

# Exogenous Surfactant Replacement Therapy of Hyaline Membrane Disease in Premature Infants

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*We conducted a clinical trial to assess whether surfactant-TA given within the first six hours of life could improve oxygenation and reduce the ventilatory support in premature infants with hyaline membrane disease (HMD) during the first 24 hours of life. Eight premature infants with severe HMD requiring ventilation were treated, at a mean age of 2.72 hours, with a single intratracheal instillation of surfactant-TA (120mg/kg). Arterial oxygenation improved dramatically as reflected by the increase of the a/A PO<sub>2</sub> ratio and PaO<sub>2</sub> to about 2 times the pretreatment values within 3 hours after surfactant treatment. And thus, oxygen concentrations (FiO<sub>2</sub>) could be reduced and remained significantly lower than pretreatment values during the first 24 hours after treatment. Infants given surfactant-TA required lower mean airway pressure (MAP) and had a significantly decreased ventilatory index (VI) during the first 24 hours after treatment, which reflect the decreased requirement for ventilatory support. Chest radiograph scores significantly improved within 24 hours after treatment compared with pretreatment scores. In this trial, we found that a single intratracheal dose of surfactant-TA given to infants with HMD resulted in improved respiratory status and radiographic findings during the first 24 hours after treatment.*

**Key Words:** Surfactant Replacement Therapy, HMD in premature infants

Hyaline membrane disease (HMD) is the most significant pulmonary disorder in the newborn human infant. Advances in respiratory care and management of premature infants have greatly improved the outcome in newborn infants with HMD (Gregory *et al.* 1971). Nevertheless, this disease remains an important cause of mortality and morbidity in the very premature infant (Farrell and Avery 1975).

Therefore, there is a search for therapeutic modalities to prevent HMD or to ameliorate the severity of the disease, and thus reduce mortality and morbidity in the very premature infant, which would be of great value in these infants. More appropriate would be restoration of the basic defect that leads to the development of HMD. Exogenous surfactant replacement therapy appears to be a possible means of accomplishing this goal (Gitlin *et al.* 1984).

In 1980, Fujiwara *et al.* first reported the clinical application of surfactant replacement in patients with HMD using lyophilized artificial surfactant (modified

bovine surfactant). A dramatic improvement in gas exchange and decreased need for oxygen and ventilatory support were demonstrated in these infants within hours of surfactant replacement. This report triggered a number of studies concerning the potential of this new therapeutic approach.

In 1985, Vidyasagar *et al.* undertook a detailed physiologic study of premature baboons and established the effectiveness of surfactant-TA in reversing the physiologic, radiologic, and histologic changes seen in a primate HMD model, with marked indications of clinical improvement. Promising results have also been shown by several authors using various surfactant preparations as prophylaxis (Enhorning *et al.* 1985; Halliday *et al.* 1984; Kendig *et al.* 1988. Kwong *et al.* 1985; Merritt *et al.* 1986; Shapiro *et al.* 1985; Ten Centre Study Group, 1987) or as treatment (Collaborative European Multicenter Study Group, 1988; Fujiwara *et al.* 1987; Gitlin *et al.* 1987; Hallman *et al.* 1985; Horbar *et al.* 1989; Konishi *et al.* 1988; McCord *et al.* 1988) for HMD in premature infants.

Though there has been a recent worldwide trend of extensive use of surfactants in HMD of premature infants, there has been no clinical trial for surfactant replacement therapy in Korea. So we conducted a clinical trial to assess whether surfactant-TA given within the first six hours of life would improve ox-

Received August 4, 1989

Accepted November 3, 1989

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ygenation and restore sufficient lung function to permit a reduction in ventilatory support in preterm infants with HMD during the first 24 hours of life.

## PATIENTS AND METHODS

### Patients

This study was conducted between November 1987 and May 1988 at the Neonatal Intensive Care Unit of Yonsei University Medical Center. Eight preterm infants with birth weights of 1000-1800gm were enrolled in the study and treated with surfactant-TA within six hours of life. All infants had clinical and radiological findings of HMD and required mechanical ventilation with oxygen concentrations of 50% or more to maintain an arterial  $PO_2$  above 50mmHg. These babies were all seriously ill and had a median age at the start of mechanical ventilation of less than 30 minutes.

### Surfactant administration

The surfactant-TA (Tokyo Tanabe Co. Ltd., Tokyo, Japan) used in this study has been previously characterized by Fujiwara *et al.* (1980, 1987), Tanaka *et al.* (1986), Taeusch *et al.* (1986) and Konishi *et al.* (1988), and testing of multiple batches in an animal model has shown it to be very effective.

### Instillation Technique

One hundred and twenty mg/kg of surfactant-TA dissolved in 4ml saline (30mg of surfactant-TA per ml) was administered as described by Fujiwara *et al.* (1980, 1987) and Konishi *et al.* (1988). One-fifth (0.5-1ml) of the total amount warmed up to body temperature (37°C) was instilled into each of the four lung quadrants and mainstem bronchus via an intratracheal tube (5 Fr).

The infant was turned to four different positions-right and left lateral with head positioned up and later down during instillation. Between instillations of surfactant-TA, the infant was ventilated manually with an Ambu bag for about 1 min, using 100% oxygen. Vital signs and transcutaneous  $PO_2$  were continuously monitored during administration of surfactant.

After instillation, which took 5-10 min, the infant was reconnected to the ventilator (Sechrist IV-100B), using the same settings for  $FiO_2$ , PIP, PEEP, frequency and I:E ratio as before instillation. To evaluate the immediate effects of surfactant, the ventilator settings were maintained for about 30 min. Then the ventilator settings were modified according to the clinical

response, the aim being to maintain normal blood gases ( $PaO_2$  60-80mmHg,  $PaCO_2$  35-45mmHg) with the lowest possible levels of  $FiO_2$  and airway pressure. To achieve this goal in a patient with a favorable clinical response,  $FiO_2$  was lowered first. Subsequent adjustments included reduction of peak inspiratory pressure, frequency and the inspiration: expiration ratio.

### Assessment

To evaluate the effects of surfactant treatment, arterial blood gas measurements, ventilator settings, and oxygen requirements were recorded at frequent intervals during the first 24 hours of life.

The blood gas variables calculated were arterial to Alveolar  $PO_2$  ratio (a/A  $PO_2$  ratio). The a/A  $PO_2$  ratio has been shown to accurately reflect gas exchange in acute pulmonary disease within a wide range of  $FiO_2$  values and was calculated using a standard alveolar gas equation (Gilbert and Keighley 1974): a/A  $PO_2 = PaO_2 / PAO_2$ ,  $PAO_2 = (760-47) \times FiO_2 - PaCO_2 / 0.8$

The ventilatory variables analyzed for significant trend were mean airway pressure (MAP) and ventilatory index (VI), which were calculated from the following equations (Hallman *et al.* 1985; Merritt *et al.* 1986; Kendig *et al.* 1988):

$$MAP = \frac{f \cdot (PIP-PEEP)}{60} \times Ti + PEEP, \quad VI = \frac{FiO_2 \cdot MAP}{PaO_2}$$

These variables gave a reliable indication of the requirements for ventilatory support.

Each chest radiograph was taken about one hour before surfactant treatment, one to six hours after surfactant treatment and at subsequent intervals depending on the clinical course in the individual case. For all patients, the chest radiograph was taken on the supine, A-P projection.

In order to provide an assessment of the radiographic severity of HMD, chest radiographs prior to treatment and 24 hours posttreatment were retrospectively evaluated by a radiologist (Suh JS) without knowledge of treatment and were scored by the following system modified from Edwards *et al.* (1985):

- Air-bronchogram:
  - 1 = normal
  - 2 = extension into lower parts of the lung or slightly visible air-bronchogram
  - 3 = wide spread of air-bronchogram
- Density:
  - 0 = normal
  - 1 = slightly fine reticular pattern
  - 2 = moderate confluent density

3 = severe consolidation or parenchymal density

4 = white lung

We arbitrarily divided each lung into two zones because of asymmetric clearing. And then four zones were scored and the average of the combined score of four zones was obtained in each patient. The Wilcoxon's rank-sum test for pre-and posttreatment samples was used for statistical evaluation.

## RESULTS

Tables 1,2, and 3 show baseline data on the patients and on the severity of HMD, based upon arterial blood gas measurements,  $\text{FiO}_2$  and MAP requirements, and chest radiographs.

The clinical data are summarized in Table 1. Eight preterm infants with a mean gestational age of  $29.9 \pm 2.8$  weeks (range 26-33 weeks) and a mean birth

**Table 3. Severity of HMD in chest films obtained before and after treatment with surfactant-TA within 24 hours using chest X-ray scoring method**

Case No.	Before treatment	After treatment
Marked effective		
4 (KMH)	6	3
8 (PHJ)	6	3
3 (KEY)	6	3
5 (YHK)	7	4
Effective		
7 (CSN)	7	6
1 (ASS)	7	6
2 (LHW)	4	3
No change		
6 (LYS)	5	5
Total	48	33*

\*  $p < 0.01$  by Wilcoxon's rank-sum test compared with before treatment

**Table 1. Clinical data of neonates with hyaline membrane disease before surfactant-TA treatment**

Case	B.W. (gm)	G.A. (wks)	Sex	Delivery	Apgar score 1 min/5 min	Age starting respirator therapy (hr)	Age at surfactant treatment (hr)
1. ASS	1,030	29	M	C/S*	2/7	0.4	2
2. LHW	1,040	26	M	V/D**	out born	5.0	6
3. KEY	1,150	26	M	V/D	1/4	0.5	0.25
4. KMH	1,540	32	M	C/S	2/4	0.25	2.5
5. YHK	1,580	29	F	V/D	4/5	0.25	5.5
6. LYS	1,590	32	F	C/S	5/7	1.0	1.5
7. CSN	1,610	33	F	C/S	1/4	0.65	2.5
8. PHJ	1,800	32	F	C/S	3/6	0.25	1.5
mean $\pm$ SD	1,425 $\pm$ 308.9	29.9 $\pm$ 2.8			2.6 $\pm$ 1.5/5.3 $\pm$ 1.38	1.04 $\pm$ 1.62	2.72 $\pm$ 2.01

\* Cesarean section

B.W.: birth weight

\*\* Vaginal delivery

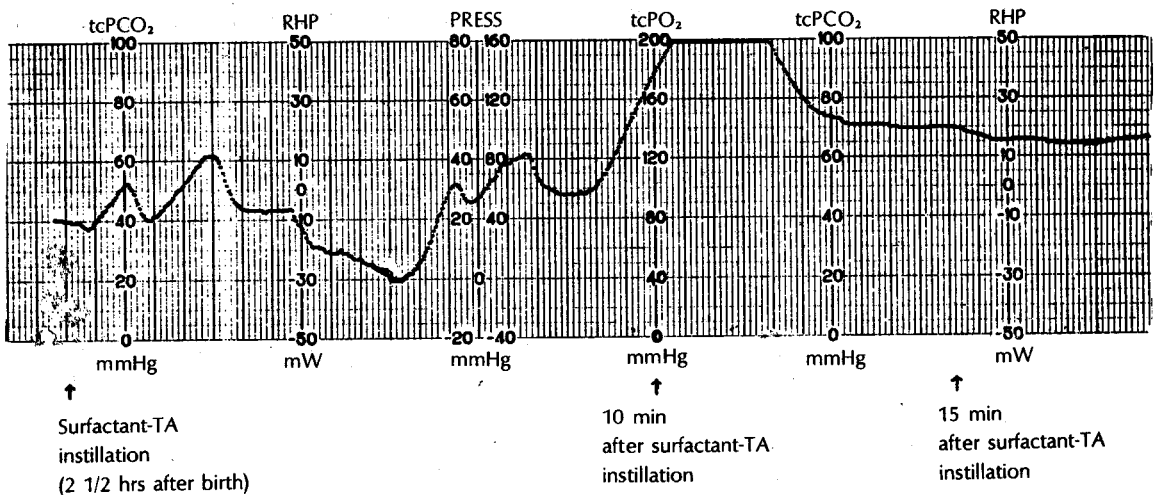
G.A.: gestational age

**Table 2. Immediate effects of surfactant-TA treatment in 8 neonates with HMD**

(mean $\pm$ SD)

Parameter	Before treatment	After treatment	
		15 min	1 hour
$\text{PaO}_2$ (mmHg)	62.9 $\pm$ 22.2	118.9 $\pm$ 48.2*	125.4 $\pm$ 34.9*
$\text{PaCO}_2$ (mmHg)	43.4 $\pm$ 20.9	43.1 $\pm$ 18.3	40.3 $\pm$ 15.7
PH	7.35 $\pm$ 0.11	7.33 $\pm$ 0.13	7.35 $\pm$ 0.12
$\text{FiO}_2$	0.72 $\pm$ 0.20	0.70 $\pm$ 0.20	0.65 $\pm$ 0.23
MAP (CmH <sub>2</sub> O)	12.06 $\pm$ 3.81	12.3 $\pm$ 3.57	12.6 $\pm$ 3.6
a/A $\text{PO}_2$	0.16 $\pm$ 0.09	0.29 $\pm$ 0.14*	0.32 $\pm$ 0.14*

\*  $p < 0.05$  by Wilcoxon's rank-sum test compared with before surfactant instillation



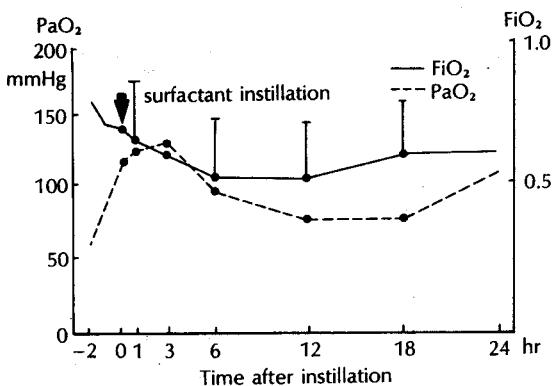
**Fig. 1.** Immediate effects of surfactant-TA on transcutaneous oxygen tension in case 4 (KMH).

\* Ventilator settings before surfactant-TA instillation:

$FiO_2$  0.6

PIP/PEEP 20/4

MAP 10.2



**Fig. 2.** Sequential changes of  $FiO_2$  and  $PaO_2$  during the first 24 hours after surfactant-TA instillation.

weight of  $1,425 \pm 308.9$  gm (range 1,030-1,800 gm) were investigated. All had a clinical diagnosis of HMD with typical chest X-ray findings and required assisted ventilation at the mean age of  $1.04 \pm 1.62$  hours (range 15 min-5 hours). Their mean age at the time of surfactant instillation was  $2.72 \pm 2.01$  hours (range 15 min-6 hours). Three were born by normal spontaneous vaginal delivery and five by cesarean section due to a severe form of preeclampsia with fetal distress in 4 cases and abruptio placentae in 1 case.

Five were resuscitated immediately after birth due to severe perinatal asphyxia.

### Clinical effects

Soon after instillation of surfactant-TA, the skin color of the infants was markedly flushed and the peripheral circulation seemed to increase in all infants. The chest looked more compliant and the resistance in ambu bagging was markedly reduced. On auscultation of the chest, all infants showed a disappearance of harsh, sandpaper-like, dry breath sounds with good air entry in both lung fields.

### Effect of surfactant replacement on blood gases

Within 10-15 min after surfactant-TA treatment, all patients showed an immediate improvement in oxygenation and gas exchange as reflected by increased average values for  $PaO_2$ ,  $TcPO_2$ , and  $a/A PO_2$  ratio (Table 2, Fig. 1, Fig. 2 and Fig. 4). These were maintained during the first 24 hours of life after a single dose of surfactant-TA treatment (Fig. 2 and Fig. 4).

A continuous tracing of transcutaneous  $PO_2$  ( $TcPO_2$ ) during the administration of surfactant-TA (in case 4) is shown in Fig. 1. During the administration of surfactant-TA, the oxygen tension dropped slightly, but within 10 minutes after surfactant instillation, transcutaneous  $PO_2$  increased dramatically from

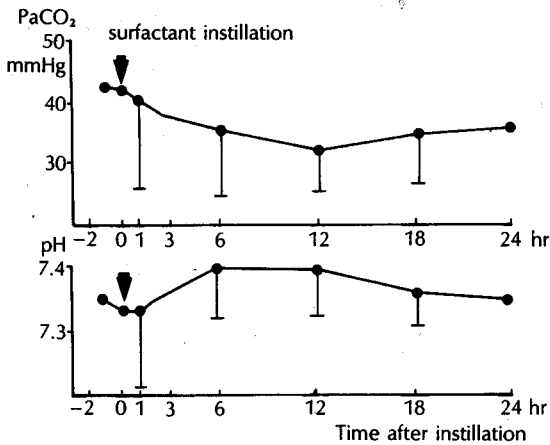


Fig. 3. Changes of arterial pH and  $\text{PaCO}_2$  values during the first 24 hours after surfactant-TA instillation.

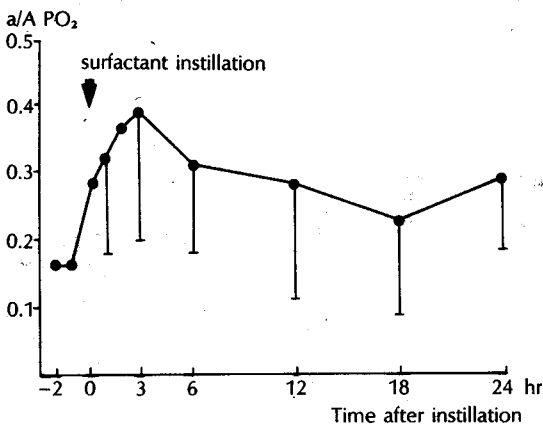


Fig. 4. Sequential changes of a/A  $\text{PO}_2$  ratio during the first 24 hours after surfactant-TA instillation.

80mmHg to 200mmHg or more (Fig. 1).

Arterial blood gas measurements, a/A  $\text{PO}_2$  ratio, and ventilatory requirements ( $\text{FiO}_2$  and MAP) immediately before and shortly after treatment are shown in Table 2. Within 15 min after surfactant-TA treatment, arterial  $\text{PO}_2$  increased dramatically from  $62.9 \pm 22.2$  mmHg to  $118.9 \pm 48.2$  mmHg, and then to  $125.4 \pm 34.9$  mmHg at 1 hour after treatment, which was statistically significant at  $p < 0.05$  compared with the pretreatment values. The a/A  $\text{PO}_2$  ratio was also increased immediately after surfactant-TA treatment within the effective range which was statistically significant at  $p < 0.05$  by Wilcoxon's rank-sum test.  $\text{FiO}_2$  was

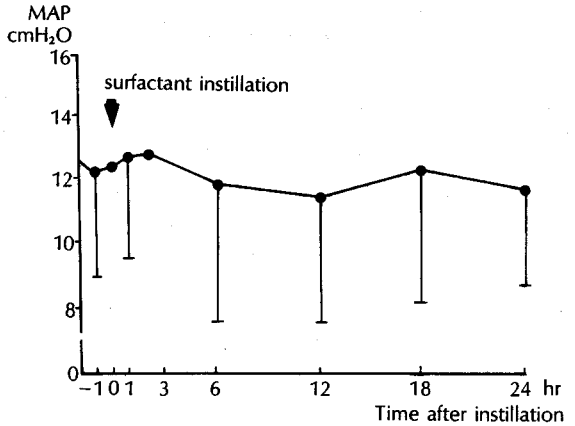


Fig. 5. Sequential changes of MAP during the first 24 hours after surfactant-TA instillation.

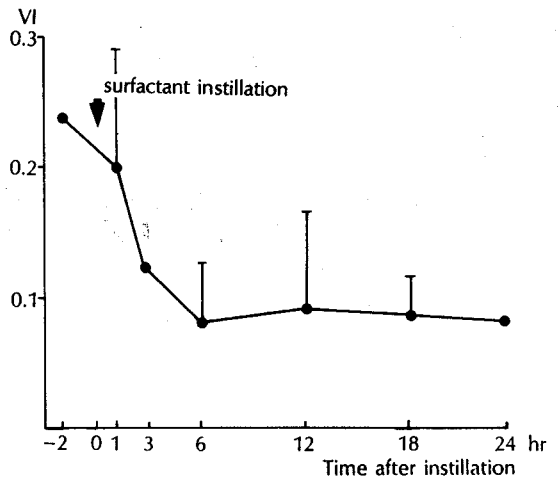
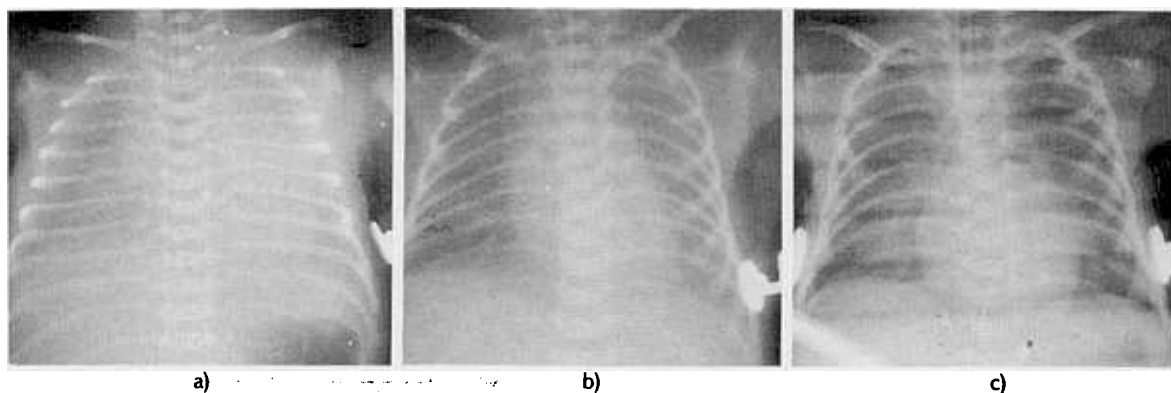


Fig. 6. Sequential changes of ventilatory index during the first 24 hours after surfactant-TA instillation.

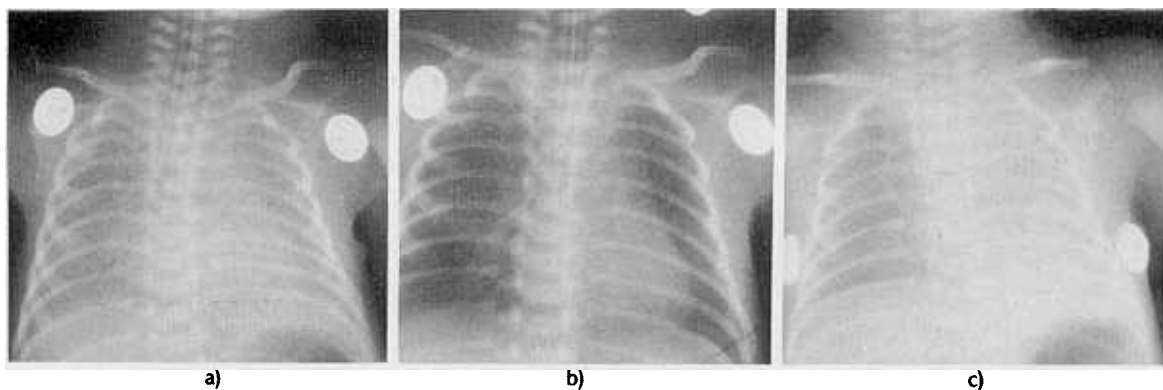
decreased about 7 percent within 1 hours after surfactant-TA treatment, but the pH,  $\text{PaCO}_2$  and MAP were not remarkably changed during this same period (Table 2).

Sequential changes of  $\text{FiO}_2$  and  $\text{PaO}_2$  during the first 24 hours after surfactant-TA treatment are shown in Fig. 2. After surfactant treatment, the oxygen requirement ( $\text{FiO}_2$ ) was immediately decreased in most cases (7/8). So we were able to lower the inspired oxygen concentration ( $\text{FiO}_2$ ) from an average value of  $0.72 \pm 0.2$  to  $0.52 \pm 0.21$  ( $p < 0.05$ ) within 6 hours of surfactant treatment. Then the arterial oxygen tension



**Fig. 7 a-c.** Sequential chest radiograph findings after surfactant-TA treatment in case 5 (YHK).

- a) At two hours of age, pretreatment film shows wide-spread air bronchogram and lung (score = 7).
- b) At the fifth hour following surfactant treatment, radiograph shows partial clearing (score = 4).
- c) Subsequent film at the 20th hour shows continued clearing (score = 2).



**Fig. 8 a-c.** Sequential chest radiograph findings after surfactant-TA treatment in case 4 (KMH).

- a) At one hour of age, film shows severe HMD (score = 7).
- b) At four hours of age, one-hour post-treatment film shows near complete clearing (score = 1).
- c) Subsequent film at 20 hours of age, shows asymmetric deterioration in the left lung (score = 3).

( $\text{PaO}_2$ ) was maintained at optimal levels with the lower  $\text{FiO}_2$  during the first 24 hours after surfactant treatment (Fig. 2).

During this same period, arterial  $\text{PCO}_2$  fell from  $43.4 \pm 20.88 \text{ mmHg}$  to  $32 \pm 6.76 \text{ mmHg}$  and pH rose from  $7.35 \pm 0.11$  to  $7.39 \pm 0.074$ . But these changes occurred within the normal ranges of blood gas measurements (Fig. 3).

The a/A  $\text{PO}_2$  ratio is a useful indicator of pulmonary gas exchange within a wide range of  $\text{FiO}_2$  values. Fig. 4 shows the sequential changes in the a/A  $\text{PO}_2$  ratio during the first 24 hours after surfactant-TA treatment. The a/A  $\text{PO}_2$  ratio increased from an initial  $0.16 \pm 0.09$

to  $0.39 \pm 0.162$  ( $p < 0.05$ ) at 3 hours after surfactant treatment and then decreased to  $0.29 \pm 0.105$  at 24 hours. This immediate increment of a/A  $\text{PO}_2$  ratio (average values) reflects effective gas exchange after surfactant treatment. This response, judged by average values, is then a lasting response for the first 24 hours after surfactant treatment according to the criteria of Taeusch *et al.* (1988).

#### Effect of surfactant replacement on ventilatory requirements

The sequential changes in ventilatory requirements

are shown in Fig. 5 and Fig. 6. The mean airway pressure was slightly decreased to about 1.3 cmH<sub>2</sub>O at 12 hours after surfactant treatment and was maintained within a similar range during the first 24 hours after treatment. But the ventilatory index was dramatically decreased which was statistically significant compared with the pretreatment values. This finding reflects the decreased requirement for ventilatory support after surfactant treatment.

### Effect of surfactant replacement on chest radiographs

All patients had radiologic findings of HMD before surfactant treatment. The scores for the severity of HMD on radiograph before and after surfactant instillation are presented in Table 3. There were significant differences between pre and post-treatment scores (48 vs 33,  $p < 0.01$ ).

The first pulmonary radiographs after surfactant treatment showed clearing of both lungs dramatically in most cases (7/8), with reduced haziness throughout both lungs and a less prominent air bronchogram (Fig. 7).

It took six hours on average for clearing of HMD radiographically, ranging from three to twenty four hours. In case 4 (KMH), the first hour radiograph after surfactant treatment showed a well inflated lung as compared with the initial one (Fig. 8). In case 1 (LYS), there was no remarkable change radiographically. However, the clinical amelioration of HMD was notable for cases with both decreased FiO<sub>2</sub> and increased a/A PO<sub>2</sub> ratio. In some cases, there was some radiographic evidence of deterioration of the respiratory condition within 24 hours after the initial improvement following surfactant administration. Complete clearing of HMD was observed on the fourth day of life in general.

## DISCUSSION

Treatment of premature infants with exogenous surfactant is a promising new therapy for hyaline membrane disease (HMD). The result of this study provides evidence that surfactant-TA given after the development of severe HMD in premature infants decreases their ventilatory and oxygen needs and improves chest radiograph findings within 24 hours after treatment.

The major demonstrable effects of surfactant-TA therapy were reduction of the FiO<sub>2</sub> requirements and MAP, improvement of the a/A PO<sub>2</sub> ratio and reduction of the ventilatory index during the first 24 hours after treatment. It is during these critical hours that

complications such as pulmonary air leakage or intraventricular hemorrhage frequently occur. As well, death from progressive ventilatory failure primarily occurs in the first 1-2 days of life, a period when benefits from surfactant therapy might be expected. HMD can be treated effectively by instillation of the surfactant, and the beneficial outcome in infants treated with surfactant can be ascribed to the effect of the surfactant on pulmonary function (Hallman *et al.* 1985).

The effects of exogenous surfactant in HMD are probably similar to the effects attributed to endogenous surfactant. The improvement in gas exchange and decreased need for ventilatory support with surfactant therapy presumably are due to the exogenous surfactant spreading throughout the distal airways and air spaces, causing reduced alveolar surface tension during the respiratory cycle (Taeusch *et al.* 1988).

By reducing the surface tension in the alveolar and bronchiolar lining layers, the exogenous surfactant promotes uniform alveolar expansion and enhances resorption of fluid from the airspaces. The improved aeration of the alveolar compartment reduces the intrapulmonary right-to-left shunting and leads to a striking increase in the a/A PO<sub>2</sub> ratio. These beneficial effects of surfactant replacement may reverse or ameliorate the course of HMD, even in severely ill patients, as illustrated by the sustained clinical improvement in several clinical trials (Collaborative European Multicenter Study Group 1988; Enhorning *et al.* 1985; Fujiwara *et al.* 1987; Horbar *et al.* 1989; Kwong *et al.* 1985; Noack *et al.* 1987; Shapiro *et al.* 1985). It is evident from the present study that the rapid therapeutic response should be carefully monitored to avoid excessively high PaO<sub>2</sub> levels.

The surfactant preparation used in this study is surfactant-TA, an organic solvent extract of bovine lungs enriched with synthetic lipid, which is currently used by Fujiwara *et al.* (1980, 1987) and in other clinical trials (Charon *et al.* 1989; Gitlin *et al.* 1987; Konishi *et al.* 1988; Raju *et al.* 1987; Soll *et al.* 1988). We chose surfactant-TA because this preparation was extensively studied through several controlled clinical trials and has an established efficacy and short-term benefit in managing respiratory distress syndrome.

The excellent effects of surfactant-TA on the mechanical properties of the lung were demonstrated by several authors through in vitro and in vivo experiments. Ikegami *et al.* (1987) demonstrated that surfactant-TA had the best in vitro surface properties and the greatest surface tension-lowering ability with small areas of surface compression in comparison of four surfactants in a preterm lamb HMD model.

Vidyasagar *et al.* (1985) also demonstrated that surfactant-TA had a remarkable effect on lung function in immature baboons with HMD. Taeusch *et al.* (1986) has characterized surfactant-TA using selected tests and assays of surfactant function and has confirmed that surfactant-TA has positive features that may be important predictors of therapeutic effectiveness.

Exogenous surfactant replacement in HMD effectively improves lung function- mechanical properties (compliance) and gas exchange. Most of the results of surfactant treatment showed a striking improvement in oxygenation which allowed  $\text{FiO}_2$  to be reduced immediately after surfactant instillation (Collaborative European Multicenter Study Group 1988; Enhorning *et al.* 1985; Fujiwara *et al.* 1987; Gitlin *et al.* 1987; Hallman *et al.* 1985; Horbar *et al.* 1989; Kendig *et al.* 1988; Konishi *et al.* 1988; Kwong *et al.* 1985; McCord *et al.* 1988; Merritt *et al.* 1986).

In our study, immediate improvement in oxygenation was seen in all patients with about a two-to three-fold increment in  $\text{PaO}_2$  from the pretreatment values, so that the oxygen concentration ( $\text{FiO}_2$ ) could be reduced to about half the pretreatment values in all except one patient (CSN, case 7). The average values of oxygen concentration remained significantly lower than the pretreatment values during the first 24 hours after surfactant treatment (Fig. 2). These results are well in accord with those of others as described above.

Surfactant replacement usually has an immediate therapeutic effect in infants with HMD, even if the baby is treated at a fairly advanced stage of the disease, when both clinical and radiologic measures of lung function indicate severe parenchymal injury (Collaborative European Multicenter Study Group 1988). Hallman *et al.* (1985) have previously demonstrated that human surfactant, administered endotracheally to very low birth-weight infants with ventilatory failure caused by severe HMD, reverses the progressive hypoxemia and improves the  $\text{a/A PO}_2$  ratio while decreasing the mean airway pressure and oxygen requirements. These results suggested that administration of surfactant in infants with severe HMD might reduce its severity. This in turn might reduce the need for mechanical ventilation and exposure to higher concentrations of oxygen, thus decreasing the frequency of pulmonary complications and the incidence of BPD and death from HMD.

In most of the published trials, a variety of continuous variables reflecting the magnitude of oxygen requirements and ventilatory support were examined. These variables include a number of individual

measurements such as  $\text{FiO}_2$ , MAP, and ventilatory rate as well as several calculated factors such as the  $\text{a/A PO}_2$  ratio, Alveolar-arterial oxygen gradient, and a number of indices of ventilation. Infants receiving surfactant tended to have a lower requirement for ventilatory pressure. When we examined the trends for MAP and VI, infants given surfactant-TA required lower MAP and had significantly decreased VI during the first 24 hours after treatment, which reflect the decreased requirement for ventilatory support. This result is very consistent with those reported by Fujiwara *et al.* (1987), Hallman *et al.* (1985), Kendig *et al.* (1988) and Merritt *et al.* (1986).

Surfactant-TA given early in the course of severe HMD leads to a prompt and sustained improvement in oxygenation. In our study, the major effect was improvement of the  $\text{a/A PO}_2$  ratio during the first 24 hours after treatment. Infants receiving surfactant showed, within 1 hour, a dramatic improvement of oxygenation as reflected by a nearly two-fold increase of the  $\text{a/A PO}_2$  ratio. This initial, immediate, striking increase in the  $\text{a/A PO}_2$  ratio reflects improved gas exchange after surfactant treatment and this effect was sustained within the effective range during the first 24 hours after treatment.

A comparison between the present results and those obtained by other investigators (Collaborative European Multicenter Study Group 1988; Fujiwara *et al.* 1987; Gitlin *et al.* 1987; Hallan *et al.* 1985; Horbar *et al.* 1989; Konishi *et al.* 1988; Raju *et al.* 1987) is hampered by differences in the severity of lung disease. In our patients, the average value for  $\text{a/A PO}_2$  ratios was 0.16, and the values in the babies enrolled in the trials of Raju *et al.* (1987), Horbar *et al.* (1989), Fujiwara *et al.* (1987) and Konishi *et al.* (1988) were similar to ours with initial  $\text{a/A PO}_2$  ratios of 0.15, 0.15, 0.16, 0.16, respectively. They reported a striking improvement of oxygenation within one to four hours, as reflected by a two-to three-fold increase of the  $\text{a/A PO}_2$  ratios. This finding is consistent with our results.

In our study, the magnitude of initial response to surfactant administration was striking, but there was a gradual decrease from the highest  $\text{a/A PO}_2$  values beginning 3 hours after treatment and continuing up until 18 hours (Fig. 4). We thought that this was probably due to the fact that this initial beneficial effect was not maintained during the subsequent course, which is probably related to the dose of surfactant used in this study or the duration of surfactant function in the air-alveolus interphase.

One of the factors affecting the efficacy of administered surfactant is the amount of protein in the airways (Ikegami *et al.* 1983). The surfactant supplied



thus would have to compete with and counteract the inhibitory effects of plasma components accumulating in the airways. The striking and acute improvement in oxygenation and compliance achieved with surfactant treatment suggests that the administered dose of surfactant was at least sufficient to counteract the inhibitory effect of plasma proteins that were already present in the airways before treatment. However, this initial beneficial effect was not sustained in a significant proportion of infants, as evidenced by a decrease in a/A  $PO_2$  ratio from the initial highest values.

There is no precise information about how long surfactant components will stay in the alveoli after surfactant treatment in human preterm infants. In the lungs of term lambs, the surfactant may have a half-life of as long as 7 days (Glatz *et al.* 1982). The relatively shorter period of effectiveness of administered surfactant-TA seen in several studies may represent either consumption or inactivation of surfactant by inhibitors accumulating in the airways before the recycling of administered surfactant components, or the new synthesis and release of endogenous surfactant (Konishi *et al.* 1988). This possibility is supported by Konishi *et al.* (1988) in that low-dose infants (60mg/kg) who had a relapse responded well to the second dose, indicating that the first low dose was not sufficient.

Unanswered questions concerning surfactant therapy relate to the optimal dose and the timing and frequency of surfactant administration. We used a single high dose of surfactant-TA (120mg/kg) because the high dose regimen resulted in greater clinical improvement and proved more effective in prolonging the response due to its ability to overcome the problem of inhibition; moreover, it can increase the alveolar surfactant pool size sufficiently to prevent the progression of lung disease, thereby decreasing the protein leak into the airways (Jobe *et al.* 1983; Jobe *et al.* 1984).

A number of randomized clinical trials of surfactant replacement therapy in very premature infants have been reported during the past 4 years. A variety of surfactant preparations and different strategies for surfactant administration have been used. But the optimal dose of surfactant, and optimal preparations of surfactant are not yet known. At present, no prospective trial has yet compared preventive and rescue strategies, and the optimal time to treat newborns with surfactant has not been determined. In these clinical trials, two strategies for the treatment of infants—prevention or rescue trials—have been used.

The prevention trials have used surfactant treatment before the infant's first breath or within minutes of delivery to modify the course of HMD in infants

at high risk for the syndrome. The rescue trials have used surfactants to treat infants with established respiratory distress syndrome. The rescue trials have used several different surfactant preparations, including protein-free synthetic surfactants (Wilkinson *et al.* 1985), surfactant extracted from human amniotic fluid (Hallman *et al.* 1985; Lang *et al.* 1988) and surfactants extracted from other mammalian sources (Collaborative European Multicenter Study Group 1988; Fujiwara *et al.* 1987; Gitlin *et al.* 1987; Horbar *et al.* 1989; Konishi *et al.* 1988; McCord *et al.* 1988; Raju *et al.* 1987). The prevention trials have used calf lung surfactant extract (Enhörning *et al.* 1985; Kendig *et al.* 1988; Kwong *et al.* 1985; Shapiro *et al.* 1985), surfactant-TA (Soll *et al.* 1988), human surfactant (Merritt *et al.* 1986) and artificial surfactant (Halliday *et al.* 1984; Ten Centre Study Group 1987). Several studies have used multiple doses of surfactant (Hallman *et al.* 1985; Konishi *et al.* 1988; Lang *et al.* 1988; Merritt *et al.* 1986; Ten Centre Study Group 1987) whereas the others have used a single dose (Collaborative European Multicenter Study Group 1988; Enhörning *et al.* 1985; Fujiwara *et al.* 1987; Gitlin *et al.* 1987; Halliday *et al.* 1984; Horbar *et al.* 1989; Kendig *et al.* 1988; Kwong *et al.* 1985; McCord *et al.* 1988; Shapiro *et al.* 1985; Raju *et al.* 1987; Soll *et al.* 1988; Wilkinson *et al.* 1985). The relative benefits of early preventive therapy and of the later treatment of infants with established respiratory distress syndrome (RDS) are also unclear. Late treatment may be less effective as a result of respirator-induced lung injury and the inactivation of surfactant by proteins present in alveolar edema fluid. On the other hand, prophylactic treatment necessitates the administration of surfactant to many infants in whom severe RDS would not develop.

These clinical trials were varied in terms of their patient selection criteria, the surfactant preparations used, and the timing and dosage of surfactant administration. Despite the differences in study design, the intratracheal administration of surfactant resulted in improved blood gas values and reduced oxygen requirements or lower ventilator settings in all of these trials.

The chest radiograph is useful and reliable in assessing the severity and progression of HMD (Tudor *et al.* 1976) and correlates fairly closely with pathologic findings (Singleton 1981) and with clinical severity (Giedion *et al.* 1973; Kero and Mäkinen 1979). It is reasonable to expect that the radiographic features of HMD—granularity, air bronchograms, and underinflation, which reflect the microatelectasis of surfactant deficiency—might be modified by the administration of surfactant and thus provide an additional measure

of therapeutic efficacy (Edwards et al. 1985).

Recently, several authors reported radiographic studies using various surfactant preparations (Edwards et al. 1985; Mortenson et al. 1987; Soll et al. 1987; Wood et al. 1987). In these studies, they showed that surfactant therapy was effective and has changed the radiologic evaluation of lung disease. Clinical and radiographic improvement occurred in the first hours of life when severity of HMD is usually greatest. Edwards et al. (1985) demonstrated a significant improvement in the severity of HMD on the basis of radiologic evaluation using human surfactant as a postventilatory treatment. Wood et al. (1987) conducted a randomized, controlled study using radiographic grading criteria, which indicates that preventilatory exogenous surfactant replacement with calf lung surfactant extract mitigates HMD. This radiographic data provided evidence supportive of the efficacy of surfactant replacement in moderating HMD in premature infants and this moderating effect was thought to occur mainly in the first 24 hours of life.

Mortenson et al. (1987) also reported a striking improvement of lung aeration in the first chest films taken after surfactant instillation in all patients. He suggested that these radiologic findings were associated with a dramatic improvement of oxygenation and a significant reduction of the right-to-left shunt. But Soll et al. (1987) reported radiographic findings associated with surfactant-TA treatment which showed no significant differences in chest radiograph scores before and after treatment. They also encountered difficulties in applying this simplified scoring method.

In our study we assessed the radiographic features of HMD after surfactant-TA treatment to note the presence and degree of any amelioration resulting from surfactant therapy. Our results shows that surfactant instillation significantly improves the chest radiograph scores within the first 24 hours after treatment and this is associated with a dramatic improvement of oxygenation in all patients. Our findings are well in accord with those reported by others (Edwards et al. 1985; Mortenson et al. 1987; Wood et al. 1987).

## CONCLUSION

In this clinical trial, we found that a single high intratracheal dose of surfactant-TA given to infants with HMD who required assisted ventilation resulted in improved respiratory status and radiographic findings during the first 24 hours after treatment. This is the first successful clinical trial of surfactant replacement therapy in Korea.

We anticipate that this study will activate surfac-

tant replacement therapy of HMD in Korea.

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