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Clinicopathological Analysis of Premature Infants Treated with Artificial Surfactant

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Abstract

Objective: Our aim was to obtain new information about the relationship between infant responses to surfactant replacement therapy and histopathological changes in vital organs.

Study design: To accomplish this, the autopsy findings and clinical backgrounds of 41 very low birth weight infants (gestational week 25.6 ± 2.3; birth weight 806.4 ± 251.6 g) who had died after receiving surfactant replacement therapy were reviewed, and those who responded to therapy were compared with those who did not. Responders were infants in whom the required FiO_2 declined by >20% or mean airway pressure declined by >20% within six hours of instilling surfactant (n=18); non-responders were infants who did not meet those criteria (n=23).

Result: Gestational age, birth weight and time at treatment were similar in responders and non-responders, but survival was significantly longer in responders. The incidences of hyaline membrane disease, pulmonary interstitial emphysema, hemorrhagic necrosis and parenchymal degeneration of the liver and kidney were all higher in non-responders, whereas the incidences of bronchopulmonary dysplasia and pneumonia were higher in responders. Prior to treatment, acidosis and hypothermia were significantly more severe in non-responders, and perinatal complications, such as fetal distress and intrauterine infection, were observed more often in non-responders. Substantial degradation of vital organs had already occurred during the early postnatal or intrauterine life of the non-responders, which would be expected to interfere with the clinical response to instilled surfactant.

Conclusion: It is anticipated that in the future improved monitoring of immature fetuses will be indispensable to improve intrauterine fetal management and to achieve better control over the timing and mode of delivery. (J Nippon Med Sch 2000; 67: 330—334)

Key words: artificial surfactant, respiratory distress syndrome (RDS), premature infants

Introduction

Surfactant replacement therapy has contributed greatly to reducing the mortality and morbidity caused by respiratory distress syndrome (RDS) among premature infants[1,2]. Moreover, preliminary reports have noted that surfactant is also effective against various other neonatal pulmonary diseases, including meconium aspiration syndrome (MAS), pul-

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monary hemorrhage and persistent pulmonary hypertension[3]. However, not all infants respond to surfactant treatment, even in the absence of pulmonary hypoplasia or congenital anomalies. The factors that influence the clinical response to surfactant have been documented in several studies[4, 6, 11], as have the pulmonary pathology and histology of infants treated with surfactant[7, 10]. In the present study, we have extended those earlier findings by analyzing the autopsy findings and available clinical data on a group of very low birth weight infants who died after receiving surfactant replacement therapy. The aim of this study was to identify the relationship between pathological changes in vital organs and clinical response to surfactant.

Patients and Methods

All reports on neonatal and infantile autopsies performed in the Department of Pathology at the Japanese Red Cross Medical Center over the twelve-year period during which surfactant treatment was available (1985～1996) were reviewed. Selected for analysis were infants who had appropriate birth weights for their gestational age, who weighted less than 1,500 g at birth and who were treated with surfactant; those who had pulmonary hypoplasia, significant congenital anomalies or chromosomal abnormalities were excluded. Ultimately, 41 infants with gestational ages ranging from 21 to 30 weeks (mean: 25.6 ± 2.3 weeks) and birth weights ranging from 316 to 1,480 g (806.4 ± 251.6 g) were included. Clinical diagnosis of RDS was made by chest X ray (criteria by J. Bomsel[18]) and a stable microbubble test, and all of the infants received mechanical ventilation and tracheal instillation of bovine surfactant (Surfactant TA: 120 mg/kg). For the purposes of this study, the infants were divided into two groups according to the clinical response to the surfactant replacement therapy. If within six hours after instillation of the surfactant the supplied oxygen concentration was reduced by more than 20%, or the mean airway pressure (MAP) was attenuated by at least 20%, as compared with pretreatment levels, the infants were considered to be responders (n=18); infants who did not fulfill these criteria were considered to be non-responders (n=23). These criteria were chosen because initial response may be affected by various pathophysiological conditions, such as PDA and air-leaks which sometimes occur just a few hours after surfactant administration. Clinical backgrounds (gestational age, birth weight, survival period, perinatal history, time at treatment, pre-treatment acid-base balance and body temperature) and autopsy findings on vital organs were analyzed and compared between the two groups. Pretreatment acid-base balance and body temperature were evaluated just after admission to our center. Autopsy specimens were prepared in the standard manner, and then stained with hematoxylin-eosin and examined microscopically. The histopathological parameters evaluated were hyaline membranes, pulmonary hemorrhage, pulmonary interstitial emphysema, pneumonia, bronchopulmonary dysplasia (BPD) and parenchymal damage in vital organs other than the lung (i.e. liver, kidney and adrenals). Statistical comparisons between the groups were made using Student's-t or χ^2 test with Yate's correcting method. Values of $p < .05$ were considered statistically significant.

Result

Gestational age and birth weight were similar in the responders and non-responders, and 94% (17/18) of the responders were diagnosed with RDS and 78% (18/23) of the non-responders showed RDS. The infants who were diagnosed as non-RDS were as follows: one responder had severe asphyxia owing to abruptio of the placenta; three had been exposed to intrauterine infection; one had experienced intraventricular hemorrhage (IVH) at birth; and the last was an extremely immature neonate non-responders weighing only 340 g. Almost equal numbers of RDS cases were diagnosed in each group. The gestational ages of 35 babies who were diagnosed with clinical RDS were 25.6 ± 2.3 weeks, and the other six non-RDS basies 25.5 ± 2.3 weeks. There was no significant difference between these two groups. On the other hand, the survival period was significant prolonged in the responders ($p<0.01$) (**Table 1**). These infant responders died of complications later, after pulmonary adaptation had been achieved. The mode of delivery

Table 1 Patient profiles

	responders	non-responders
Number of patients	18	23
Gestational aeg(weeks)	25.8±2.1	25.3±2.4
Birth weight(g)	864.4±242.2	761.0±249.1
Survival period(days)**	28.7±34.4	1.7±3.6
Clinical RDS	17(94%)	18 (78%)

RDS : Respiratory Distress Syndrome **p < 0.01

Table 2 Perinatal factors

	responders	non-responders
Number of patients	18	23
Fetal distress	6(33%)	11(48%)
Intrauterine infection	5(28%)	7(30%)
Oligohydramnios	0(0%)	7(30%)

Table 3 Clinical data

	responders (18)	non-responders (23)
Time at treatment(postnaltal hours)		
−30 min	5(28%)	8(35%)
30 min −4 hours	8(44%)	11(48%)
4 hours−	5(28%)	4(17%)
Pre-treatment		
Body temperature(℃)*	35.8±0.9	35.1±1.2
pH**	7.253±0.07	7.089±0.148
Base exess**	−7.2±3.4	12.7±6.4

**p< 0.01 *p< 0.05

Table 4 Clinical complications

	responders (18)	non-responders (23)
IVH(Grade ≧Ⅱ)	9(50%)	11(48%)
s-PDA**	11(61%)	3(13%)
Sepsis**	7(39%)	0(0%)
Intestinal perforation *	6(33%)	1(4%)

IVH: Intraventricular Hemorrhage. s-PDA: symptomatic Patent Ductus Arteriosus **p < 0.01 *p< 0.05

Table 5 Pulmonary pathology

	responders (18)	non-responders (23)
Hyaline membarene**	5(28%)	16(70%)
Interstitial emphysema	5(28%)	12(52%)
Pulmonary hemorrhage	11(61%)	9(39%)
Pneumonia**	9(50%)	2(9%)
BPD *	4(22%)	0(0%)

BPD: Bronchopulmonary Dysplasia **p<0.01 *p< 0.05

Table 6 Pathology of other organs

		responders (18)	non-responders (23)
Liver		8(44%)	9(39%)
	Hemorrhagic necrosis	3	5
	Parenchymal degeneration	5	4
Kidney	Corticomedullary necrosis	4(22%)	10(43%)
Adrenal	Bilateral hemorrhage	3(17%)	3(13%)

did not influence the clinical response to surfactant replacement therapy; the rate of cesarian section was 22 % in the responders, and 13% in the non-responders. Among all the patients, 22 (54%) babies were born in our perinatal center. The ratio of inborn infants was 44% in responders, and 61% in non-responders, which was not statistically significant. Fetal distress, diagnosed by fetal heart rate monitors, intrauterine infection due to premature rupture of the membrane or maternal pyrexia higher than 38℃ within 48 hours of delivery, was found slightly more often in the non-responders, though the differences were not statistically significant. Pregnancies with oligohydramnios, detected by obstetrical echography, were solely associated with non-responders (**Table 2**). The timing of surfactant replacement therapy was almost the same in the two groups, but hypothermia ($p<0.05$) and severe acidosis ($p<0.01$) prior to treatment were more frequently observed in the non-responders (**Table 3**). Both of these findings were considered to be tightly correlated with the clinical response to instillated surfactant. With respect to clinical complications, the incidences of patent ductus arteriosus with clinical heart failure ($p<0.01$) (symptomatic PDA; s-PDA), intestinal perforations ($p<0.05$) and blood culture-proved sepsis ($p<0.01$) were significantly higher in the responders (**Table 4**). The histopathological findings are summarized in **Tables 5** (lung) and **6** (liver, kidney and adrenals). Hyaline membrane disease and pulmonary interstitial emphysema were frequently observed in the non-responders, with the incidence of the former being significantly greater than in the responders ($p<0.01$). On the contrary, the incidence of pneumonia was significantly higher in responders ($p<0.01$), and

BPD was only observed in the responders ($p<0.05$). There were no differences between the two groups in the incidences of hemorrhagic necrosis or parenchymal degeneration of the liver and adrenals, whereas such histopathological changes in the kidney were more frequently found in the non-responders (**Table 6**).

Discussion

Several reports focusing mainly on histological changes in the lung have commented on the pathology of surfactant-treated infants[7–10]. The present study extends those earlier findings by analyzing the complete autopsy findings of infants who died following surfactant replacement therapy and by examining other factors that may have influenced the clinical outcome in those cases. Between the two groups, the degree of histological derangements in the lung and other vital organs were not statistically different except for hyaline membrane formation. However, the existence of severe acidosis and hypothermia prior to treatment implied that these changes had already occurred during the early life of the non-responders. The clinical responses to surfactant replacement treatment may vary. Retrospective analyses of several randomized clinical trials showed that infants with perinatal asphyxia or severe respiratory distress at the time of treatment often respond poorly[6,11]. In our study, the presence of acidosis or hypothermia in the non-responders prior to treatment suggests that the infants' conditions had declined soon after birth and/or during the antenatal period. While the incidence of hemorrhagic or parenchymal degeneration of the liver and adrenals was similar among the responders and non-responders, the presence of these conditions in the kidneys was noted more frequently in the non-responders. The incidence of s-PDA was greater among the responders, most likely because successful surfactant therapy dramatically decreased pulmonary vascular resistance, leading to an increased left-to-right shunt through the ductus arteriosus[11]. Infection-related problems, such as blood culture-proved sepsis and intestinal perforations, were also observed more frequently in the responders, presumably because they survived longer. There is no doubt about the therapeutic efficacy of surfactant replacement in cases where respiratory problems in infants are caused by surfactant deficiency[12]. Moreover, it has been suggested that surfactant replacement may also be effective against neonatal diseases other than RDS[3]. Unfortunately, pathophysiological conditions such as asphyxia, congenital pneumonia and pulmonary hemorrhagic edema may interfere with the clinical response to surfactant[6,11]. We found a significantly higher incidence of hyaline membrane disease in the non-responders, whereas BPD was found only in the responders. With respect to BPD, repair and remodeling of lung parenchyma could be seen within several hours of the onset of injury, at a time when epithelial debris and hyaline membranes are being cleared. Such histological features are characteristic of progressive damage and continuing repair, but are followed by the onset of hyaline membrane disease in developing lungs[13], like those of the non-responders. In addition, the responders had a higher incidence of pneumonia than the non-responders, because they experienced more secondary infections during prolonged ventilation. Thus, prolonged survival is likely to have been responsible for at least some of the differences in the features of the pulmonary pathologies seen in the two groups.

The clinical response to surfactant may also be affected by other therapies (e.g. prenatal steroids) as well as by the timing of the treatment, the dosage of surfactant administered and ventilatory management[5,6,14,15]. A meta-analysis in randomized clinical trials of prenatal steroid therapy before surfactant replacement showed conclusive benefits not only for the lung maturation, but also prevention of necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and neonatal mortality[16]. Nevertheless, prenatal steroid therapy is still controversial, particularly in case with intrauterine infections[17]. In our series, evidence of maternal infection was observed in 16 cases (39%). Data on maternal steroid administration were not available for this study, but at of the time of treatment, surfactant dosages and ventilatory management were all similar in the two groups. Nevertheless, the morphological damage observed in vital organs other than the lung in the non-responders were as severe as those of the responders, especially in the kid-

neys.

In conclusion, pretreatment acidosis, hypothermia, and marked histological changes such as hyaline membrane formation were observed more frequently in the non-responders. This fact indicate that derangements of the vital organs other than the lungs has already occurred during the early life in very low birth weight infants, whether or not they respond to surfactant replacement therapy. It is anticipated that in the future, improved monitoring of immature fetuses will be indispensable to improved intrauterine fetal management and better control over the timing and mode of delivery.

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