Efficacy of surfactant at different gestational ages for infants with respiratory distress syndrome

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Abstract: Since exogenous surfactant replacement therapy was first used to prevent respiratory distress syndrome (RDS), it has become the main method for treatment of RDS. However, in some infants, death is inevitable despite intensive care and surfactant replacement therapy, especially in near-term and term infants. The main purpose of this study was to compare the therapeutic effect of pulmonary surfactant for infants at different gestational ages and to investigate whether exogenous surfactant replacement therapy is effective for all newborns with RDS. Data on surfactant replacement therapy, including blood gas, oxygenation function parameters and therapy results, were collected from 135 infants who were diagnosed with RDS during three years at a tertiary neonatal intensive care unit. According to gestational age, the subjects were classified into three groups as follows: group 1: gestational age <35 weeks (n=54); group 2: 35 weeks ≤ gestational age <37 weeks (n=35); group 3: gestational age ≥37 weeks (n=46). Six hours after surfactant was given, there were significantly better blood gas results in group 1 and worse results in groups 2 and 3. Similar oxygenation function parameter results were observed in the three groups. In addition, there was a trend toward an increased rate of repeated surfactant administration with increasing gestational age. For near-term and term infants, the efficacy of surfactant therapy was not as good as it was for preterm infants. The causes of RDS in near-term and term infants might be different from those in preterm infants and should be studied further.

Keywords: Surfactant, respiratory distress syndrome, infants, gestational age

Introduction

Respiratory distress syndrome (RDS) is one of the most important causes of morbidity and mortality in newborn infants, especially those born prematurely [1-3]. The conventional idea states that its etiology includes developmental immaturity of the lungs, particularly of the surfactant synthesizing system. Since exogenous surfactant replacement therapy was first used to prevent RDS, several clinical studies have demonstrated its therapeutic effects [4-7], and exogenous surfactant replacement therapy has become the main method for treatment of RDS. However, in some infants, death is inevitable despite intensive care and surfactant replacement therapy. Recent studies have suggested that in addition to pulmonary surfactant deficiency, there are other causes leading to RDS, especially in near-term and term infants [8-11].

The main purpose of this study was to compare the therapeutic effect of pulmonary surfactant in infants of different gestational ages and to investigate whether exogenous surfactant replacement therapy is effective for all newborns with RDS. To the best of our knowledge, this study is the first to examine the combined effects of gestational age and surfactant replacement therapy in newborns with RDS.

Materials and methods

A retrospective analysis was conducted at a tertiary pediatric neonatal intensive care unit (NICU) in Daping Hospital, Third Military Medical University. A total of 168 neonates with RDS who received surfactant therapy were recruited between January 2010 and February 2013.

The NICU admitted both in-born infants and out-born infants transported from 80 hospitals in Chongqing and nearby areas. All the out-born infants received surfactant therapy after birth.
infants were transported by an ambulance staffed by a transport team consisting of one neonatologist and one or two nurses.

The diagnosis of RDS was based on clinical manifestations and chest X-ray findings [12]. The clinical signs and symptoms of RDS were respiratory distress, tachypnea, nasal flaring, groaning, and cyanosis after birth. The typical X-ray picture of RDS showed a grainy shadow, air bronchogram, and white lungs. Grade 1 involved a slight reticular (slight granular) decrease in transparency of the lung with no certain difference from normal findings. Grade 2 involved a slight decrease in transparency with an air bronchogram that overlaps the heart. Grade 3 involved a somewhat stronger decrease in transparency and a blurry dia
daphragm and heart. Grade 4 involved practically homogenic lung opacity [13]. The X-ray images were judged by two radiologists blinded to the patient’s condition.

Infants were excluded if they had any congenital malformation, inherited metabolic abnormality, intrauterine infection, Rh/Rh incompatibility, pneumonia, pulmonary hypertension, meconium aspiration syndrome, or asphyxia (Figure 1). The clinical characteristics of all the infants were recorded.

A total of 135 newborns with RDS who satisfied the inclusion criteria were managed in the conventional manner according to the existing protocols at the NICU. The subjects were classified into three groups as follows: group 1, gestational age <35 weeks (n=54); group 2, 35 weeks ≤ gestational age <37 weeks (n=35); and group 3, gestational age ≥ 37 weeks (n=46).

According to the severity of RDS, different primary modes of ventilation were provided for the subjects. Nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive pressure ventilation (NIPPV) were provided for RDS of grades 1 and 2, and High-frequency oscillatory ventilation (HFOV) and conventional mechanical ventilation (CMV) were provided for RDS of grades 3 and 4. All infants with RDS were given surfactant as soon as practicably possible (within 24 h after birth). The primary treatment was 200 mg/kg doses of porcine surfactant, and 100 mg/kg was administered in cases that required repeated treatment. To ensure homogenous distribution of the surfactant throughout the lungs, each dose was divided into 4 quarter doses, and each quarter dose...
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The infants were evaluated for blood gas and oxygenation function parameters. Data regarding clinical outcomes including the need for intubation, duration of ventilation, survival rate, hospitalization time and rate of repeated surfactant administration (giving surfactant more than once) were collected and analyzed. Statistical analysis of the data was performed using paired-samples T tests, one-way ANOVA, or chi-square test and expressed as mean ± standard deviation (SD), or percentage. The wide SD of the mechanical ventilation times suggested that the data were non-normally distributed; therefore, Mann-Whitney rank sum test was used for comparison and expressed as median. P<0.05 was accepted as statistically significant. The Statistical Package for the Social Sciences (SPSS) program (16.0 for Windows software, LEAD Technology, Inc) was used.

Results

Clinical characteristics of the infants

The mean birth weights in the three groups were 1.70±0.35 kg, 2.27±0.54 kg and 2.98±0.51 kg, respectively, with a significant difference between the groups (P<0.05). In group 1, 38 neonates (70%) were male, and 16 (30%) were female; in group 2, 19 neonates (54%) were male, and 16 (46%) were female; in group 3, 32 neonates (70%) were male, and 14 (30%) were female; the sex distribution was similar among the three groups (P>0.05). There were 31 neonates (57%) born by cesarean section in group 1, 31 (89%) in group 2 and 37 (80%) in group 3, and there was a significant difference in the delivery mode among the three groups (P<0.05). The Apgar scores in the 5th minute in the three groups were 9.26±1.23, 9.66±0.80 and 9.57±0.75, respectively, which indicated that the difference was not significant (P>0.05) (Table 1). The severity of RDS among the three groups was also not significant (P>0.05) (Table 2).

Blood gas analysis before and after surfactant administration

Although there was a trend toward higher pH with increasing gestational age, the difference in pH before surfactant administration among the three groups was not significant (P>0.05). Six hours after the surfactant was given, there was a significant increase in the pH of group 1 (P<0.01), but there was no significant difference in pH before and after surfactant administration in groups 2 and 3 (P>0.05). Before surfactant administration, the difference in PaO₂ was not significant among the three groups, but there was a significant difference among the three groups six hours after the surfactant was given. After therapy, PaO₂ was significantly increased compared in group 1 (P<0.01), not significantly different in group 2 (P>0.05), and significantly decreased in group 3 (P<0.01). In addition, the difference in PaCO₂ among the three groups before surfactant administration was not significant (P>0.05), but there was a significant difference among the three groups after surfactant therapy (P<0.05). Six hours after surfactant was given, PaCO₂ was significant decreased in group 1, significantly increased in group 3 (P<0.05), and not significantly different in group 2 (P>0.05) (Table 3).

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**Table 1. Clinical characteristics of the infants in all groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Birth weight (g)</th>
<th>Male (%)</th>
<th>Cesarean section (%)</th>
<th>Apgar score (5th minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=54)</td>
<td>1.70±0.35</td>
<td>70</td>
<td>57</td>
<td>9.26±1.23</td>
</tr>
<tr>
<td>Group 2 (n=35)</td>
<td>2.27±0.54</td>
<td>54</td>
<td>89</td>
<td>9.66±0.80</td>
</tr>
<tr>
<td>Group 3 (n=46)</td>
<td>2.98±0.51</td>
<td>70</td>
<td>80</td>
<td>9.57±0.75</td>
</tr>
</tbody>
</table>

P value: 0.000 0.24 0.002 0.128

Data are presented as mean ± SD, or percentage. Group 1: Gestational age <35 weeks; group 2: 35 weeks ≤ gestational age <37 weeks; group 3: gestational age ≥37 weeks.

**Table 2. Severity of RDS in all groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>RDS 1st−2nd, n (%): RDS 3rd−4th, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=54)</td>
<td>33 (61): 21 (39)</td>
<td>0.635</td>
</tr>
<tr>
<td>Group 2 (n=35)</td>
<td>21 (60): 14 (40)</td>
<td></td>
</tr>
<tr>
<td>Group 3 (n=46)</td>
<td>24 (52): 22 (48)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) of patients. RDS: respiratory distress syndrome. According to the severity, RDS were divided into four grades: RDS 1st, RDS 2nd, RDS 3rd, and RDS 4th.
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Table 3. Blood gas analysis before and after surfactant therapy in all groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>6 h after treatment</th>
<th>P value</th>
<th>Before treatment</th>
<th>6 h after treatment</th>
<th>P value</th>
<th>Before treatment</th>
<th>6 h after treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PH</td>
<td></td>
<td></td>
<td>PaO₂</td>
<td></td>
<td></td>
<td>PaCO₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=54)</td>
<td>7.17±0.10</td>
<td>7.23±0.14</td>
<td>0.001</td>
<td>60.83±9.35</td>
<td>64.94±12.00</td>
<td>0.016</td>
<td>46.65±8.59</td>
<td>43.63±11.07</td>
<td>0.033</td>
</tr>
<tr>
<td>Group 2 (n=35)</td>
<td>7.18±0.08</td>
<td>7.17±0.14</td>
<td>0.618</td>
<td>63.29±8.70</td>
<td>58.46±14.15</td>
<td>0.085</td>
<td>46.00±6.13</td>
<td>49.46±12.16</td>
<td>0.112</td>
</tr>
<tr>
<td>Group 3 (n=46)</td>
<td>7.19±0.09</td>
<td>7.18±0.14</td>
<td>0.613</td>
<td>63.63±11.11</td>
<td>57.52±14.90</td>
<td>0.007</td>
<td>44.50±7.24</td>
<td>50.26±11.13</td>
<td>0.003</td>
</tr>
</tbody>
</table>

P value

Data are presented as the mean ± SD.

Table 4. Oxygenation function parameters before and after surfactant therapy in all groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>6 h after treatment</th>
<th>P value</th>
<th>Before treatment</th>
<th>6 h after treatment</th>
<th>P value</th>
<th>Before treatment</th>
<th>6 h after treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FiO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=54)</td>
<td>47.50±18.24</td>
<td>41.70±22.78</td>
<td>0.011</td>
<td>7.28±4.48</td>
<td>6.46±5.61</td>
<td>0.194</td>
<td>0.26±0.11</td>
<td>0.42±0.27</td>
<td>0.000</td>
</tr>
<tr>
<td>Group 2 (n=35)</td>
<td>42.14±13.30</td>
<td>50.63±24.08</td>
<td>0.046</td>
<td>6.20±3.41</td>
<td>9.70±7.13</td>
<td>0.008</td>
<td>0.28±0.12</td>
<td>0.30±0.22</td>
<td>0.585</td>
</tr>
<tr>
<td>Group 3 (n=46)</td>
<td>43.63±15.56</td>
<td>49.47±27.14</td>
<td>0.000</td>
<td>6.50±3.64</td>
<td>11.51±8.81</td>
<td>0.000</td>
<td>0.36±0.14</td>
<td>0.28±0.25</td>
<td>0.782</td>
</tr>
</tbody>
</table>

P value

Data are presented as the mean ± SD, OI=MAP×FiO₂×100, PaO₂/PaCO₂= (760-47)×FiO₂/PaCO₂/0.8.

Table 5. Therapeutic outcomes in all groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Endotracheal Ventilation (%)</th>
<th>Mechanical ventilation time (h, median)</th>
<th>Survival rate (%)</th>
<th>Hospitalization time (d)</th>
<th>Repeated surfactant rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=54)</td>
<td>44</td>
<td>71.02</td>
<td>85</td>
<td>13.33±8.42</td>
<td>19</td>
</tr>
<tr>
<td>Group 2 (n=35)</td>
<td>60</td>
<td>68.29</td>
<td>80</td>
<td>9.10±3.93</td>
<td>37</td>
</tr>
<tr>
<td>Group 3 (n=46)</td>
<td>57</td>
<td>64.24</td>
<td>89</td>
<td>8.89±4.06</td>
<td>39</td>
</tr>
</tbody>
</table>

P value

Data are presented as number (percentage) of patients, median, or mean ± SD.

Oxygenation function parameters before and after surfactant administration

The difference in FiO₂ before surfactant administration was not significant among the three groups (P>0.05), but there was a significant difference after surfactant therapy (P<0.05). After the surfactant was given, there was significantly lower FiO₂ in group 1 and significantly higher FiO₂ in groups 2 and 3 (P<0.05). For oxygen index (OI), the difference before surfactant therapy was not significant (P>0.05), but there was a significant difference among the three groups six hours after surfactant administration (P<0.05). After therapy, there was no significant difference in group 1 (P>0.05), but significantly higher OI values were found in groups 2 and 3 (P<0.05). Similarly, there was also no significant difference in PaO₂/PaCO₂ among the three groups before surfactant therapy (P>0.05), but the difference after surfactant therapy was significant (P<0.05); PaO₂/PaCO₂ was significantly improved in group 1 (P<0.05), but no significant difference was found in groups 2 and 3 (P>0.05) (Table 4).

Therapeutic outcomes

There were no significant differences among the three groups with respect to tracheal intubation, mechanical ventilation time or survival rate (P>0.05). The differences in hospitalization time and rate of repeated surfactant administration were significant among the three groups (P<0.05 and P<0.05, respectively). There was a trend toward decreased hospitalization time with increasing gestational age but a trend toward an increased rate of repeated surfactant administration with increasing gestational age (Table 5).

Discussion

RDS is the dominant clinical problem faced by preterm infants. The incidence of RDS decreases with advancing gestational age, from approximately 60-80% in infants born at 26-28 weeks to approximately 15-30% in those born at 32-36 weeks [14, 15]. RDS in preterm neonates is well known to be caused by a deficien-
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cy or dysfunction of pulmonary surfactants. The physiological functions of surfactants include the ability to lower surface tension and the ability to rapidly adsorb and spread, which is associated with the respiratory cycle. However, in some infants, death is inevitable despite intensive care and surfactant replacement therapy, especially in near-term and term infants. Recently, the burden of RDS in near-term and term infants has been highlighted, and more and more studies have suggested that the clinical presentation in near-term and term infants may be different from that observed in very preterm infants [16-18]. So far, no trials comparing the efficacy of surfactant replacement therapy in infants at different gestational ages have been performed. The present study was designed to determine whether surfactant replacement therapy in infants at different gestational ages had different outcomes.

In addition to pulmonary surfactant deficiency and structural immaturity of the lungs, other risk factors for the development of RDS have been reported. Gerten et al [10] found that at any given gestational age, the incidence of RDS is greater for infants born by caesarean section, especially without established labor, than for those born by vaginal delivery. The reasons for the increased risk of respiratory morbidity are most likely a combination of delayed removal of lung fluid and lack of cortisol response associated with spontaneous labor [19]. Our data indicate that the rate of cesarean section was rather high in all groups. In addition to dystocia, other potential reasons include the one-child policy, medical tangle, giant baby, or lack of a well-performed painless childbirth. The cesarean section rate of preterm infants in our research was in keeping with the average rate of cesarean section in China [20]. However, the rates of cesarean section were significantly higher in the near-term and term baby groups than in the premature group. The high rate of cesarean section without labor most likely contributed to the development of RDS in the near-term and term babies, and so the delayed removal of lung fluid and lack of cortisol response were important reasons for RDS in the near-term and term infants.

According to available evidence [19, 21], pulmonary surfactant deficiency is not the main reason for RDS in near-term and term infants. The causes of respiratory distress in these types of infants include transient tachypnea of the newborn (TTN), pneumonia and pulmonary hypertension. For most of the infants in this specific group of patients, surfactant therapy is not the primary therapeutic option. Helve et al [22] studied the correlation among lung fluid clearance, pulmonary surfactant deficiency and RDS. They reported that RDS resulting from surfactant deficiency occurred mainly in infants <35 weeks of gestational age and that RDS resulting from the delayed removal of lung fluid was higher in near-term and term infants than in preterm infants. These results strongly support the findings of the present study. In the present study, there was a significant increase in pH six hours after surfactant therapy in the preterm group, whereas no difference was observed in the near-term and term groups. At six hours after surfactant instillation, there was significantly higher PaO\textsubscript{2} in preterm infants and significantly lower PaO\textsubscript{2} in term babies; no significant difference was found in near-term babies. Meanwhile, there was significantly lower PaCO\textsubscript{2} in the preterm group and significantly higher PaCO\textsubscript{2} in the term group after surfactant administration; no difference was observed in the near-term group. Similar results were observed in oxygenation function parameters in all groups. In the light of these results, we could conclude that significantly better blood gas conditions and oxygenation function parameters were associated with surfactant therapy in infants <35 weeks of gestational age compared with the near-term and term infants, suggesting that surfactant replacement therapy for RDS was more effective in premature infants <35 weeks of gestational age than in near-term and term infants.

Tsakalidis et al [23] reported that premature infants treated with a single dose of surfactant could usually be successfully extubated. The requirements for retreatment could be attributed to other pathogenic mechanisms. Similarly, the most important finding of our study was that most of the preterm babies <35 weeks of gestational age received surfactant only once but that in the near-term and term groups, more babies needed multiple doses of surfactant. The severity of RDS among the three groups was not significant. This finding is in accordance with literature data supporting
that the pathogenic mechanism of RDS in near-
term and term infants is different from that in
premature infants <35 weeks of gestational
age [24, 25].

This study has some limitations resulting from
its retrospective structure. Patient inclusion
was based on the need for surfactant therapy
in infants with RDS, and infants who did not
accept surfactant therapy were excluded. Thus,
not all the infants with RDS were included in the
patient cohort, and the results do not reflect all
patients with RDS.

In conclusion, our study clearly shows that
among newborn infants who were diagnosed
with RDS, preterm babies <35 weeks of gesta-
tional age had a better response to surfactant
treatment than near-term and term babies. For
the near-term and term infants, the effect of
surfactant replacement therapy was not as
good as expected. In addition to a deficiency or
dysfunction of pulmonary surfactants, other
factors, such as the rapid clearance of fetal
lung fluid, might play a key role in the pathogen-
esis of RDS in near-term and term infants and
should be examined in future studies.

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Disclosure of conflict of interest

None.

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costeroids between 24 and 34 weeks of gesta-
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