·论著(译文)·

Surfactant Replacement Therapy for the Prevention of the Neonatal Respiratory Distress Syndrome in Preterm Infants

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Abstract: Objective To study the efficacy of pulmonary surfactant (Exosurf) in the prevention of the neonatal respiratory distress syndrome (RDS) in preterm infants. **Methods** A prospective clinical trial was conducted. To prevent RDS, a single dose of pulmonary surfactant (Exosurf) was administered intratracheally in 25 preterm infants at a high risk of developing RDS as the prophylaxis group, and another 25 preterm babies who received no surfactant administration formed the control group. **Results** The preterm infants in the prophylaxis group received a prophylactic dose of surfactant (67.5 mg/kg) within 0.25 to 6 hours (3.4 ±1.9 hours) after delivery. Oxygenation in these babies was markedly improved and their clinical symptoms were relieved after the administration of surfactant. The durations of supplemental oxygen administration, assisted ventilation and hospitalization in the prophylaxis group, were (9.5 ±6.9) days, (2.6 ±3.8) days and (40.8 ±17.8) days respectively, which were significantly shortened compared with those of the control group ($P < 0.05$). Although the incidence of RDS and mortality in the prophylaxis group (20 % and 8 %) seemed to be lower than those of the control group (32 % and 12 %), there was no statistical differenc ($P > 0.05$). **Conclusions** Prophylactic administration of surfactant can improve oxygenation, relieve symptoms, and shorten the duration of supplemental oxygen administration, assisted ventilation and hospitalization. It has a relief effect on RDS in preterm infants.

Key words: Prematurity; Respiratory distress syndrome; Pulmonary surfactant; Prophylactic administration

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In 1959, Avery and Mead reported that the neonatal respiratory distress syndrome (RDS) was due to the deficiency in pulmonary surfactant. Their study laid a foundation for the prevention and treatment of RDS. Antenatal glucocorticoid administration to the mother has been the mainstay for the prevention of RDS for a long time, and surfactant replacement therapy is usually used to rescue the administration of RDS in preterm infants. The first trial of prophylactic administration of surfactant was conducted by Enhorning et al in 1985. Since then, there has been a new strategy for the prevention of RDS. Up to now, there have been few clinical trials of prophylactic administration of surfactant in China. The primary objective of this paper is to study the efficacy of pulmonary surfactant (Exosurf) in the prevention of RDS in preterm infants. We hope to explore possible justification for the performance of a randomized clinical controlled trial of prophylactic administration of surfactant.

1 Methods

The trial was carried out between July, 1997 and February, 2000 at the Neonatal Intensive Care Unit of the Maternal and Child Health Hospital of Guangdong Province. Infants at high a risk of developing RDS were eligible for the trial if they met the following criteria: (1) infants with a birth weight of less than 1500 gm or less than 32 weeks' gestation; (2) no antenatal glucocorticoid administration to the mother; and (3) no RDS changes in the chest radiograph before the admission to hospital or surfactant administration. The preterm infants were assigned to two groups, namely the prophylaxis group and the control group, the former including 25 infants who were administered with surfactant and the latter including 25 infants who had no surfactant administra-

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tion. The general clinical data of the two groups are listed below.

Table 1 General clinical data of the preterm infants in the prophylaxis group and the controls

Group	Case	Male	Female	Age (hours)	Gestational Age (weeks)	Birth Weight (g)	1 - min Apgar Scores:	
							1～3 min	4～7 min
Control	25	15	10	2.3 ±1.6	31.1 ±1.2	1239.2 ±121.7	3	10
Prophylaxis	25	15	10	2.4 ±2.1	30.4 ±1.7	1221.2 ±278.2	3	9

The infants received prophylatic administration of surfactant if they met the following criteria: (1) birth weights < 1500 gm or gestational age < 32 weeks; (2) the mother had received no antenatal glucocorticoid therapy; (3) there was an evidence to approve lung immaturity or surfactant deficiency in the preterm infants; (4) the baby might be accompanied by perinatal asphyxia, meconium aspiration, and other complications; and (5) the economic condition of the family permitted.

Exosurf Neonatal is a protein - free synthetic surfactant and was supplied as a vial of sterile powder together with a vial of sterile diluent. Each vial contained 108 mg Dipalmitoyl phosphatidylcholine (DPPC) as a sterile, a white, freeze-dried powder with hexadecanol, tyloxapol and sodium chloride.

The preterm infants at a high risk of developing RDS received 67.5 mg of colfosceril palmitate per kg birth weight via the endotracheal tube soon after being admitted. A sterile syringe was filled with 8 ml sterile, preservative - free water for injections to ensure adequate mixing of the vial contents of Exosurf and it was warmed in the hand prior to administration. Exosurf was administered intratracheally by instillation through a 5 French end - hole catheter inserted into the infant's endotracheal tube with the tip of the catheter protruding just beyond the end of the endotracheal tube above the infant's carina (the rapid speed method) or from a syringe into the endotracheal tube via the side-port on a special endotracheal adaptor (the slow speed method)[2]. The infant's airway was cleared by suction before administration. Endotracheal suctioning or other remedical action was unnecessary within 6 hours unless clear - cut signs of airway obstruction were present.

Infants receiving surfactant were frequently monitored with the colour of skin, respiration, heart rate, blood pressure and transcutaneous measurements of oxygen saturation ($TcSaO_2$). Blood gas data were collected at 1, 2, 6, 12 and 24 hours after each surfactant dose. Chest X - ray was taken to observe the changes of the lungs in the baby who received surfactant administration. Study failure was defined as reaching the RDS criteria[3]: (1) the infants presented the clinical presentation of developing respiratory distress, (2) the infants presented weakening respiration of both lungs when being auscultated; (3) the chest x - ray showed diffuse and generalised fine granular opacification, giving rise to a ground glass appearance of both lung fields accompanied by air bronchograms. When alveolar collapse became more severe and more generalised, the lung fields became 'white'. All data are presented as mean ±SEM. The effects of surfactant on blood gas, such as pH, PaO_2 and $PaCO_2$ at different time points before and after the dosing were compared by the analysis of the general linear model multivariate procedure. The durations of supplemental oxygen administration and ventilation were compared between the groups with Student *t* test. The frequencies of death and RDS were compared with the chi-square test. Statistical analyses were performed at the Department of Information, Maternal and Child Health Hospital of Guangdong Province (SPSS program, version 8.0).

2 Results

By study design, all preterm infants in the prophylaxis group had endotracheal intubation and received a single dose of surfactant at 15 minutes to 6 hours after birth. Twenty - one cases of the group were administered with the rapid speed method and the other 4 cases with the slow speed method. Endotracheal tube reflux occurred during the dosing procedure in 7 cases. No cyanosis, apnea, bradycardia, and oxygen desaturation occurred and blood pressures were kept stable after the surfactant administration. Fifteen cases were given supplemental oxygen administration with a hood after the instillation of surfactant via the endotracheal tube. The other 10 cases were

treated with mechanical ventilation because of the combination with severe asphyxia, the meconium aspiration syndrome, infectious pneumonia and repeated apnea.

There was improvement in their respiration, the colour of the skin turned to ruddy, and transcutaneous measurements of oxygen saturation increased at 20 minutes to 30 minutes after the surfactant administration in the babies in the prophylaxis group. After the surfactant administration, PaO2 and pH in the prophylaxis group increased and PaCO2 decreased than compared with those before the surfactant administration. PaO2, pH and PaCO2 in the control group changed slightly. The results of blood gas analysis before and after prophylactic administration of surfactant are shown below.

Table 2 Results of blood gas analysis before and after the prophylactic administration of PS

Time	PaO_2(kPa)		$PaCO_2$(kPa)		pH	
	Prophylaxis	Control	Prophylaxis	Control	Prophylaxis	Control
Presurfactant	7.3 ±2.3	7.4 ±1.8	6.6 ±1.3	6.4 ±1.3	7.30 ±0.09	7.31 ±0.07
6 h Postsurfactant	9.3 ±2.4	9.0 ±1.5	5.1 ±1.2	5.6 ±1.1	7.40 ±0.08	7.37 ±0.06
24 h Postsurfactant	8.9 ±1.3	8.9 ±1.4	5.3 ±1.1	5.5 ±0.7	7.37 ±0.08	7.37 ±0.07
Main Effect	$F = 3.820$, $P < 0.01$		$F = 7.751$, $P < 0.001$		$F = 6.300$, $P < 0.001$	
Group Effect	$F = 0.532$, $P > 0.05$		$F = 1.328$, $P > 0.05$		$F = 0.563$, $P > 0.05$	
Time Effect	$F = 7.150$, $P < 0.01$		$F = 17.482$, $P < 0.01$		$F = 14.249$, $P < 0.01$	
Interaction	$F = 0.134$, $P > 0.05$		$F = 1.231$, $P > 0.05$		$F = 1.220$, $P > 0.05$	

Chest radiograph showed no RDS changes in the 50 preterm infants at admission or before the surfactant administration. Five cases achieved RDS criteria, who presented progressive respiratory distress symptoms and their chest radiograph showed RDS changes in the prophylaxis group at 8 hours to 24 hours after the surfactant administration. Four of the 5 infants had grade Ⅱ RDS and 1 had grade Ⅰ RDS. Of these patients with RDS, there were 2 infants who were treated with mechanical ventilation. In the control group, 8 cases met RDS criteria and their chest radiograph showed RDS changes, of whom 4 were grade Ⅱ, 2 were grade Ⅳ, 1 was grade I, and 1 was grade Ⅲ at 3 hours to 12 hours after birth. The incidence of RDS was 32%. Six of the cases with RDS were treated with mechanical ventilation. There was no significant difference in the incidence of RDS between the two groups.

The duration of requirement for supplemental oxygen was 3 days to 29 days (mean time was 9.5 ± 6.9 days) in the 25 preterm infants of the prophylaxis group. Twelve cases of them required treatment of mechanical ventilation due to RDS, severe asphyxia, the meconium aspiration syndrome, pneumonia, repeated apnea, etc. The duration of mechanical ventilation was 2 days to 16 days (mean time was 2.6 ± 3.8 days) in these patients. In the control group, the duration of requirement for supplemental oxygen was 3 days to 24 days (mean time was 13.1 ±6.5 days), 13 cases required treatment of mechanical ventilation and the duration of mechanical ventilation was 2 days to 19 days (mean time was 4.3 ±3.2 days). There was significant difference in the duration of requirement for supplemental oxygen and mechanical ventilation between the two groups (t value was 1.899 and 1.711, respectively; $P < 0.05$).

The complications, such as lung infection, pulmonary hemorrhage, ductus arteriosus, apnea, intraventricular hemorrhage, and bronchopulmonary dysplasia, which occurred in the two groups are listed in Table 3.

Table 3 Complications

	Prophylaxis Group	Control Group
Lung Infection	5	7
Pulmonary Hemorrhage	4	2
PDA	2	1
Apnea	2	0
IVH	2	2
BPD	1	1
Pneumothorax	0	2
Atelectasis	0	2

The survival rate, mortality and death within 3 days were 92 %, 8 % and 4 % in the prophylaxis group and 88 %, 12 % and 4 % in the control group. No significant difference between the two groups was noted in the survival rate, mortality and death within 3 days. The duration of hospitalization was 40.8 ± 17.8 days in the prophylaxis group and 53.8 ±27.8 days in the control group, with no significant difference between them (t value was 1.969; $P < 0.05$).

3 Discussion

Pulmonary surfactant is a lipoprotein material produced by airway epithelial cells called type Ⅱ pneumocytes. This lipoprotein is released into the airway, where it functions to decrease surface tension, maintain alveolar expansion, prevent progressive atelectasis and pulmonary edema, and keep the air space stable at the physiologic pressure. Numerous studies have been reported, showing that surfactant in the lungs of preterm infants born at less than 30 weeks' gestation is 10 % less than that in the full-term infants. Due to deficiency in pulmonary surfactant, preterm infants intend to suffer from RDS. Surfactant can be given as prophylactic therapy at or within 30 minutes of birth to those infants at a risk of developing RDS and the prophylactic approach can supplement deficiency in pulmonary surfactant to prevent RDS in small preterm newborns. Enhorning reported a paper, supporting the conclusion in 1985[1].

Up to now, there has been no accepted criteria of surfactant replacement therapy as a postdelivery prophylactic approach. Some doctors thought that prophylactic administration was given to the infants if they met the following criteria: (1) premature infants with a birth weight of less than 1000 gm or a gestational age of less than 28 weeks; (2) the mother had received no antenatal glucocorticoid therapy; (3) there was evidence to approve lung immaturity or surfactant deficiency in the preterm infants[3]. Some scholars also thought that infants at a high risk of developing RDS can receive prophylactic administration if they had a birth weight of less than 1250 gm or a gestational age of less than 32 weeks[4]. In China, the perinatal period is defined as from the conceptional age of 28 weeks to 7 days after birth, and there is a fat lot of extremely premature infants who were born with a birth weight of less than 1000 gm or a gestational age of less than 28 weeks. A lot of perinatal factors, such as perinatal asphyxia and the meconium aspiration syndrome, can increase the consumption of surfactant and decrease the synthesis of surfactant in the infants, so they tended to suffer from RDS. We think that the infants could be given prophylactic administration of surfactant if they met following criteria: (1) preterm infants with a birth weight of less than 1250 gm or a gestational age of less than 32 weeks; (2) the mother had received no antenatal glucocorticoid therapy; (3) there was evidence to approve lung immaturity or surfactant deficiency in the preterm infants; (4) they were accompanyed by high risk perinatal factors, such as asphyxia, meconium aspiration and syndrome.

Experimental studies have showed that serum proteins leak into the alveolar space and these proteins act as inhibitors of surfactant function in the animal with deficiency of surfactant when they begin to breath first[5]. If exogenous surfactant administration is given to the infants before the first breath, it can promote the absorption of the lung fluid and the first ventilation of the lungs, reduce the serum protein leak and promote a uniform distribution of surfactant in the lungs. Thus it is the best to give the prophylactic administration to the infants before their first breath at birth[6]. But it is very difficult to do so clinically; we think it is better that prophylactic administration of surfactant is given to the babies within 15 minutes to 30 minutes of birth or before mechanical ventilation begins[4,6]. In this study, only 1 infant received the administration within 15 minutes after birth, and the others were given prophylactic administration within 6 hours after birth and before mechanical ventilation began.

There are two methods of prophylactic administration: one is to administer rapidly though a catheter inserted into the endotracheal tube while the infant is disconnected from the ventilator, and the other is to administer at a rate slow enough to allow the surfactant suspension to pass into the lungs via the sideport of the endotracheal tube adapter without interrupting mechanical ventilation. With the former procedure, fewer symptoms of obstructed airways occurred and surfactant has a uniform distribution in the lungs. But with the latter, endotracheal tube reflux occurred occasionally resulting in endotracheal tube blockage. It can promote homogenous distribution of surfactant throughout the lungs that each part dose was administered with the infant in a different position. The

dosage of prophylactic therapy is similar to that of rescue therapy. Each dose of natural surfactant extract is 75 to 150 mg phospholipids/kg birth weight, and each dose of synthetic surfactant extract, such as Exosurf, is 67.5mg/kg. A lot of infants at a high risk of RDS should be carried out with a single dose of surfactant generally as prophylaxis, and multiple doses should be given to the infants with a poor response to surfactant. In the prophylactic group, the 25 preterm infants all received single a dose of Exosurf. Of these, 5 cases met the clinical and radiographic criteria for a diagnosis of grade Ⅰ or Ⅱ of RDS and the incidence of RDS was 20%. In the control group, 8 preterm infants met the criteria for a diagnosis of RDS and the incidence of RDS was 32%. Severity of RDS in the prophylactic group was mild than in the control group. The babies who required mechanical ventilation in the prophylactic group were fewer than those in the control group. This indicated that surfactant replacement therapy was effective in reducing the severity of RDS.

Numerous trials reporting the efficacy of surfactant for prophylaxis have been published, which indicated that prophylactic administration could reduce the death of RDS, incidence of pneumothorax and chronic lung disease, especially in neonates born at less than 27 weeks' gestation[5,7] although the Dunn study showed prophylactic administration increased the requirement of supplemental oxygen and incidence of chronic lung disease. Our study showed that days of supplemental oxygen and mechanical ventilation in the prophylactic group were obviously shortened than those in the control group and there was significant difference between the two groups ($P < 0.05$). But this study showed no difference in the death of RDS between them ($P > 0.05$). The prophylactic and the control group each had one case of chronic lung disease, but no pulmonary air leak occurred. The result was consistent with the Kattwinkel report[5,7]. The days of hospitalization in the prophylactic group were shortened than those in the control group, indicating that prophylactic administration can shorten the duration of hospitalization. It was reported that 60% of preterm infants with 29 to 30 weeks' gestation would not develop RDS, so it was not necessary to administer surfactant for prophylaxis in half of the preterm infants[5]. If prophylactic administration was given to these babies, it would increase medical cost, unnecessary incubation of some neonates, and destabilization of neonates at resuscitation. The efficacy and safety of prophylactic surfactant administration will be further studied.

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