Original Article

Pulmonary Outcomes of Early Extubation in Extremely Premature Infants (Gestational Age: 25–26 Weeks) with Synchronized Nasal Intermittent Positive-Pressure Ventilation

Eun Mi Choi, M.D., Jae Hyun Park, M.D., Chun Soo Kim, M.D., and Sang Lak Lee, M.D.
Department of Pediatrics, Keimyung University Dongsan Medical Center, Daegu, Korea

ABSTRACT

Purpose: To investigate the pulmonary outcomes of early extubation (within the first 24 hours of life) with synchronized nasal intermittent positive pressure ventilation (NIPPV) in extremely premature infants born at 25–26 weeks’ gestation.

Methods: Medical records of extremely premature infants (gestational age: 25–26 weeks) born and admitted to the Keimyung University Dongsan Medical Center between January 2015 and December 2015 (n=42) were reviewed retrospectively. The early extubation group included infants who were extubated within the first 24 hours of life and was compared with a control group that included infants who remained ventilated beyond the first 24 hours of life. Extubation failure was defined as the need for reintubation within 72 hours after extubation.

Results: Of the 35 enrolled infants, 22 (62.9%) were extubated within the first 24 hours of life. No significant differences in perinatal factors were observed between the early extubation and control groups. Between the two groups, the incidence rates of extubation failure (18.2% [4/22] vs. 7.7% [1/13], \( P=0.39 \)), reintubation (50.0% [11/22] vs. 46.2% [6/13], \( P=0.84 \)), mortality (18.2% [4/22] vs. 15.4% [2/13], \( P=0.83 \)), and the combined rates of clinical bronchopulmonary dysplasia (BPD) or death (40.9% [9/22] vs. 38.5% [5/13], \( P=0.89 \)) did not significantly differ.

Conclusion: Early extubation (within the first 24 hours of life) with synchronized NIPPV is safe and effective in the extremely premature infants born at 25-26 weeks’ gestation, and does not indicate increased risks of extubation failure and other morbidities.

Key Words: Extremely premature infants, Noninvasive ventilation

INTRODUCTION

Surfactant replacement and invasive mechanical ventilation are used to treat respiratory
distress syndrome (RDS) in premature infants. Although surfactant replacement in premature infants decreased the incidence of bronchopulmonary dysplasia (BPD), persistent invasive mechanical ventilation after surfactant replacement is the major risk factor of BPD. Early surfactant administration followed by extubation involving nasal continuous positive airway pressure (NCPAP) or nasal intermittent positive pressure ventilation (NIPPV) has been shown to decrease the incidence of BPD in very low birth weight infants (VLBW) in observational studies, and minimizing the need for mechanical ventilation via endotracheal tube in the first week of life.

NIPPV is a noninvasive mode of ventilation that uses a nasal interface that augments the infant’s spontaneous breath efforts by providing a backup rate. It is effective in premature infants who require respiratory support, as it reduces the incidence of premature apnea and atelectasis, and improves ventilation-perfusion matching while decreasing extubation failures. The incidence of BPD was also reduced in infants managed by NIPPV. In comparison with NCPAP, NIPPV reduced the need for endotracheal ventilation in premature infants with early extubation after receiving early surfactant for RDS.

Synchronized NIPPV can improve chest wall stability and pulmonary mechanics by decreasing thoracoabdominal motion asynchrony, increasing flow delivery by increasing the peak inspiratory pressure (PIP) to higher than the positive end-expiratory pressure (PEEP), increasing tidal and minute volumes, and decreasing work of breathing.

Although some studies from Korea investigated the therapeutic effect of NIPPV or CPAP in premature infants, studies on extremely premature infants are limited. In this study, we aimed to investigate the pulmonary outcomes of early airway extubation (within the first 24 hours of life) with synchronized NIPPV in extremely premature infants born at 25–26 weeks’ gestation.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 42 extremely premature infants born at 25–26 weeks’ gestation who were admitted to the neonatal intensive care unit (NICU) of Keimyung University Dongsan Medical Center between January and December 2015. Two infants with perinatal asphyxia (Apgar score at 5 min ≤3), three infants with perinatal infection, and two infants who were transferred to another hospital were excluded.

All the infants received cardiopulmonary resuscitation in the delivery room according to the Neonatal Resuscitation Program (NRP) by the American Academy of Pediatrics and the American Heart Association. Endotracheal intubation was immediately performed upon delivery, and an exogenous surfactant (Curosurf®, Chiesi Pharmaceuticals, Parma, Italy) was immediately administrated as part of prophylactic therapy at a dose of 200 mg/kg. The second dose of the exogenous surfactant was administrated to infants who had persistent respiratory distress and received ventilator care without decreased mean airway pressure or oxygen requirement at 6 hours after the initial dose. The ventilator was set in the synchronized intermittent mandatory ventilation (SIMV) mode to facilitate weaning from the mechanical ventilator. The criteria for extubation were as follows: PIP <15 cmH₂O; PEEP <7 cmH₂O; intermittent mandatory ventilator rate <15 breaths per minute; and fraction of inspired oxygen (FiO₂) <0.3, which were not different from those in other studies.

Caffeine citrate (Neocaf®, loading dose, 20 mg/kg) was intravenously administrated before extubation. The decision to extubate within the first 24 hours of life or to continue with mechanical ventilation was at the attending neonotologist’s discretion.

After airway extubation, nasal respiratory support was provided via a nasal prong by using the Medijet NCPAP System (MedinMedical Innovations GmbH, Puchheim, Germany), which was set in the synchronized NIPPV mode. During synchronized NIPPV, PIP was started at 10–15 cmH₂O, PEEP was set at 6–9 cmH₂O, inspiratory time was set at 0.6s, and the backup or mandatory rate was set between 20 and 30 breaths per minute. The FiO₂ was adjusted to maintain SpO₂ at 88–95%.

The early extubation group, which included infants extubated within the first 24 hours of life, was compared with the control group, which included infants who remained ventilated beyond the first 24 hours of life. Extubation failure was defined as the need for reintubation within 72 hours after extubation. The criteria were as follows: respiratory acidosis (PaCO₂ >65 mmHg of two consecutive blood gases); FiO₂ >0.4 to maintain SpO₂ at 88–95%; and apnea episodes that required bag/mask ventilation.

The following variables were analyzed for the perinatal factors: gestational age (GA), birth weight (BW), delivery mode, sex, multiple gestation, antenatal steroid use, pregnancy-induced hypertension (PIH), preterm premature rupture of membrane
Neonatal Med 2016 May;23(2):81-87  
http://dx.doi.org/10.5385/nm.2016.23.2.81  

(PPROM), oligohydramnios, and Apgar score at 5 min.

The outcomes after airway extubation were characterized by the rates of extubation failure, the need for endotracheal ventilation at 7 days of age, reintubation, pulmonary hemorrhage, air leak syndrome, intraventricular hemorrhage (IVH) grade ≥3, patent ductus arteriosus (PDA) treated with ibuprofen or surgical ligation, necrotizing enterocolitis (NEC) modified Bell’s stage >II, pneumoperitoneum detected on abdominal radiography, bowel perforation detected on explorative laparotomy, mortality, and combined rates of clinical BPD or death.

Among survived infants, the neonatal morbidities during hospitalization included days on endotracheal ventilation, days on nasal respiratory support, days on supplemental oxygen via a nasal prong without positive pressure support, days on total parenteral nutrition (TPN), clinical BPD, postnatal dexamethasone use for BPD prevention, and retinopathy of prematurity (ROP) requiring treatment. Clinical BPD was defined as the need for supplemental oxygen or positive pressure support at 36 weeks postmenstrual age.

Statistical analyses

SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Perinatal factors, variables associated with acute pulmonary outcomes and neonatal morbidities were compared between the two groups by using the Student’s t-test and Fisher exact test. A P-value <0.05 was considered statistically significant.

RESULTS

Of the 35 infants, 22 (62.9%) were extubated within the first 24 hours after birth. The mean time to airway extubation was 18.8±3.4 hours in the early extubation group and 40.5±27.7 hours in the control group.

The comparison of the perinatal factors between the early extubation and control groups is shown in Table 1. No significant differences in GA, BW, delivery mode, sex, multiple gestation, antenatal steroid use, PIH, PPROM, oligohydramnios, and Apgar score at 5 min were observed between the two groups.

The outcomes after airway extubation are shown in Table 2. The incidence of extubation failure in the early extubation group (18.2%, 4/22) was higher than that in the control group (13.3%, 2/15), but the difference was not statistically significant (P=0.69). In terms of the need for endotracheal ventilation at 7 days of age, no significant difference was found between the two groups (31.8% [7/22] vs. 7.7% [1/13], P=0.10). Of the 35 enrolled infants, 17 (48.6%) required reintubation during hospitalization. PDA ligation was performed in 13 infants and was the most common cause of reintubation. Exploratory laparotomy, the second common cause of reintubation, was performed in 6 infants because of pneumoperitoneum. Bowel perforation was not detected in 2 of 6 infants who underwent exploratory laparotomy. Reintubation derived from compression of the nasal septum by the nasal prongs was not developed. Between the two groups, no significant differences were found in the mortality (18.2% [4/22] vs. 15.4% [2/13], P=0.83) and the combined rates of clinical BPD or death (40.9% [9/22] vs. 38.5% [5/13], P=0.89). The incidence of other neonatal morbidities also did not significantly differ between the two groups (P>0.05).

Among survived infants, the neonatal morbidities during hospitalization are shown in Table 3. The time on endotracheal ventilation in the early extubation group (6.1±8.5 days) was longer than that in the control group (4.0±3.2 days), but the difference was not statistically significant (P=0.44). The times on nasal respiratory support and supplemental oxygen without positive pressure support were not significantly different between the two groups (P>0.05). Between the two groups, no significant differences were found in the rates of clinical BPD (27.8% [5/18] vs. 27.35% [3/11], P=0.98) and postnatal dexamethasone use for BPD prevention (44.4% [8/18] vs. 54.5% [6/11], P=0.67).

Table 1. Comparison of the Perinatal Factors between the Early Extubation and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Early extubation (n=22)</th>
<th>Control (n=13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>25.6±0.5</td>
<td>25.4±0.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>874±116</td>
<td>839±143</td>
<td>0.44</td>
</tr>
<tr>
<td>C-sec, n (%)</td>
<td>22 (100%)</td>
<td>12 (92.3%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>15 (68.2%)</td>
<td>6 (40.0%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Multiple gestation, n (%)</td>
<td>4 (18.2%)</td>
<td>3 (23.1%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Antenatal steroid use, n (%)</td>
<td>21 (95.5%)</td>
<td>13 (100%)</td>
<td>0.44</td>
</tr>
<tr>
<td>PROM, n (%)</td>
<td>12 (54.5%)</td>
<td>9 (69.2%)</td>
<td>0.39</td>
</tr>
<tr>
<td>PIH, n (%)</td>
<td>2 (9.1%)</td>
<td>0</td>
<td>0.26</td>
</tr>
<tr>
<td>Oligohydramnios, n (%)</td>
<td>3 (13.6%)</td>
<td>2 (15.4%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Apgar score, 5 min</td>
<td>7.5±0.6</td>
<td>7.3±0.9</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Abbreviations: PPROM, preterm premature rupture of membrane; PIH, pregnancy-induced hypertension.
Table 2. Comparison of the Neonatal outcomes after Airway Extubation

<table>
<thead>
<tr>
<th></th>
<th>Early extubation (n=22)</th>
<th>Control (n=13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to extubation (hr)</td>
<td>18.8 ± 3.4</td>
<td>40.5±27.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Extubation failure, n (%)</td>
<td>4 (18.2%)</td>
<td>1 (7.7%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Reintubation, n (%)</td>
<td>11 (50.0%)</td>
<td>6 (46.2%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Endotracheal ventilation at 7 days of age, n (%)</td>
<td>7 (31.8%)</td>
<td>1 (7.7%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Air leak syndrome, n (%)</td>
<td>1 (4.5%)</td>
<td>2 (15.4%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Pulmonary hemorrhage, n (%)</td>
<td>2 (9.1%)</td>
<td>1 (7.7%)</td>
<td>0.89</td>
</tr>
<tr>
<td>IVH grade≥3, n (%)</td>
<td>1 (4.5%)</td>
<td>1 (7.7%)</td>
<td>0.70</td>
</tr>
<tr>
<td>PDA requiring treatment, n (%)</td>
<td>13 (59.1%)</td>
<td>9 (69.2%)</td>
<td>0.55</td>
</tr>
<tr>
<td>NEC (Modified Bell's Stage≥II), n (%)</td>
<td>4 (18.2%)</td>
<td>3 (23.1%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Pneumoperitoneum, n (%)</td>
<td>5 (22.7%)</td>
<td>1 (7.7%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Bowel perforation, n (%)</td>
<td>3 (13.6%)</td>
<td>1 (7.7%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>4 (18.2%)</td>
<td>2 (15.4%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Clinical BPD* or death, n (%)</td>
<td>9 (40.9%)</td>
<td>5 (38.5%)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Plus-minus values are mean±SD.

*Clinical BPD was defined as the need for supplemental oxygen or positive pressure support at 36 weeks postmenstrual age.

Table 3. Among Survived Infants, Neonatal Morbidities during Hospitalization

<table>
<thead>
<tr>
<th></th>
<th>Early extubation (n=18)</th>
<th>Control (n=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days on endotracheal ventilation</td>
<td>6.1±8.5</td>
<td>4.0±3.2</td>
<td>0.44</td>
</tr>
<tr>
<td>Days on nasal respiratory support</td>
<td>60.1±11.0</td>
<td>56.±16.6</td>
<td>0.51</td>
</tr>
<tr>
<td>Days on supplemental oxygen without positive respiratory support</td>
<td>0.1±0.4</td>
<td>0</td>
<td>0.45</td>
</tr>
<tr>
<td>Supplemental oxygen or positive pressure support at 28 days of age, n (%)</td>
<td>18 (100%)</td>
<td>10 (90.9%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Days on TPN</td>
<td>38.5±23.7</td>
<td>42.5±29.6</td>
<td>0.70</td>
</tr>
<tr>
<td>Clinical BPD*, n (%)</td>
<td>5 (27.8%)</td>
<td>3 (27.3%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Postnatal dexamethasone use for BPD prevention, n (%)</td>
<td>8 (44.4%)</td>
<td>6 (54.5%)</td>
<td>0.67</td>
</tr>
<tr>
<td>ROP requiring treatment, n (%)</td>
<td>3 (16.7%)</td>
<td>1 (9.1%)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Plus-minus values are mean±SD.

* Clinical BPD was defined as the need for supplemental oxygen or positive pressure support at 36 weeks postmenstrual age.

Abbreviations: TPN, total parenteral nutrition; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity.

DISCUSSION

The rate of early extubation (within the first 24 hours of life) using synchronized NIPPV was 59.5%, and the rate of successful early extubation without extubation failure was 81.8%. Our data support the application of early extubation (within the first 24 hours of life) with synchronized NIPPV, which indicate a success rate that exceeds the previously reported rates\textsuperscript{27,28}. Al Faleh et al. reported that the rate of early extubation (in the first 48 hours of life) with CPAP in extremely low birth weight infants (ELBWI) was 32% and that the rate of successful extubation was 80%\textsuperscript{28}. In other previous trials, the rates of extubation failure with NIPPV were reported to range from 5% to 15% in VLBWI\textsuperscript{29-31}.

Ramanathan et al.\textsuperscript{6} reported that 17% of infants born at 26-29 weeks' gestation needed endotracheal ventilation at 7 days of age in the NIPPV group. Because of lower gestational age in the present study, it might be associated with the higher rates in the need for endotracheal ventilation at 7 days of age.

Fluctuating cerebral blood flow (CBF) is associated with the development of IVH\textsuperscript{29,30}. High PCO\textsubscript{2} levels have been associated with the development of IVH, which contributes to the fluctuating CBF\textsuperscript{31,32}. However, in a recent multicenter study\textsuperscript{33}, permissive hypercapnia did not increase the risk of IVH. In the present study, we targeted the maintenance of capillary PCO\textsubscript{2} levels ≤65 mmHg. The incidence of IVH grade ≥3 in the early
extubation group was lower compared to those reported in the control group and in the latest nationwide survey (GA 25-26 weeks: 19.9%\textsuperscript{14}).

Invasive mechanical ventilation is a major risk factor of BPD\textsuperscript{2}. The time on endotracheal ventilation in this present study was relatively shorter compared to those reported in previous studies\textsuperscript{6,13}. According to the latest nationwide survey\textsuperscript{35}, the combined rates of BPD or death were 68.7% at 25 weeks GA and 58.9% at 26 weeks GA. In the present study, the combined rate of clinical BPD or death was about 40%. The duration of invasive ventilator use was a significant risk factor of ROP according to a latest nationwide survey\textsuperscript{36}. The incidence of ROP requiring treatment in the early extubation group was higher than that in the control group, but relatively lower than that in the latest nationwide survey\textsuperscript{36}. However, no clear benefit was demonstrated for the use of synchronized NIPPV in terms of lowering the incidence rates of BPD or ROP. Further evidence of efficacy is needed.

Pneumoperitoneum as a complication of barotrauma is a rare condition resulting from mechanical ventilation\textsuperscript{37}. It is interesting that pneumoperitoneum without bowel perforation developed in two infants who were receiving synchronized NIPPV. In a previous study, gastric perforation developed in neonates who were receiving NIPPV\textsuperscript{38}. However, intestinal perforation was not associated with NIPPV use in the other studies\textsuperscript{9-13,16}. Further studies are needed to clarify whether pneumoperitoneum is a complication of nasal respiratory support.

Massive pulmonary hemorrhage within the first 5 days of life is a major cause of early death in ELBW\textsuperscript{39,40}. In this study, massive pulmonary hemorrhage developed in two infants who were receiving synchronized NIPPV, which led to their deaths. However, no clear evidence shows that nasal respiratory support increases the risk of fatal massive pulmonary hemorrhage.

In conclusion, early extubation (within the first 24 hours of life) with synchronized NIPPV is safe and effective in the extremely premature infants born at 25-26 weeks’ gestation, and does not indicate increased risks of extubation failure and other morbidities. The lack of a comparative investigation of episodes of apnea or bradycardia between the two groups is a limitation of this study. Further prospective studies, preferably larger-scale randomized controlled trials that incorporate NIPPV and NCPAP comparisons, are needed to assess the effectiveness of synchronized NIPPV in extremely premature infants.

REFERENCES


