Efficacy study of pulmonary surfactant combined with assisted ventilation for acute respiratory distress syndrome management of term neonates

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Abstract. The clinical efficacy of pulmonary surfactant (PS) combined with assisted ventilation was assessed for acute respiratory distress syndrome (RDS) management of term neonates. The total sample size was of 60 subjects. Group I: Experimental group, 30 cases were treated with standard of care with tracheal intubation, mechanical ventilation and PS (100-200 mg/kg). In case of hypoxaemia present even after 12 h standard of care was administered again, up to 4 times. Group II: Control group, 30 cases treated with conventional tracheal intubation and mechanical ventilation. PaO_2, PaO_2/FiO_2 and X-ray were compared between the two groups after 24-h treatment. Analysis of the results indicate that the PS combined with ventilation can improve the clinical symptoms and blood gas analysis index of ARDS neonates. The PaO_2, $PaCO_2$, PaO_2/FiO_2 levels were improved in the two groups after treatment, the improvement effect of the experimental group was better than in the control group, $P<0.05$. The surfactant therapy is proved to be effective as preventive and rescue treatment of NRDS in term neonates. This result is supported by conventional concepts and clinical confirmation in patients with lung injury-associated respiratory failure.

Introduction

Surfactant deficiency is major cause of neonatal mortality which ultimately results in respiratory failure/distress. Series of events occurs with tachypnoea (respiratory rate more than 60/min in a resting baby), decreased lung compliance, increased airway resistance. Respiratory distress comprises of retraction, grunting and tachypnoea or sometimes it is also associated with central cyanosis-like associated signs.

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Practically two different presentations may be found in preterm babies: i) Progressive distress; and ii) transient distress. Progressive RD may be due to respiratory distress syndrome (RDS). Transient RD may be found due to hypoglycemia, hypothermia or asphyxia. RD in term neonates have different causes: i) At birth, due to transient tachypnoea of the newborn (TTNB); ii) before birth, due to meconium aspiration syndrome (MAS); iii) at the end of 7 days of life, RD may be due to pneumonia; and iv) shock and hepatomegaly may be due to cardiac causes. Commonest reasons include TTNB, RDS or hyaline membrane disease and meconium respiration syndrome. Remarkable but less common causes are septicemia, pneumothorax and non-pulmonary cause (CHD, polycythemia and anemia) (1,2).

Pulmonary diseases contribute as a major cause for respiratory distress in near term or term born infants; however cardiac, metabolic and neurologic causes also have a role in development of RD (3-5). Maximum chest X-rays of the study have been observed with hyperinflation and fluid in fissures. The lung parenchyma was clear excluding perihilar zones (2-5).

Differential diagnosis of RDS in newborn can be categorized based on causative aspects like most common and less common but significant causes. Iatrogenic RDS or hyaline membrane disease is one of the prime causes of neonatal morbidity and mortality after elective C section (5-9). Hyaline membrane diseases (RDS) is one of the commonest causes for neonatal RD (9,10). It has been observed that infants delivered at 37-38 weeks of pregnancy have more risk of the disease (11). To reduce hospital stay for babies with RD after elective C section, it is advisable to administer betamethasone and prolong the delivery till 39 weeks of gestational age (12).

Bovine and porcine surfactants are used for the neonates of RDS in ICU. The results of these surfactants were analyzed and found to be statistically significant (13,14). Male neonates are more prone to mortality in RDS and ultimately the mortality rate is higher (15). The common phenomenon in term and post term infants is MAS which is another reason for RDS. Many resuscitation experts advise to apply suction to oropharynx of newborn just after delivery of the head. These experts also endorse intubation as well as suction of the airway especially for the depressed newborns with meconium in the liquor (16,17). Intubation is strongly recommended prior to beginning chest compressions. If intubation is not successful or not feasible, a laryngeal mask may be used as quoted in NRP 7th edition.

During delivery, if meconium stained liquor is observed by the obstetrician, oropharyngeal and nasopharyngeal suctioning of newborn is not approved. In infants with decreased APGAR score, endotracheal suctioning is performed soon after delivery. Respiratory distress in newborns is managed with disease specific and supportive treatments. This treatment involves surfactants, oxygen supply, parenteral fluids, ventilation and antibiotics. Antibiotics are used in cases of bacterial infection induced neonatal respiratory distress (18-21).

TTN can be recovered in 5 days and it is not harmful for lung function. Birth weight and gestational age are deciding factors in RDS while MAS is very well treated with newer therapies (22).

Acute lung injury if associated with acute RDS (ARDS) can cause surfactant dysfunction in pubescent and children. Exogenous natural surfactants are used in children with ARDS in one RCT. The results of this study were helpful to decrease demand of oxygen and mortality in experimental group (23). Various non-randomized clinical trials have noted that surfactant therapy helped to ameliorate ventilation characteristics (CO_2 removal and oxygenation) in children with ARDS (24). Larger trials are expected to find out the benefits of exogenous surfactant. Surfactant use remarkably reduces: i) Mechanical ventilation period and ii) stay in ICU.

This therapy also revamped ventilation characteristics in one meta-analysis (oxygenation and elimination of carbon dioxide). It is considered as an exploratory therapy for the treatment of respiratory failure as number of infants included in the trial was very few. Recent synthetic surfactant preparations, schedule of the first dose, frequent dose indications are still debatable issues for surfactant therapies in such patients (25). Surfactants benefits for diseases other than RDS should be elucidated with various trials.

This study aimed to assess the effectiveness of pulmonary surfactant (PS) merged with assisted ventilation for ARDS management of term neonates.

Materials and methods

Patients. Xuzhou University Institutional Ethics Committee approval was obtained. Informed consent/assent form was procured from the parents of the participants of the study. The total sample size was comprised of 60 subjects. In the observation group, 30 cases were treated with standard of care tracheal intubation mechanical ventilation and PS (100-200 mg/kg), if hypoxemia persisted for more than 12 h drug was administered again, up to 4 times.

Grouping. Control group also comprised of 30 cases. Conventional tracheal intubation and mechanical ventilation was used for management of control group participants. PaO_2, PaO_2/FiO_2 and X-ray were compared between the two groups after 24 h treatment.

Inclusion criteria. The inclusion criteria for ARDS includes the abnormally rapid breathing (tachypnoea), intercostals retraction and grunting, demanding increased flow of inspired O_2 generally to <30-40%, with normal serum culture reports and X-ray chest showing hyperinflation and perihilar band. RDS is confirmed by normal serum culture and X-ray chest with reticular granularity i.e., alveolar collapse appearance and airway becomes visible and contains inflammatory exudates and fluid which is characteristic but not pathognomonic in appearance, meconium stained liquor, presence of meconium in the trachea. X-ray chest showing flattened diaphragm, over distention of lungs and alveoli, shaggy opacities, i.e., the features of MAS.

Those cases of congenital pneumonia included cases in which the absolute neutropenia count was <2,000 ml with favourable C-reactive protein and blood culture. X-ray chest with features of well-defined site of lung consolidation, as an area of increased density within a specific lobe i.e., lobar infiltration.

Previous ARDS diagnostic criteria. Congenital heart disease as a non-pulmonary cause of pediatric ARDS diagnostic criteria currently used in 1994 AECC. ARDS standards are as follows: i) Hypoxemia acute onset; ii) chest showed infiltration of both lung shadows; iii) no evidence of congestive heart failure; and iv) continuous hypoxemia, ALI: PaO_2/FiO_2 300 mmHg or when SpO_2 is <98%, SpO_2/FiO_2 315 mmHg, ARDS: PaO_2/FiO_2 200 mmHg or when SpO_2 is <98%, SpO_2/FiO_2 235 mmHg.

ARDS diagnostic criteria in this study. For this study the following diagnostic criteria were used (similar to ARDS criteria being used in China): i) Gestational age >37 weeks; ii) acute onset, onset time to birth within 28 days; iii) associated diseases, there is serious primary disease such as infection, shock, hypoxia and inhalation in the original disease onset or deterioration after a few hours to 1-2 days, the emergence of progressive dyspnea, and cyanosis occurrence. In the back, armpit or chest auscultation of breath sounds, and fine wet rhales, oxygen partial pressure/inspired oxygen concentration (PaO_2/FiO_2) <26.7 kPa (200 mmHg); iv) X-ray changes: Double-lung texture increased, thickening, blurred, showing diffuse small patchy infiltration with compensatory emphysema, for the most early manifestations; large areas of double lung fields, asymmetric and fuzzy edge infiltration shadow. The hilum of the most dense, the brightness of the lungs is generally lower and glass-like, with bronchial signs. Double lung field general density increased, heart shadow is unclear, while the lung performance is the most important; and v) echocardiography showed no left atrial hypertension.

Statistical analysis. The above measured results were statistically processed by SPSS version 17.0 (IBM, Armonk, NY, USA). The data measured are represented as mean ± standard deviation, and the t-test was used. $P<0.05$ was condidered to indicate a statistically significant difference.

Results

Comparisons were made between the PS group and the control group in the general and observed situations.

The results of the study revealed that the male and female ratio in the PS group was 19:11 and in the control group was 17:13. Average gestation age in the PS group was 38.67±1.33 while in the control group was 38.61±0.94. The mean birth weight in the PS group was 3.383±571 and in the control group

Table I. Comparison of the general situation and observed indicators in PS group and the control group.

Project	Therapy group (n=30)	Control group (n=30)	Statistics	P-value
Male/female (n)	19:11	17:13	-	0.792
Gestational age (weeks)	38.67±1.33	38.61±0.94	t=0.128	0.9
Birth weight (g)	3.383±571	3.502±404	t=0.568	0.577
Primary disease (n)				
Selective cesarean section	7	8		
Asphyxia	6	6		
Amniotic fluid or meconium inhalation	6	8		
Infection	9	7		
Complication (n)				
Pulmonary hemorrhage	0	1		
Pneumonia	1	2		
Subependymal hemorrhage	0	0		
Air leakage	0	1		
PPHN	3	4		
BPD	0	0		
Respiratory time (days)	6.3±2.8	8.5±3.2	t=2.651	0.015
Hospitalization (days)	13.0±3.2	15.5±4.2	t=2.567	0.018

PS, pulmonary surfactant.

Table II. Comparison of MAP values in the mechanical ventilation + PS group and mechanical ventilation group only.

Groups	Before treatment	6 h after treatment	12 h after treatment	24 h after treatment
Mechanical ventilation and PS group	13.41±0.28	11.32±0.99	10.13±1.19	9.06±0.91
Mechanical ventilation group only	13.52±0.23	13.87±0.68	11.61±0.71	10.30±0.68
t-value	0.956	7.06	3.532	3.625
P-value	0.351	0	0.002	0.002

PS, pulmonary surfactant.

Table III. Comparison between the mechanical ventilation + PS group and control group for the PaO_2, $PaCO_2$ and PaO_2/FiO_2.

Group	PaO_2	$PaCO_2$	PaO_2/FiO_2
Observation group			
Before treatment	49.34±11.15	50.2±6.73	70.16±12.38
6 h after treatment	65.8±10.82	41.09±5.29	119.03±12.58
12 h after treatment	68.7±6.16	42.1±4.68	225±14.29
24 h after treatment	70.5±5.15	39.18±4.38	247±12.79
Control group			
Before treatment	45.8±10.13	52.38±4.82	70.4±12.94
6 h after treatment	54.8±5.5	47.64±2.97	104.79±11.65
12 h after treatment	55.21±6.09	47.09±4.85	186.95±16.82
24 h after treatment	60.8±5.56	45.29±5.47	202.17±11.57

Compared with the group before treatment, P<0.05; compared with the control group after treatment, P<0.05. PS, pulmonary surfactant; PaO_2/FiO_2, oxygen partial pressure/inspired oxygen concentration.

was 3.502±404. All the parameters including the general and observed showed non-significant P-value. The sex ratio, gestation age and birth weight revealed to be non-significant with P-value of 0.79, 0.9 and 0.5, respectively. Stay in the hospital i.e., average number of days in the control group was more as compared to PS group with the t-value of 2.5 and showed statistical significance of p<0.05 (Table I).

Comparison of MAP values in the mechanical ventilation + PS group and mechanical ventilation group showed that the MAP values were more in the mechanical ventilation group only in all the parameters such as before treatment, 6 h after treatment, 12 h after treatment, 24 h after treatment. But the MAP values showed statistical significant results with significant P-value in the 6 h after treatment, 12 h after the treatment, 24 h after treatment as 0, 0.02, 0.02, respectively (Table II).

The analysis of results indicates that the PS and combined ventilation can improve the clinical symptoms and blood gas analysis index of ARDS neonates. The PaO_2, $PaCO_2$, PaO_2/FiO_2 levels were improved in the two groups after treatment, the improvement of the experimental group was satisfactory compared to that of the control group, P<0.05.

The comparison was made between the mechanical ventilation + PS group and control group for the PaO_2, $PaCO_2$ and PaO_2/FiO_2. The level of PaO_2 in the experimental group and control group was continually increasing with the duration of time starting from before treatment, then 6 h after the treatment, 12 h after the treatment and highest after the 24 h after the treatment. The level of $PaCO_2$ in the experimental group and control group was continually decreasing with the duration of time starting from before treatment, then 6 h after the treatment, 12 h after the treatment and lowest after the 24 h after the treatment.

The ratio of PaO_2/FiO_2 in the observational group and control group was continually increasing with the duration of time starting from before treatment, 6 h after the treatment, 12 h after the treatment and highest after 24 h after the treatment (Table III).

Discussion

Previous studies and literature review suggested that the neonatal ARDS and preterm children with NRDS have clinical dyspnea and severe hypoxemia. Studies suggested that there are pathophysiological changes evident in cases of deficiency of PS. Pathological changes are observed right from alveolar wall

to the terminal bronchioles by eosinophilic transparent film. However, the pathogenesis of the two is different in the incidence of the population, clinical manifestations and X-ray (26). ARDS causes pulmonary capillary endothelial cell damage leading to pulmonary interstitial and alveolar exudative edema.

PS damage leads to alveolar atrophy or atelectasis and premature children hyaline membrane disease pathology. Surfactant deficiency appears as diffuse fine granular infiltrates on the radiograph. Air bronchograms are generated by pulmonary edema and it has a principal role in development of RDS. Excess lung fluid is attributed to epithelial injury in the airways, decreased concentration of sodium-absorbing channels in the lung epithelium, and a relative oliguria in the first 2 days after birth in premature infants. Physiological changes in PS deficiency caused by alveolar atrophy and atelectasis (27).

Acute inflammatory lung injuries are studied in animal models *in vivo* for surfactant dysfunction. Inhibitor motivated activity reductions and huge entire exhaustions are surfactant dysfunctions. Acute respiratory pathology in animal models with ALI/ARDS *in vivo* has been improved by the use of exogenous surfactant therapy and is well-documented (28,29). In multiple trials, surfactant therapy is proved to be capable of preventing and treating NRDS in preterm infants.

Decreased risk of bronchopulmonary dysplasia, pneumothorax, interstitial emphysema and mortality has been observed due to surfactants for NRDS treatments: i) Numerous doses resulted in greater; and ii) amelioration in oxygenation and ventilator necessity trend toward improved survival and this improvement is established after numerous doses of surfactant (30,31).

NRDS is more common in premature children. Authors have suggested the vice versa phenomenon, the smaller the gestational age and the higher is the incidence. Neonatal ARDS is manifested by excessive inflammation caused by the secondary reduction of PS, compositional changes or dysfunction. Some authors have suggested that the neonatal lung development or maturity if not completely achieved, it adds to disease manifestation. The neonatal lung airway and alveoli are smaller with less surface areas as compared to adults, however 'metabolic rate' is higher in neonates than the adults.

Neonatal pulmonary vascular tissue is rich, with poor elastic tissue development, less gas and more blood, so these characteristics make the neonatal lung more prone to infection. Neonatal alveolar interval is too thick to conduct the gas exchange. Neonatal ARDS is mostly secondary to MAS, congenital pneumonia, sepsis, viral pneumonia, pulmonary haemorrhage and partial or complete SP-B defects.

If condition is associated with severe infection, inhalation, shock or hypoxia then the neonatal lung inflammatory reaction is out of control. Pulmonary edema, alveolar type II epithelial cell synthesis and secretion of PS reduced meconium directly inhibit the PS function. In PS dysfunction if added with increased alveolar surface tension, alveolar collapse, further aggravating the pulmonary edema, atelectasis, decrease lung compliance and make lung function worse. So, the PS deficiency is the main cause of NRDS and is the main pathological factors. PS inactivation or defects occur in most lung diseases.

Clinical studies have also suggested that in conditions like neonatal meconium aspiration with amniotic fluid syndrome, respiratory distress after shock, aspiration pneumonia, sepsis, CPAP treatment can not relieve symptoms of dyspnea. Mechanical ventilation treatment generally requires relatively high pressure, which induces lung capacity in children with lung injury, oxygen poisoning and other symptoms. Whereas in ARDS mechanical ventilation pressure is required to be higher due to aggravated symptoms, leading to further lung injury, leading to pulmonary haemorrhage, air leak and other serious complications.

As the lack of PS in the pathogenesis of ARDS is an important part, so giving children with exogenous PS compensation can effectively relieve symptoms in children, improve alveolar energy, reduce pulmonary vascular resistance and reduce pulmonary artery pressure (32-36). Exogenous surfactants have been shown to increase oxygenation in the near term of hypoxia induced acute respiratory distress. The inflammatory lung injury is severe in meconium aspiration syndrome and caused by meconium which obstructs the airway by aspiration during labour (32-36). Meconium immediately inhibits surfactant activity of the lung.

Auten *et al* (32) and Khammash *et al* (35) in term newborns with meconium aspiration when treated with exogenous surfactant showed sufficiently great improvements in lung function in an uncontrolled study. Findlay *et al* (36) surfactant treated group in 40 term newborns in RCT showed improved oxygenation, reduced period of mechanical ventilation, decreased incidence of pneumothorax. By cohort study, Lotze *et al* found that the use of exogenous surfactants could significantly reduce the need of ECMO in term infants with severe respiratory failure. In a prospective study Lotze *et al* also reported that multiple doses of surfactant reduced the ECMO treatment time for infants who needed ECMO (33,34).

Our results showed that the PS and combined ventilation can improve the clinical symptoms and blood gas analysis index of ARDS neonates. Clinical trials revealed that inhaled nitric oxide reduces pulmonary artery pressure and improves arterial oxygenation in both adults and infants, or children with ARDS.

Combination of exogenous surfactant therapy and inhaled nitric oxide (INO) is based on their corresponding mechanisms of action for gas exchange and enhancing ventilation. Additional improvement in performance of lung from use of exogenous surfactant INO was shown in lambs with inadequacy of surfactant and congenital diaphragmatic hernia, as well as other animal models of ARDS (37,38).

In conclusion, exogenous surfactant therapy can be used in prevention and management of NRDS in term neonates. Some patients described herein, taking part in this study with lung injury associated respiratory distress can be treated with surfactant therapy as per clinical confirmation and fundamental science suggestions. Surfactant therapy in term newborns with meconium aspiration is found sufficiently useful. Use of PS is widely used as a standard intervention in many neonatal intensive care units. This therapy is also found fruitful in infants and children with lung-injury related ARDS from infections caused by viruses or bacteria. There is still scope for long-term follow-up study on the long-term efficacy and side effects of PS in the treatment of term neonates with ARDS. Other important aspects in treatment such as drug use time, dosage and repeated drug use needs more testing in clinical trial set up with larger sample sizes.

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