Original Article
A comparative study of two noninvasive positive pressure ventilation modes combined with Curosurf in the treatment of respiratory distress syndrome in premature infants

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Abstract: Objective: To compare the efficacy of two noninvasive positive pressure ventilation modes combined with Curosurf in the treatment of respiratory distress syndrome in premature infants. Methods: A prospective study was conducted on 82 premature infants with neonatal respiratory distress syndrome, including 47 males and 35 females. The infants were divided into two groups using the random number table method, with 41 patients in each group. Non-invasive high-frequency ventilation combined with Curosurf treatment was used in the observation group, and bi-level positive airway pressure ventilation combined with Curosurf treatment was used in the control group. The clinical efficacy in the two groups was observed. The arterial partial pressure of oxygen (PaO₂), the arterial partial pressure of carbon dioxide (PaCO₂), and the oxygenation index (OI, PaO₂/FiO₂) were measured before treatment and at 1 hour, 6 hours, 12 hours, 24 hours, and 72 hours after treatment. The non-invasive ventilator treatment time, oxygen inhalation time, hospitalization time, and complications were recorded. Results: The total effective rate in the observation group was 95.12%, which was higher than the total effective rate in the control group (82.93%, P>0.05). After 1 h and 72 h of treatment, the PaO₂ in the observation group was higher than it was in the control group (P<0.05). After 1 h, 6 h and 12 h of treatment, the PaCO₂ in the observation group was lower than it was in the control group (P<0.05). After 24 h and 72 h of treatment, the OI in the observation group was higher than it was in the control group (P<0.05). The non-invasive ventilator treatment time, oxygen inhalation time, and hospitalization time in the observation group were lower than they were in the control group (P<0.05). The incidence of complications in the observation group was 4.88%, which was lower than it was in the control group (21.95%, P<0.05). Conclusion: Compared with the combination of bi-level positive airway pressure ventilation and Curosurf treatment, the use of non-invasive high-frequency oscillatory ventilation combined with a pulmonary surfactant can accelerate the time needed for carbon dioxide removal, shorten the treatment time, and reduce the occurrence of complications, which is worth of further clinical applications.

Keywords: Neonatal respiratory distress syndrome, non-invasive high-frequency ventilation, bi-level positive airway pressure ventilation, efficacy comparison

Introduction
Neonatal respiratory distress syndrome (NRDS) refers to a condition in which neonatal lung development is not fully mature, and respiratory failure is the main clinical manifestation due to the lack of pulmonary surfactant (PS). It is more common in premature babies [1] and can be accompanied by symptoms such as progressive dyspnea, cyanosis, dyspnea, and pale complexion [2-4]. NRDS is characterized by acute onset, severe illness, rapid progression, and a high mortality rate [5], and its incidence rate is on the rise in China. A Korean study in 2015 found that the incidence of NRDS in very low birthweight newborns can reach 28.9%, and the mortality rate can be as high as 11.9% [6]. Another European study found that the incidence of NRDS in newborns at 28 weeks of gestational age was 80%, compared with 90% at 24 weeks of gestational age [7].

Clinically, mechanical ventilation combined with pulmonary surfactant is used to treat NRDS
and achieve a remarkable curative effect. The representative drug of pulmonary surfactant is poractant alfa injection (Curosurf) [8-10]. With the development of medical technology, non-invasive ventilation technology has gradually replaced mechanical ventilation, and the treatment of NRDS with non-invasive ventilation technology combined with a pulmonary surfactant is currently recognized [11]. At present, non-invasive ventilation is mainly non-invasive positive pressure ventilation. The common ones include: nasal continuous positive pressure ventilation, nasal intermittent positive pressure ventilation, and hot humidification and high flow nasal catheter ventilation. However, one study found that there are some adverse reactions to non-invasive positive pressure ventilation, for example, carbon dioxide retention, hypoxemia, and the effect on the gastrointestinal tract [12]. Based on the above problems, the improvement of positive pressure ventilation, bi-level positive airway pressure ventilation (BiPAP), is used for the treatment of NRDS and is characterized by fewer adverse reactions and a good curative effect [13]. BiPAP is a new type of non-invasive ventilation treatment model to appear recently. It works by adjusting high and low pressure levels and time, and it has a wide range of clinical applications [13, 14]. Studies have shown that the use of BiPAP can effectively reduce ventilator work, increase tidal volume, significantly improve the ventilation perfusion ratio of children, improve PaO₂, reduce PaCO₂, and increase functional residual capacity. It has significant efficacy and few complications [15].

In recent years, another new type of noninvasive positive pressure ventilation, noninvasive high-frequency oscillatory ventilation (NHFOV) has begun to be used in clinical practice. The study found that it not only has the characteristics of non-invasive positive pressure ventilation, that is, little trauma, but it also has the advantages of not needing respiratory synchronization, good carbon dioxide removal, a small volume, and small barotrauma [16]. NHFOV can effectively avoid the respiratory support therapy that occurs after tracheal intubation in mechanical ventilation and can reduce the incidence of post-treatment complications [17, 18]. However, there are few studies on the efficacy of BiPAP and NHFOV combined with pulmonary surfactant (PS) in the treatment of NRDS. Therefore, this study aimed to compare the efficacy of these two noninvasive positive pressure ventilation modes combined with PS in the treatment of NRDS.

Materials and methods

General data

A prospective study was conducted in 82 premature infants with neonatal respiratory distress syndrome admitted to the Department of Obstetrics in our hospital from January 2017 to April 2019, including 47 males and 35 females. They were divided into two groups using the random number table method, with 41 patients in each group. Non-invasive high-frequency ventilation combined with Curosurf treatment was used in the observation group, and bi-level positive airway pressure ventilation combined with Curosurf treatment was used in the control group. Informed consent was obtained from the family members of all the included children, and the study was approved by the Ethics Committee of the First People's Hospital of Wenling.

Inclusion and exclusion criteria

Inclusion criteria: The patients met the diagnostic criteria in the 2016 European Guidelines for the Prevention and Treatment of Neonatal Respiratory Distress Syndrome [7]; gestational age <37 weeks; hospitalized within 12 hours after birth; progressive dyspnea at 6 hours after birth.

Exclusion criteria: Children with heart and liver disease; those with an intrauterine infection; those with aspiration pneumonia or wet lungs; those with a congenital genetic disease; those with congenital malformations.

Methods

Poractant alfa (Curosurf, Chiesi Pharmaceutical Co., Ltd., Germany) was instilled into the trachea of all the enrolled NRDS children under tracheal intubation. The poractant alfa injection was put into the syringe at a dose of 200 mg/kg, and then it was injected once and quickly into the lungs with tracheal intubation of a thin catheter under a sterile operation to make it quickly and evenly dispersed. After the instillation was completed, the trachea cannula was removed. PaO₂ and PaCO₂ were observed according to the blood gas analysis. The obser-
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Table 1. Comparison of the general data between the two groups

<table>
<thead>
<tr>
<th></th>
<th>Observation group (n=41)</th>
<th>Control group (n=41)</th>
<th>χ²/t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male:female)</td>
<td>24:17</td>
<td>26:15</td>
<td>0.205</td>
<td>0.651</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>33.2±1.4</td>
<td>33.5±1.5</td>
<td>0.932</td>
<td>0.354</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>1.82±0.33</td>
<td>1.84±0.41</td>
<td>0.253</td>
<td>0.801</td>
</tr>
<tr>
<td>Mode of parturition (Natural childbirth:cesarean section)</td>
<td>5:36</td>
<td>4:37</td>
<td>0.125</td>
<td>0.724</td>
</tr>
<tr>
<td>NRDS classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>25</td>
<td>24</td>
<td>0.051</td>
<td>0.822</td>
</tr>
<tr>
<td>Grade III</td>
<td>16</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenatal glucocorticoid use rate</td>
<td>15 (36.58%)</td>
<td>14 (34.15%)</td>
<td>0.053</td>
<td>0.817</td>
</tr>
<tr>
<td>Apgar score</td>
<td>5.8±1.4</td>
<td>6.0±1.5</td>
<td>0.466</td>
<td>0.643</td>
</tr>
</tbody>
</table>

Note: NRDS: Neonatal respiratory distress syndrome.

effective + effective)/total number of patients. PaO₂, PaCO₂, and the oxygenation index (OI) were determined before the non-invasive treatment, after 1 hour, 6 hours, 12 hours, 24 hours, and 72 hours of treatment.

Secondary outcome measurements: Non-invasive ventilator treatment time, oxygen inhalation time, and hospitalization time were recorded. Complications such as pulmonary gas leakage, nasal injury, apnea syndrome, and intracranial hemorrhage were recorded.

Statistical analysis

SPSS 17.0 software (Asia Analytics Formerly SPSS, China) was used for the statistical analysis. The continuous variables were expressed as the mean ± standard deviation (X ± sd). Variables that conformed to a normal distribution and homogeneity of variance were analyzed using an independent sample t test and denoted by t. A paired t-test was used to compare the variables before and after treatment in the same group. The multi-time comparisons were performed using a repeated measures analysis of variance, and if there were differences, further pairwise comparisons were made using an LSD analysis. The enumeration data were expressed as % and analyzed using a Pearson chi-squared test, denoted by χ². P<0.05 was considered significantly different.

Results

Comparison of the general data between the two groups

There were no significant differences in gender, gestational age, birth weight, mode of parturition.
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Comparison of the clinical effects between the two groups

The total effective rate of the observation group was 95.12%, which was higher than the rate of the control group (82.93%), but there was no significant difference (P>0.05). See Table 2.

Comparison of the changes in PaO$_2$, PaCO$_2$ and OI at different time points in the two groups

A repeated measures analysis of variance showed that there was a significant difference in PaO$_2$ between the two groups at different time points (P<0.001). Before treatment, and at 6 hours, 12 hours, and 24 hours after treatment began, there were no differences in PaO$_2$ between the two groups (P>0.05). After treatment for 1 hour and 72 hours, the PaO$_2$ in the observation group was higher than it was in the control group (P<0.05). There was a significant difference in the PaCO$_2$ between the two groups at different time points (P<0.001). There was no difference in PaCO$_2$ between the two groups before treatment, and at 24 hours and 72 hours after treatment began (P>0.05). The PaCO$_2$ in the observation group was lower than it was in the control group at 1 hour, 6 hours, and 12 hours after treatment began (P<0.05). There was a significant difference in OI between the two groups at different time points (P<0.001). There was no difference in OI between the two groups before treatment, and at 1 hour, 6 hours, and 12 hours after treatment began. The OI of the observation group was higher than it was in the control group at 24 hours and 72 hours after treatment began (P<0.05). See Tables 3-5 and Figure 1.

Discussion

Neonatal respiratory distress syndrome (NRDS) is a common respiratory disease in neonates. It is called neonatal hyaline membrane disease because of its unique pathological manifestations. The study found that the main pathophysiological manifestation of NRDS is the lack of pulmonary surfactant (PS), which causes the alveolar surface tension to decrease, the alveoli to shrink, and the oxygen exchange to decrease as the blood flows through the atelectasis alveoli, resulting in a decrease in blood oxygen. The body is in an anoxic state, and hypoxia further leads to damage to the vascular endothelium, eventually resulting in damage to pulmonary vascular function and structure [20]. It is currently recognized that the use of non-invasive ventilation technology combined with a pulmonary surfactant is the best treatment for NRDS [11]. Based on this, this study found that there is no statistically significant difference between the two non-invasive ventilation methods combined with PS in the treatment of NRDS. It indicated that both noninvasive ventilation regimens had a good response to NRDS, which is consistent with previous studies [13-18].

Previous studies found when premature infants with respiratory failure were treated with...
NHFOV, PaCO₂ was significantly decreased and PaO₂ was increased [21]. Another study found that after the treatment of noninvasive positive pressure ventilation for 7 days, the use of NHFOV for 2 h could also result in a decrease in PaCO₂ [22]. The study found that BiPAP could effectively improve OI, increase PaO₂ and reduce PaCO₂ in children with NRDS [23]. In
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### Table 6. Comparison of non-invasive ventilator treatment time, oxygen inhalation time, and hospitalization time in the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Non-invasive ventilator treatment time (h)</th>
<th>Oxygen inhalation time (h)</th>
<th>Hospitalization time (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation (n=41)</td>
<td>85.46±22.32</td>
<td>95.12±25.31</td>
<td>11.34±3.52</td>
</tr>
<tr>
<td>Control (n=41)</td>
<td>96.48±26.21</td>
<td>110.24±29.48</td>
<td>15.67±5.28</td>
</tr>
<tr>
<td>t</td>
<td>2.051</td>
<td>2.492</td>
<td>4.373</td>
</tr>
<tr>
<td>P</td>
<td>0.044</td>
<td>0.015</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 7. Comparison of the complications between the two groups

<table>
<thead>
<tr>
<th>Complications</th>
<th>Observation (n=41)</th>
<th>Control (n=41)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary gas leakage</td>
<td>0 (0.00)</td>
<td>2 (4.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal injury</td>
<td>1 (2.44)</td>
<td>2 (4.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea syndrome</td>
<td>1 (2.44)</td>
<td>2 (4.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0 (0.00)</td>
<td>2 (4.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total incidence (%)</td>
<td>2 (4.88)</td>
<td>9 (21.95)</td>
<td>5.145</td>
<td>0.023</td>
</tr>
</tbody>
</table>

In this study, the changes of PaO₂, PaCO₂, and OI at different time points were compared. PaCO₂ at 1 h, 6 h and 12 h after starting NHFOV treatment was lower than BiPAP, indicating that NHFOV cleared PaCO₂ earlier than BiPAP. There were some differences in PaO₂ between the two groups after 72 h of treatment, and there were differences in OI after 24 h and 72 h of treatment, indicating that both NHFOV and BiPAP could improve blood oxygen and the oxygenation index. This study found that the non-invasive ventilator treatment time, oxygen inhalation time, and hospitalization time were lower in children with NHFOV treatment than BiPAP, which might be related to the fact that NHFOV treatment cleared PaCO₂ faster and improved PaO₂ and OI faster than BiPAP treatment.

In terms of complication studies, previous studies have found that NHFOV can effectively improve alveolar ventilation function, promote carbon dioxide excretion, improve the symptoms of dyspnea, and reduce lung injury and pneumothorax [24]. Another study found that the NHFOV mode in newborns can significantly reduce the occurrence of apnea and reduce the lowering of blood oxygen or the heart rate [18]. In this study, the incidence of complications with NHFOV treatment was found to be lower than that of BiPAP, which was consistent with the above studies.

The sample size of this study was small, and the observation time was short. It is necessary to further expand the sample size and increase the observation time in order to study the long-term recovery after treatment in both groups.

In summary, the use of non-invasive high-frequency oscillatory ventilation combined with a pulmonary surfactant can accelerate the time needed for carbon dioxide removal, shorten the treatment time, and reduce the occurrence of complications, and it is worth further clinical application.

**Disclosure of conflict of interest**

None.

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