

Surfactant TA Therapy for Premature Infants with Severe Respiratory Distress Syndrome: Clinical Trial of Two Cases

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ABSTRACT

Two cases of premature infants with severe respiratory distress syndrome requiring mechanical ventilation were treated with surfactant TA [bovine surfactant]. Gestation age was 28 and 30 weeks. Infants weighing 996 and 1200 g were instilled with catheter through intratracheal route with 120 mg/kg and 100 mg/kg surfactant TA, ages when treated were 6 and 7 hours after birth respectively. Both medications improved oxygenation, increased a/APO2 ratio with reducing mean airway pressure markedly within 6 hours post-surfactant treatment. It is effective to treat premature newborns with severe respiratory distress syndrome with surfactant.

Key words: *Respiratory distress syndrome, surfactant replacement therapy, mean airway pressure, arterial to alveolar oxygen tension ratio.*

The respiratory distress syndrome is a common disease in premature newborns and remains the main cause of neonatal mortality. In 1959, Avery and Mead⁽¹⁾ reported that infants dying of the respiratory distress syndrome had abnormally high surface tensions, and suggested that pulmonary surfactant was deficient.

Exogenous surfactant replacement therapy has been shown to be an effective treatment for neonatal respiratory distress syndrome in a number of non-randomized^(2,3,4) and randomized controlled trials⁽⁵⁻¹³⁾. Most results showed improved oxygenation, reduced pulmonary air leak,

incidence of bronchopulmonary dysplasia and mortality.

We report the results obtained after using of surfactant TA in two cases of premature infants with severe respiratory distress syndrome in our unit.

Case 1

A female was born to G₂P₂ mother via vaginal delivery with 28 wks of gestation age. Mother got high fever with cloudy amniotic fluid and had premature rupture of membrane. Birth weight was 996 grams. Because of apnea and generalized cyanosis, resuscitation with ambu

bag contained 100% oxygen was done through endotracheal tube immediately. She was transferred to our unit and was connected with ventilator with available setting. Surfactant TA [120 mg/kg] was instilled into the both lungs through an endotracheal tube with catheter at 6 hours after birth. Oxygenation improvement with reducing FiO_2 , mean airway pressure and increasing in a/APO_2 ratio were noted 3 hours after surfactant treatment [Fig. 1]. Blood transfusion was given in order to anemia. Unfortunately, the infant's condition got worse on the second day of life. Chest X-ray revealed cardiomegaly and congestion of lung fields [Fig. 3C]. Fluid restriction and indomethacin were ordered due to patent ductus arteriosus with congestive heart failure. She was died at 40 hours of life. Blood culture grew *E. coli* bacteria. This case

had respiratory distress syndrome combined with sepsis. After surfactant TA treatment the patient had short time improvement in oxygenation. Eventually, she died of sepsis and patent ductus arteriosus.

Case 2

A female infant was delivered vaginally by G_2P_2 mother with 30 wks of gestation age. The pregnancy had been uncomplicated until spontaneous onset of labor. She was outborn infant with 1200 grams of birth weight. The Apgar score was 4 at 1 min and 5 at 5 min. Because of cyanosis, subcostal retraction and grunting, she was transferred to our NICU at four hours of age. Ambu bagging was done several times during transportation due to apnea and generalized cyanosis. Chest X-ray revealed ground glass

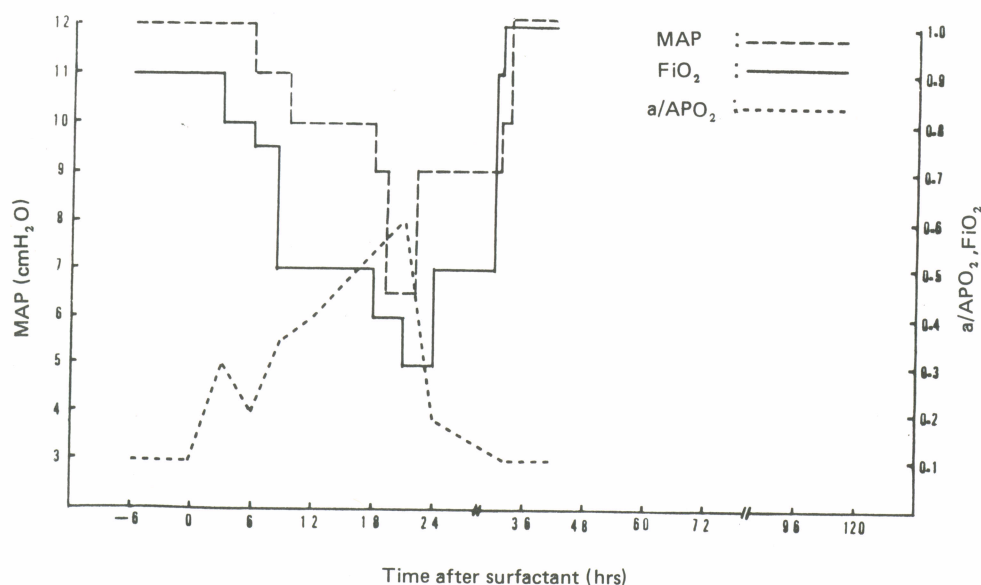


Fig. 1. Changes in arterial/alveolar oxygen tension ratio (a/APO_2), fraction of inspired oxygen (FiO_2) and mean airway pressure (MAP, cmH₂O) before and after 120mg/kg dose of surfactant TA treatment in RDS-infant, birth weight 996g. Surfactant was given at time 0.

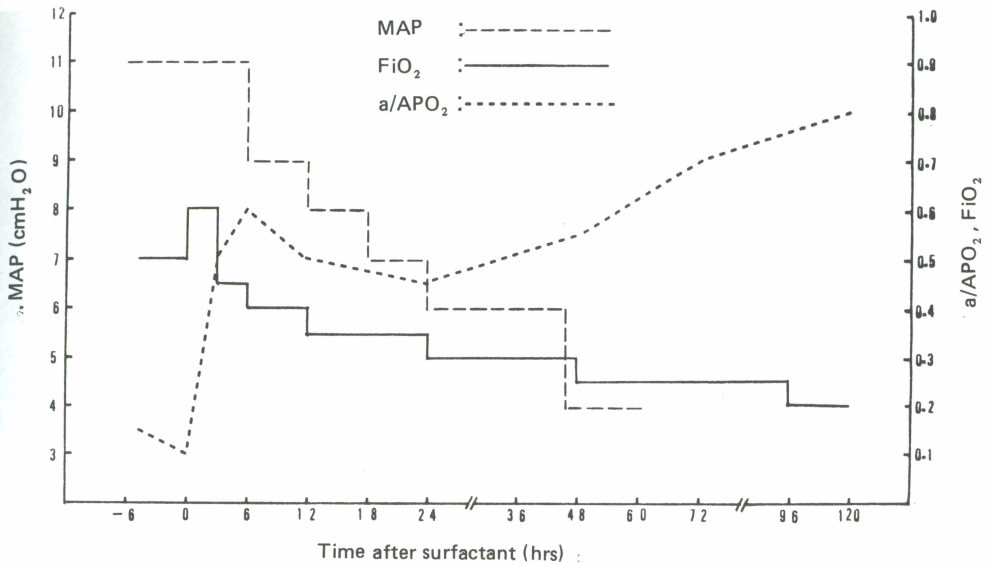
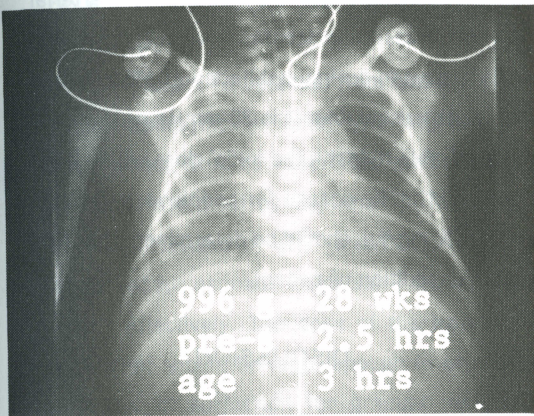
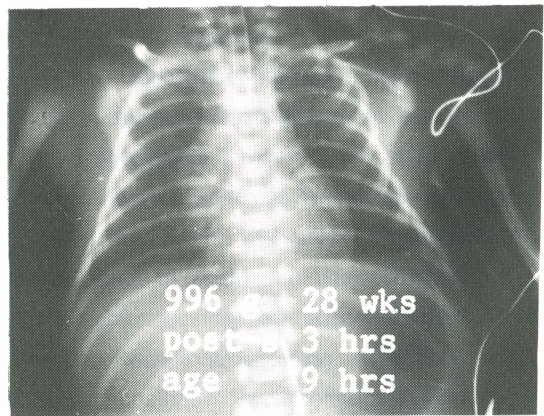


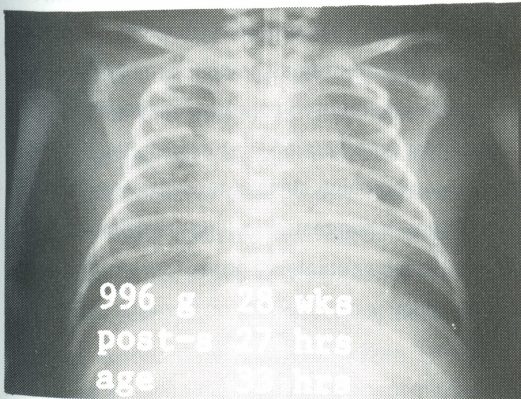
Fig. 2. Changes in arterial/alveolar oxygen tension ratio (a/APO_2), fraction of inspired oxygen (FiO_2) and mean airway pressure (MAP, cmH₂O) before and after 100mg/kg dose of surfactant TA treatment in RDS-infant, birth weight 1200g. Surfactant was given at time 0.



(A)



(B)



(C)

Fig. 3. Chest radiographs of RDS-infant (birth weight 996g) showed (A) ground glass and air bronchogram pattern before surfactant treatment. (B) good aeration with normal heart size 3 hours after surfactant treatment.

Fig. 3C. Chest radiograph of RDS-infant (birth weight 996g) revealed increased pulmonary blood flow leading pulmonary edema with cardiomegaly 27 hours after surfactant treatment.

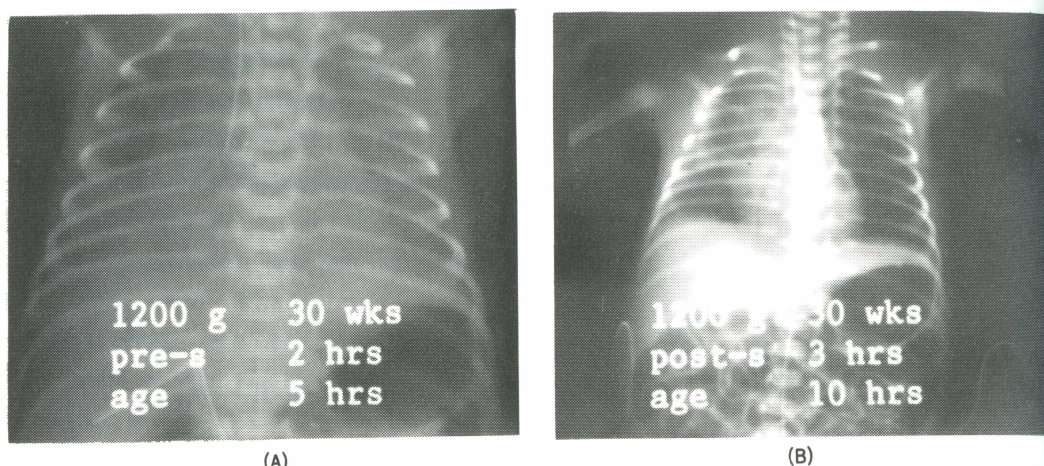


Fig. 4. Chest radiographs of RDS-infant (birth weight 1200g) showed (A) ground glass and air bronchogram pattern before surfactant treatment. (B) good aeration with normal heart size 3 hours after surfactant treatment.

with air bronchogram pattern and microbubble stability test of gastric aspiration was weak. Intubation was performed immediately under the diagnosis of severe respiratory distress syndrome. Surfactant TA [100 mg/kg] was instilled into the lungs through an endotracheal tube via catheter in five divided doses at 7 hours of age. Three hours after post-surfactant treatment the condition got increase of a/APO_2 ratio, decrease of MAP and FiO_2 [Fig. 2]. Chest X-ray showed much improvement in aeration of lung fields [Fig. 4A,B]. Cardiac and cranial ultrasonographic evaluation revealed normal. She was extubated from mechanical ventilation at 58 hours of age and changed to use nasal prong CPAP for 120 hours. She was discharged with 2300 g of body weight.

DOSAGE AND ADMINISTRATION

The content of one vial surfactant TA 120 mg was suspended in physiologic saline 4 ml and instilled a dose of 120 mg/kg into the trachea in 4 or 5 divided doses. The body position was changed to up,down, right and left respectively

while the administration of each divided dose, one dose to one direction, so that the drug will be evenly distributed throughout the entire pulmonary field. Monitoring transcutaneous arterial oxygen pressure is necessary while bagging with 100% oxygen during instillation of each dose in order to ensure that it is 80 mmHg or higher. It is desirable to instill the initial dose within 8 hrs after birth. The dosage for additional treatment, 60 - 120 mg/kg, should be determined according to the condition of patient.

DISCUSSION

Numerous surveys have confirmed that respiratory distress syndrome develops in about 60% to 80% of premature newborn of less than 32 weeks gestation, and some of them require ventilatory intervention⁽¹⁴⁾. Respiratory distress syndrome has high surface tensions and lack of surfactant is suggested in lung immaturity, and it needs high ventilatory setting therapy and has high incidence of serious complications and mortality.

Pulmonary surfactant is a complex mixture

of proteins and lipids which is approximately 90% lipid and 10% protein⁽¹⁵⁾. The lipids are mainly phospholipids. Dipalmitoyl phosphatidylcholine [DPPC] is the predominant lipid species in pulmonary surfactant. Pure DPPC alone can produce the very low surface tensions characteristic of pulmonary surfactant, but does not produce surface films with the rapid spreading, adsorption, and stability properties characteristic of natural surfactant⁽¹⁶⁾.

The second important lipid in pulmonary surfactant is phosphatidylglycerol [PG], be suggested as being important for the stabilization of tubular myelin which may contribute to surface-film formation, and the interconversion of pulmonary surfactant form⁽¹⁵⁾. Phosphatidylglycerol is the best indicator of fetal lung maturity, it is unnecessary for good pulmonary surfactant⁽¹⁷⁾.

Surfactant TA obtained from healthy bovine lung contains phospholipids, free fatty acid and triglycerides at fixed ratio. This surfactant has been characterized by Fujiwara⁽¹⁸⁾. Taeusch et al⁽¹⁹⁾ and Tanaka et al⁽²⁰⁾ and had studied in treatment for neonatal respiratory distress syndrome effectively. The dose of the exogenous surfactant should be large enough to provide a reservoir of surfactant for gradual replenishment of the surface film. High dose surfactant TA [120 mg/kg] replacement therapy is more effective than low dose [60 mg/kg] therapy⁽²¹⁾.

For this reason we used high dose [120 mg/kg and 100 mg/kg] to treat our two cases. The microbubble stability test⁽²²⁾ and the shake test⁽²³⁾ are indicated for lung immaturity. The present data indicated that rapid improvement of gas exchange, reflected by significant reduction in fraction of inspired oxygen [FiO_2] and mean airway pressure, increase in the a/APO_2

ratio within 6 hours after treatment [Fig. 1, Fig. 2]. The a/APO_2 has been shown accurately to reflect oxygenation in acute lung disease within a wide range of FiO_2 value⁽²⁴⁾. Most of the chest radiographic abnormalities gradually resolved. The radiograph correlates fairly closely with pathologic finding⁽²⁵⁾ and with clinical severity⁽²⁶⁾. Chest radiograph showed ground glass pattern and air bronchogram resolved, good aeration with normal heart size 3 hours after treatment [Fig. 3 A, B, Fig. 4 A, B].

Unfortunately, the first case got worse at the second day of life. Chest radiograph [Fig. 3C] revealed increased pulmonary blood flow leading pulmonary edema 27 hours after treatment. Finally patient died of *E. coli* sepsis and patent ductus arteriosus, even if medication with antibiotics, fluid restriction and indomethacin. The second case had no patent ductus arteriosus and intraventricular hemorrhage as evaluated by ultrasonograph. She was ventilated with time-cycle respirator [Sechrist] for 58 hours and then nasal prong CPAP within 120 hours. Short-term use of high concentration of oxygen and positive pressure ventilation may not develop bronchopulmonary dysplasia. She was well and gained weight during admission in the following days.

Recently exogenous surfactant treatment has shown to be effective for premature infants with respiratory distress syndrome. It is agreed that natural surfactant is more effective than synthetic ones in improving survival and complications of respiratory distress syndrome^(26,27,28). Studies of surfactant replacement is given only to babies who are very ill with respiratory distress syndrome^(5,11-13), have shown a reduced incidence of pulmonary interstitial emphysema, pneumothorax, bronchopulmonary dysplasia in

treated infants, but no reduction in incidence of intraventricular hemorrhage^(5,11-13). So far available informations indicated that no long-term adverse effect of replacement therapy with heterologous surfactant treatment for neonatal respiratory distress syndrome.

In a premature infant with respiratory distress syndrome treated by surfactant, the deterioration in respiratory status after initial improvement may be the first sign of significant patent ductus arteriosus. A prostaglandin synthetase inhibitor [Indomethacin, mafenamic acid] or surgical ligation is considered if respiratory status remains unstable or deterioration. Early closure of a PDA in infants treated with surfactant may prevent further problems resulting from a large left to right shunting.

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臨床應用 Surfactant TA 於早產兒 合併嚴重呼吸窘迫症二病例報告

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用 Surfactant TA 治療二病例需要用呼吸器的嚴重呼吸窘迫症之早產兒。懷孕週數各為 28 及 30 週，嬰兒體重為 996 及 1200 公克。經由導管灌入氣管內各 120mg/Kg 及 100mg/Kg 的 Surfactant，治療時年齡為生後 6 及 7 小時。Surfactant 治療後 6 小時內顯著改善氧飽和作用(oxygenation)，增加動脈血管與肺泡氧氣張力比(a/APO₂)且降低平均氣道壓力(mean airway pressure)。用 Surfactant 治療早產兒合併嚴重呼吸窘迫症是相當有效的。