Comparison of Outcomes between Prophylactic and Rescue Therapy of Surfactant in Premature Infants

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ABSTRACT

Purpose: To compare early and later surfactant instillation in neonates with a birth weight of <1,250 g and/or less than 30 weeks’ gestation, following the changes in the National Health Insurance policy of the Republic of Korea.

Methods: Preterm infants diagnosed with respiratory distress syndrome and instilled with an exogenous surfactant from April 2006 to August 2012 were included in this study. The subjects were divided into the two groups: the prophylactic group (n=19) included neonates who were instilled with surfactant within 30 minutes after birth in the delivery or operating room, and the rescue group (n=27) included neonates who were treated with surfactant from 30 minutes to 10 hours after birth for the treatment of respiratory distress syndrome. We compared the two groups in terms of short- and long-term outcomes.

Results: The groups showed no significant difference in gestational age and birth weight. The prophylactic group had a shorter duration of mechanical ventilation of synchronized intermittent mandatory ventilation but longer parenteral nutrition and mechanical ventilation, including continuous positive airway pressure without synchronized intermittent mandatory ventilation. There are significant differences in the occurrence of long-term common complications such as patent ductus arteriosus and parenteral nutrition-associated cholestasis. The ventilation index, oxygenation index, mean airway pressure, and arterial-to-alveolar oxygen pressure ratio were lower in the prophylactic group than in the rescue group.

Conclusion: In comparison with late instillation, early surfactant instillation can reduce the period and requirement of mechanical ventilation. It also reduces the occurrence of patent ductus arteriosus and parenteral nutrition-associated cholestasis in newborns.

Key Words: Pulmonary surfactant, Very low birth weight infants, Respiratory distress syndrome

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INTRODUCTION

Many studies have been performed on surfactant administration, with regard to both prophylactic and rescue treatment. Many researchers have concluded that early instillation at the delivery site results in better outcomes such as improved survival rate, reduced oxygen and mechanical ventilation requirement, early introduction of oral feeding, cessation of parenteral nutrition, and decreased incidence and duration of invasive catheter insertion. Moreover, many researchers have compared prophylaxis and rescue therapy from the early period of birth to until shortly before discharge. However, such investigations have rarely been performed in the Republic of Korea. In Korea, until 2010, the National Health Insurance (NHI) had restricted pay for patients who did not have radiologic evidence for respiratory distress syndrome (RDS). However, chest radiographs cannot always be taken immediately after birth and radiologic findings cannot be obtained as quickly as the patient needs them. Following the policy change of the NHI in 2010, the institution began paying claims for neonates who had <1,250 g birth weight and/or less than 30 weeks’ gestational age. Consequently, many neonatal intensive care units (NICUs) in Korea began instilling artificial surfactant for neonates who meet the above-mentioned criteria just after birth, without the need to check for a positive radiologic reading for RDS. Thus, the benefits and deficits of early artificial surfactant instillation for prophylactic therapy are of interest to researchers.

MATERIALS AND METHODS

A retrospective analysis was made on infants who were born at Chung-Ang University in Korea from April 2006 to August 2012 and instilled with Surfacten™ (Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan) via an endotracheal tube at the delivery room or the NICU until 10 hours from birth. Only preterm infants (<30 weeks’ gestation) were targeted, and those who were instilled twice were excluded. We also excluded those infants who were transferred to another hospital due to the interference of the transfer and the lack of communication on the patient’s outcome.

We collected information on surfactant instillation policies. Surfacten™ was prepared in 4 mL of normal saline at the delivery room or the NICU, at room temperature without bubbles. The surfactant was instilled at 0.8 mL for each position change via a plastic catheter loaded in an endotracheal tube, and the tip of the catheter was positioned at the carina. Five point position change was performed in all-patients—supine, right and left shoulder down, and right and left leg down. These positions were set at 60 seconds each. After instillation, patients were supported with synchronized intermittent mandatory ventilation (SIMV) rather than by a high-frequency oscillator (HFO).

We divided our patients into the two groups: prophylactic and rescue. The prophylactic group consisted of newborns who were administered an exogenous surfactant less than 30 minutes after birth. The rescue group consisted of newborns who were instilled at from 30 minutes to 10 hours after birth.

We compared the patient characteristics between the two groups, including birth weight, gestational age, gender, Apgar scores, antenatal steroid administration proportion, and maternal age. Next, the serial trends in ventilation index (VI), oxygenation index (OI), mean airway pressure (MAP), and arterial-to-alveolar oxygen pressure ratio (a/APO2) were compared between the two groups for further evaluation of ventilator care. We performed arterial blood gas analysis at 30 minutes, 3 hours, and 6 hours after surfactant instillation, using the ventilator settings at each time. Then, we compared the occurrence of morbidities, including pneumothorax, pneumopericardium, patent ductus arteriosus (PDA), persistent pulmonary hypertension of newborn (PPHN), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), parenteral nutrition-associated cholestasis (PNAC), necrotizing enterocolitis (NEC), sepsis, and bronchopulmonary dysplasia (BPD), as well as the durations of hospitalization, parenteral nutrition, and ventilator care between the two groups.

We obtained statistical data by using Student’s t-test, Mann Whitney U test, correlation analysis, and repeated measures ANOVA with SPSS™ version 18 (IBM, USA). P values less than 0.05 were considered significant.

PDA was diagnosed by echocardiography, and only symptomatic cases were identified. We defined IVH as a diagnosis of higher than grade III on brain ultrasonography. The diagnosis of BPD was made in infants who needed supplemental oxygen at 36 weeks’ postmenstrual age (gestational age <32 weeks) with consistent radiographic changes (persistent hazy opacification or cyst-like pattern of density and lucency). PPHN was diagnosed by real-time echocardiography combined with the doppler flow imaging demonstrating right-to-left or bidirectional shunting across a patent foramen ovale and a ductus arteriosus, deviation of the intra-atrial septum into the left atrium and tricuspid or mitral insufficiency without other cardiac anomalies. NEC was defined...
as a diagnosis higher than stage III in the modified Bell's staging criteria\textsuperscript{13}, necessitating an operation. PNAC was defined as an elevation of serum direct bilirubin levels to >2.0 mg/dL. Sepsis was suspected with fever, hypotension, general weakness or C reactive protein (CRP) elevation and confirmed with the presence of microbes in blood culture. Pneumothorax and pneumopericardium were diagnosed using chest radiography.

**RESULTS**

A total of 46 infants were included in our study. Twenty-six (56.5\%) of the patients were male and 20 (43.5\%) were female. The prophylactic group comprised of 19 infants, whereas the rescue group comprised 27 infants. The time interval from birth to instillation was significantly different between the two groups, as we intended (12.6±6.3 vs. 143.3±114.0, \(P<0.05\)). The clinical characteristics, including gestational age and birth weight, were not significantly different between the two groups. Maternal factors also showed no significant difference (Table 1).

Between the two groups, we compared the basic parameters of disease severity, including the lengths (in days) of admission and parenteral nutrition. The length of admission of the prophylactic group was statistically significantly shorter than that of the rescue group (62.0±28.4 vs. 93.0±69.5, \(P<0.05\)).

We evaluated the duration of use of different types of mechanical ventilator assistance. The duration of ventilator care with HFO or SIMV in the prophylactic group was shorter than that in the rescue group, but the difference was not statistically significant. On the contrary, the duration of continuous positive airway pressure (CPAP) in the prophylactic group was longer than that in the rescue group, but the difference was also not statistically significant. The duration of total ventilation including HFO, SIMV, and CPAP was slightly longer in the prophylactic group than in the rescue group; however, the difference was not statistically significant (Table 2).

Arterial blood gas analysis was performed in all patients at 30 minutes, 3 hours, and 6 hours after surfactant instillation. With these data and the mechanical ventilator setting values, we obtained the values of VI, OI, MAP, and a/APO\textsubscript{2}. The prophylactic group showed a tendency toward a rapid decrease in VI, whereas VI in the rescue group was elevated at 3 hours and reduced at 6 hours after instillation. VI showed no significant difference among time points after instillation (\(P=0.173\)) and between groups (\(P=0.449\)) (Fig. 1A). The prophylactic group showed a tendency toward maintenance of the OI level, while the rescue group showed a slow reduction of the OI with time (Fig. 1B). OI values across time points (\(P=0.357\)) showed no significant difference; however, OI had a significant difference between groups (\(P=0.003\)). The MAP requirement of the prophylactic group was significantly lower than that of the rescue group (\(P=0.003\)) (Fig. 1C). The rescue group always needed higher MAP at each time point than the prophylactic group, and the difference was statistically significant (\(P<0.05\)). The chronological tendencies of both MAP decreases (\(P<0.05\)) were statistically significant. The a/APO\textsubscript{2} in the prophylactic group tended to decrease rapidly at 3 hours and become elevated at 6 hours, whereas it increased slowly in the rescue group. However, there are no significant statistical differences between groups (\(P=0.784\)) and across time points (\(P=0.337\)) (Fig. 1D). All parameters showed a significant difference between the prophylactic and rescue groups (\(P<0.05\)).

**Table 1. Patients’ Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Prophylactic group (n=19)</th>
<th>Rescue group (n=27)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>27.5±2.2</td>
<td>26.7±1.8</td>
<td>0.12</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1,069±301</td>
<td>940±219</td>
<td>0.14</td>
</tr>
<tr>
<td>Male (%)</td>
<td>11 (57.9%)</td>
<td>18 (66.7%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Cesarean section (%)</td>
<td>11 (57.9%)</td>
<td>19 (70.4%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Inborn (%)</td>
<td>19 (100%)</td>
<td>24 (88.9%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Surfactant instillation time after birth (minutes)</td>
<td>12.6±6.3</td>
<td>143.3±114.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>APGAR score</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1 minute (median)</td>
<td>4</td>
<td>5</td>
<td>0.103</td>
</tr>
<tr>
<td>5 minute (median)</td>
<td>6</td>
<td>7</td>
<td>0.389</td>
</tr>
<tr>
<td>Antenatal steroid (%)</td>
<td>7 (36.8%)</td>
<td>5 (18.5%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Maternal Age</td>
<td>31.2±4.0</td>
<td>29.9±4.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Hypertension in pregnancy</td>
<td>0 (0%)</td>
<td>2 (7.4%)</td>
<td>0.509</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>2 (10.5%)</td>
<td>4 (14.8%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Table 2 shows the morbidity rates for the prophylactic and rescue groups. The targeted diseases were pneumothorax, pneumopericardium, PDA, PPHN, ROP, IVH, PNAC, NEC, sepsis, and BPD. A correlation between groups was found with PDA ($P < 0.05$) and PNAC ($P < 0.05$). However, the other diseases showed no statistically significant difference between the two groups.

**DISCUSSION**

Maeta et al.\(^{14}\) investigated exogenous surfactant treatment in baboons, and made group comparisons between ultra-early treatment and late treatment. They found higher values in the prophylactic treatment group in terms of MAP requirement, lung-thorax compliance, and ventilation and perfusion parameters such as $a/APO_2$, using a relatively small number of subjects (n=5 or 6 in each group). In human studies, however, researchers cannot set a control group strictly as in the aforementioned study. Despite the apparent benefits, this prophylactic therapy has some drawbacks such as the possible side effects of the animal-derived surfactant, the uncontrollable crowdedness of the urgent premature-delivery room, the high cost of the surfactant itself, and the possibility of instillation in patients who do not actually have RDS.

Merrit et al.\(^{15}\) found that ROP and PDA occurred more often in prophylactic patients than in rescue patients; however, Kendig et al.\(^{16}\) refuted this observation. Rankin et al.\(^{17}\) reported on the risk of ROP with surfactant instillation, and Holmes et al.\(^{18}\), Repka et al.\(^{19}\), and Pennefather et al.\(^{20}\) studied the correlation of ROP with prophylactic surfactant therapy. These authors commonly reported that early surfactant therapy is effective for prevention of ROP. Kumar et al.\(^{21}\) reported that surfactant therapy increased the incidence of PDA. However, in our study, we found a statistically significantly lower ratio of PDA in the prophylactic group. Lee et al.\(^{22}\) reported that prophylactic group had a significantly lower PDA prevalence than rescue group as well.

Kendig et al.\(^{16}\) also maintained that earlier surfactant administration protected IVH and BPD. In our study, we found no significant relationship between surfactant administration and pneumothorax, pneumopericardium, PPHN, ROP, IVH, NEC, sepsis, and BPD. The timing of surfactant instillation had relation statistically significantly with other complications such as PDA and PNAC, which we were able to observe until discharge. Tan et al.\(^{23}\) raised the possibility of a relation with PNAC and RDS, but found little correlation. Likely, our results on the relation between the timing of surfactant instillation and PNAC had little significance because of the bias due to the small number of subjects. Brunherotti et al.\(^{24}\) reported that a reduction of ventilatory parameters decreased the occurrence of pneumothorax in newborns. We also predicted that air leakage such as that in pneumothorax and pneumopericardium would be reduced by early extubation from early surfactant instillation. However, we could not find a statistically significant relation in our results, possibly because of the small number of our total subjects.

This report describes early surfactant treatment practices in a single NICU, and is supported by a small number of cases. However, we have also studied the constant policies, including the factors

<table>
<thead>
<tr>
<th>Table 2. Comparison of Outcomes according to Treatment Groups</th>
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<tbody>
<tr>
<td><strong>Prophylactic group (n=19)</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Admission (days)</td>
</tr>
<tr>
<td>Parenteral nutrition (days)</td>
</tr>
<tr>
<td>Ventilator (days)</td>
</tr>
<tr>
<td>HFO+SIMV</td>
</tr>
<tr>
<td>CPAP</td>
</tr>
<tr>
<td>Pneumothorax</td>
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<tr>
<td>Pneumopericardium</td>
</tr>
<tr>
<td>PDA</td>
</tr>
<tr>
<td>BPD</td>
</tr>
<tr>
<td>ROP</td>
</tr>
<tr>
<td>IVH</td>
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<tr>
<td>PNAC</td>
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<tr>
<td>NEC</td>
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<tr>
<td>Sepsis</td>
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</table>
that differ in from each NICU and influence outcomes for 6 years duration.

Egberts et al.\textsuperscript{10} compared two groups with an FiO\textsubscript{2} requirement. In their study, among prophylactically treated neonates, <35% needed mechanical ventilation, 30% oxygen, 70% CPAP, and 95% required no ventilator assistance. However, simple FiO\textsubscript{2} administration is not sufficient to represent ventilator assistance requirement. To maintain arterial oxygen saturation, not only FiO\textsubscript{2} but also PIP, PEEP, respiratory ratio, and inspiration-to-expiration ratio should be considered. VI, OI, MAP, and a/APO\textsubscript{2} are the reliable parameters that altogether reflect the mechanical ventilator requirement\textsuperscript{25-27}.

Among these ventilation parameters, we found a clear difference in OI and MAP between the rescue group and the prophylactic group. Surfactant administration provides increase of pulmonary compliance and rapid and sustained response in oxygenation and gas exchange. As such, OI and MAP were decreased after surfactant instillation over time in both two groups. However, the prophylactic group showed lower OI and MAP than the rescue group significantly. All of these findings support the superiority of prophylactic therapy. During the administration interval in the two groups, the immature lung was damaged by possible barotrauma induced by mechanical ventilation and oxygen radical ions. Just

**Fig. 1.** The Tendencies of mechanical ventilation requirement parameters [(A) ventilation index, (B) oxygenation index, (C) mean airway pressure, and (D) arterial-to-alveolar oxygen pressure ratio].
after birth, a preterm baby has little endogenous surfactant and it is depleted quickly. The prophylactic therapy would protect immature alveoli before the surfactant depletion. In our results, the prevalence of BPD and ROP did not show statistically significant difference: but the prevalence of the prophylactic group was lower than that of the rescue group. With more cases, we may be able to get significant results.

In this study, we found some interesting results on the prophylactic surfactant administration. However, our subject population is too small to conclude a statistically significant result, and this may have caused several biases. In the future, more significant results may be obtained using a larger sample and stricter criteria.

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미숙아에서 폐표면활성제의 예방적 투여와 치료적 투여의 결과 비교

중앙대학교 의과대학 소아청소년과학교실
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목적: RDS로 의심 혹은 진단된 출생 체중 1,250 g 이하 혹은 출생시 재태연령 30주 미만의 신생아에게 인공 계면활성제의 투여 시간에 따른 효과를 비교하였다.

방법: 2006년 4월부터 2012년 8월까지 RDS로 진단되거나 출생 체중 1,250 g 미만 혹은 출생시 재태 연령 30주 미만이어서 인공 계면활성제를 투여한 환아들을 대상으로 연구를 진행하였다. 대상은 조기투여군(n=19)과 후기투여군(n=27)으로 나누었으며 조기투여군은 출생후부터 30분이내에 계면활성제를 투여한 환아들로 이루어져있고, 후기투여군은 출생후부터 30분에서 10시간 이내에 계면활성제를 투여한 환아들로 이루어졌다. 두 그룹간의 단기적, 장기적인 결과를 비교하였다.

결과: 그룹간에 출생 체중과 출생 시 재태연령은 통계학적으로 차이가 없었다. 조기투여군은 SIMV기간이 짧았으나 정맥 혈압 기간과 총 기계 호흡 기간이 길었다. 또한 조기투여군의 경우 PDA와 PNAC의 발생이 적었다. 또한 VI, OI, MAP, a/APO2 같은 인공호흡의 필요성을 나타내는 지표들은 조기투여군이 더 낮았다.

결론: RDS로 의심되거나 진단된 환아에게 계면활성제를 조기 투여하는 것이 기계 환기 호흡 기간과 필요성을 줄이고 PDA와 PNAC의 발생을 줄인다.