)	14 (7.14)	5.45	0.142	0.226	0.594	0.187
Selective CS	191 (65.63)	232 (59.64)	36 (73.46)	149 (76.02)	16.92	0.001	0.111	0.282	0.061
Low Apgar score	99 (34.02)	105 (26.99)	7 (14.28)	28 (14.28)	27.50	0.000	0.048	0.006	0.055
Maternal age	30.61±5.04	30.49±4.55	30.77±4.63	30.78±4.77	0.19	0.906	0.746	0.834	0.683

p_1 – P-values between group A (RDS) and group B (with inflammatory factors RDS); p_2 – P-values between group A (RDS) and group C (ARDS); p_3 – P-values between B group (with inflammatory factor RDS) and group C (ARDS).

Table 3. Comparison of treatment.

	Group A (291)	Group B (389)	Group C (49)	Group D (196)	F/χ^2	p	p_1	p_2	p_3
NO application	21 (7.21)	27 (6.94)	8 (16.32)	0 (0)	46.68	0.000	0.085	0.000	0.009
Invasive ventilator	5.00 (3.00, 8.00)	5.00 (2.00, 8.00)	6.00 (4.00, 8.00)	5.00 (2.00, 8.00)	9.19	0.027	0.010	0.332	0.037
Non-invasive ventilator	4.00 (2.00, 10.25)	4.00 (2.00, 8.00)	3.00 (2.00, 5.00)	3.00 (2.00, 5.00)	18.57	0.000	0.236	0.032	0.137
Oxygen usage	12.00 (7.00, 25.00)	10.00 (6.00, 20.00)	7.00 (5.00, 16.00)	7.00 (5.00, 12.00)	52.32	0.000	0.085	0.003	0.025
Surfactant treatment	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	1.00 (1.00, 1.75)	1.00 (1.00, 2.00)	11.90	0.008	0.834	0.030	0.032
LOS	29.00 (16.00, 54.00)	27.00 (16.00, 49.75)	19.00 (13.50, 37.00)	25.00 (16.50, 38.50)	13.02	0.005	0.734	0.009	0.008

p_1 – P-values between group A (RDS) and group B (with inflammatory factors RDS); p_2 – P-values between group A (RDS) and group C (ARDS); p_3 – P-values between B group (with inflammatory factor RDS) and group C (ARDS).

alveolar surfactant [14], resulting in inadequate alveolar surface tension during expansion, which results in atelectasis, reduced gas exchange, severe hypoxia, and acidosis. The clinical manifestations appear soon after birth and include progressive dyspnea, bruising, moist exhalation, aspiration concave depression, and respiratory failure. Clinically, however, we found that after administering pulmonary surfactant to some of the preterm infants, their clinical symptoms and oxygenation index did not show significant improvement, and this cannot be explained by cardiac factors such as increased load capacity and/or heart failure (elevated left atrial pressure). We speculate that this was caused by respiratory distress in preterm infants due to congenital alveolar surfactant deficiencies, possibly accompanied with other inflammatory

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Table 4. Comparison of complications.

	Group A (291)	Group B (389)	Group C (49)	Group D (196)	F/χ^2	p	p_1	p_2	p_3
IVH	87 (29.89)	114 (29.30)	7 (14.28)	35 (17.85)	26.24	0.010	0.456	0.147	0.226
HIE	18 (6.18)	43 (11.05)	3 (6.12)	18 (9.18)	2.24	0.525	0.170	1.000	0.707
PDA	228 (78.35)	273 (70.17)	35 (71.42)	117 (59.69)	19.70	0.000	0.017	0.284	0.857
Septicemia	25 (8.59)	29 (7.45)	4 (8.16)	7 (3.57)	4.62	0.202	0.573	1.000	0.778
BPD	53 (18.21)	60 (15.42)	4 (8.16)	7 (3.57)	24.65	0.000	0.334	0.081	0.175
ROP	24 (8.24)	21 (5.39)	0 (0.00)	5 (2.55)	10.52	0.015	0.139	0.033	0.150
NEC	11 (3.78)	15 (3.85)	0 (0.00)	2 (1.02)	5.69	0.128	0.959	0.377	0.393
PPHN	75 (25.77)	71 (18.25)	7 (14.28)	19 (9.84)	20.80	0.000	0.018	0.082	0.494
Pulmonary hemorrhage	33 (11.34)	35 (8.99)	4 (8.16)	10 (5.18)	5.68	0.128	0.314	0.509	1.000
Air leakage	1 (0.34)	5 (1.28)	2 (4.08)	2 (1.02)	5.20	0.118	0.246	0.056	0.179
Coagulation dysfunction	66 (22.68)	95 (24.42)	19 (38.77)	50 (25.51)	5.90	0.116	0.597	0.016	0.031
DIC	8 (2.74)	7 (1.79)	0 (0.00)	1 (0.51)	4.37	0.224	0.404	0.608	1.000
Purulent meningitis	12 (4.12)	16 (4.11)	2 (4.08)	2 (1.02)	4.43	0.219	0.995	1.000	1.000
Gastrointestinal bleeding	12 (4.12)	15 (3.85)	1 (2.04)	6 (3.06)	0.78	0.854	0.860	0.702	1.000
WBC	11.69 (7.73, 18.47)	12.11 (8.07, 18.38)	12.96 (9.59, 18.92)	11.06 (7.84, 13.92)	14.73	0.002	0.048	0.119	0.666
CRP	1.00 (1.00, 16.00)	1.00 (1.00, 11.00)	1.00 (1.00, 5.00)	1.00 (1.00, 1.00)	47.45	0.000	0.645	0.050	0.021
PCT	3.50 (1.18, 25.18)	4.46 (1.13, 25.80)	9.47 (2.59, 50.31)	1.45 (0.81, 13.82)	9.64	0.022	0.342	0.218	0.408

p_1 – P-values between group A (RDS) and group B (with inflammatory factors RDS); p_2 – P-values between group A (RDS) and group C (ARDS); p_3 – P-values between B group (with inflammatory factor RDS) and group C (ARDS).

factors such as ischemia, hypoxia, infection (e.g., premature rupture of membranes, amniotic fluid abnormalities, prenatal fever), inhalation, ventilator injury, trauma, poisoning, allergy, or circulatory disturbance. These inflammatory factors in the alveolar capillaries resulted in alveolar surfactant inactivation or decreased activity, which was secondary to or aggravated by respiratory distress. Speer [3] also considered RDS as an inflammatory disease.

Currently, diagnostic criteria for ARDS in children and adults have been widely recognized, but an ARDS standard for newborns was not established until 2017, by the International Multi-Center Multidisciplinary Group. They developed the corresponding newborn ARDS diagnostic criteria (Montreux standard) [6] based on review of pediatric and adult ARDS diagnostic criteria. These diagnostic criteria include: 1) Acute exacerbation (within 1 week) after clinical or possible injury; 2) Dyspnea not caused by RDS, TTN, or congenital malformations; 3) Irregular and diffusing bilateral descending light transmission, exudation or white lung, and these changes cannot be explained by other reasons such as local effusion, atelectasis, RDS, TTN, or congenital malformations; 4) Congenital heart disease that can be explained by pulmonary edema (in the absence of acute pulmonary hemorrhage and includes patent ductus arteriosus with high pulmonary blood flow), in which cardiac ultrasound can be used to confirm the cause of pulmonary edema; and 5) OI value (oxygenation index) ≥4. The clinical symptoms of neonatal ARDS are similar to those of RDS, but unlike RDS,

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ARDS generally has a relatively clear clinical picture and neonatal ARDS onset should be within 12 h after birth in order to be distinguished from NRDS without PS. In this study, all children in the ARDS group developed disease within 12 h after birth and met the Montreux criteria.

In this study, we divided the respiratory distress of preterm infants into the following 4 groups: an RDS group, an RDS accompanied by inflammatory factors group, an ARDS group, and a control group. By comparing the perinatal risk factors in each group, we found that the incidence of pregnancy-induced hypertension all 4 groups was high, and was highest in the RDS accompanied by inflammatory factors group, most likely due to pregnancy-induced uterine spiral atherosclerosis that resulted in stenosis, atresia, and insufficient placental villous gap perfusion. These could easily lead to fetal ischemia and hypoxia [15], as well as intrauterine hypoxia and acidosis, which could elicit inflammation responses transported through the placenta into the fetus to stimulate the fetus' inflammatory response [16]. Previous studies [17,18] suggested that male sex, pregnant women with diabetes, cesarean section, multiple births, placental abruption, and intrauterine distress are associated with neonatal respiratory distress. Since the infants included in our study all had respiratory distress, there were no significant differences among groups.

In terms of treatment, the ARDS group had more frequent NO use and longer dependency on invasive ventilation, but had infrequent surfactant treatment and shorter total oxygen time and hospital stay. This result is in line with the PALICC recommendation that exogenous surfactants should not be used in conventional ARDS treatment. However, it should be noted that neonatal ARDS may also cause PS secondary to PS deficiency or functional inactivation due to inflammatory responses. Therefore, in this study, some ARDS children were also treated with surfactant. Comparing the RDS accompanied by inflammatory factors group with the RDS group, the former group had longer dependency on invasive ventilation, but there was no difference in the application of surfactant treatment and NO. This result seems to be inconsistent with our experience in clinical practice, possibly due to the interference of gestational age factors. Although the RDS accompanied by inflammatory factors group required multiple surfactant treatments due to inactivation of surfactant, the proportion of preterm and ultra-low birth weight infants in the RDS group was high in this study (these children also need to be given multiple-dose surfactant treatment), resulting in no significant differences between the 2 groups.

In terms of complications, the incidence of PDA, BPD, ROP, PPHN and other complications was higher in the RDS group than in the control group, which is consistent with the results of a previous study [19]. The incidence of PDA and coagulation dysfunction was higher in the ARDS group, aside from inflammatory responses, possibly due to lung injury, apoptosis, coagulation, and fibrinolysis system imbalance. The coagulation profile of ARDS is manifested as local coagulopathy hyperfunction [20]. Although the incidence of coagulation disorders was higher in the ARDS group in this study, there was no significant difference between the 2 groups in the incidence of coagulation dysfunction and DIC. This may be because small doses of heparin sodium (10 U–12.5 U/kg, q6h–q8h) are given to prevent DIC in this unit as they are at high risk for high blood pressure and infections. Therefore, we did not find any difference in the incidence of coagulation dysfunction and DIC among groups. The incidence of air leaks in each group was low in this study, which was possibly related to moderate ventilator use. Interestingly, there was no significant difference in complications between the ARDS group and RDS accompanied by inflammatory factors groups, suggesting that these 2 diseases have similar pathophysiological changes and that inflammatory factors are involved in the pathogenesis of both.

The infection indicators such as WBC, CRP, and PCT in the 4 groups were significantly different. CRP in the ARDS group was significantly different from in the other groups, suggesting that CRP may be more reliable than the other 2 indexes in judging the occurrence of ARDS.

Conclusions

ARDS mainly occurs in late preterm newborns that are clinically dependent on iNO and invasive ventilator-assisted therapy, and the surfactant application rate is relatively lower in comparison to RDS. Newborns diagnosed with RDS accompanied by inflammatory factors need a longer period of invasive ventilation than do those with RDS alone, so the treatment is more promising. Neonatal ARDS and RDS accompanied by inflammatory factors share many similarities in pathology, physiology, treatment, and complications, which provided insight into the study of ARDS. Prospective cohort studies of respiratory distress in preterm newborns of different etiologies (ChiCTR-CPC-17013627) are needed for the study of neonatal ARDS.

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