

# Impact of Prolonged Mechanical Ventilation in Very Low Birth Weight Infants: Results From a National Cohort Study

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**Objective** To evaluate the in-hospital consequences of prolonged respiratory support with invasive mechanical ventilation in very low birth weight infants.

**Study design** A cohort study was performed using prospectively collected data from 69 neonatal intensive care units participating in the Korean national registry. In total, 3508 very low birth weight infants born between January 1, 2013 and December 31, 2014 were reviewed.

**Results** The adjusted hazard ratio for death increased significantly for infants who received mechanical ventilation for more than 2 weeks compared with those were mechanically ventilated for 7 days or less. The individual mortality rate increased after 8 weeks, reaching 50% and 60% at 14 and 16 weeks of cumulative mechanical ventilation, respectively. After adjusting for potential confounders, the cumulative duration of mechanical ventilation was associated with a clinically significant increase in the odds of bronchopulmonary dysplasia and pulmonary hypertension. Mechanical ventilation exposure for longer than 2 weeks, compared with 7 days or less, was associated with retinopathy of prematurity requiring laser coagulation and periventricular leukomalacia. The odds of abnormal auditory screening test results were significantly increased in infants who needed mechanical ventilation for more than 4 weeks. A longer cumulative duration of mechanical ventilation was associated with increased lengths of hospitalization and parenteral nutrition and a higher probability of discharge with poor achievement of physical growth.

**Conclusions** Although mechanical ventilation is a life-saving intervention for premature infants, these results indicate that it is associated with negative consequences when applied for prolonged periods. (*J Pediatr* 2017;■■■:■■■-■■■).

Respiratory support with mechanical ventilation is essential for the survival of many very preterm infants. However, prolonged mechanical ventilation is associated with numerous complications that lead to several morbidities in preterm infants.<sup>1-3</sup> Early weaning from mechanical ventilation may reduce the risk of these complications.<sup>1,4</sup> Recent investigations found that a longer cumulative duration of mechanical ventilation accounted for an increased risk of bronchopulmonary dysplasia (BPD), and that earlier attempts to extubate could decrease the incidence of BPD and the duration of hospitalization in extremely preterm infants.<sup>5,6</sup> BPD is a chronic lung disease in preterm infants that results in high mortality and prolonged hospitalization. BPD is also associated with an increased risk of growth failure and neurodevelopmental delay.<sup>7-9</sup> Clinicians and parents routinely have questions about the likelihood of survival or of complicated diseases affecting intubated preterm infants on mechanical ventilation. However, few reports have focused on the clinical outcomes related to the length of mechanical ventilation. This study aimed to evaluate the in-hospital consequences of prolonged mechanical ventilation, including mortality, in very low birth weight (VLBW) infants using a large nationwide cohort. We hypothesized that longer cumulative durations of mechanical ventilation would be correlated with mortality and other morbidities beyond chronic respiratory insufficiency.

## Methods

We performed a cohort study using prospectively collected data from 69 neonatal intensive care units participating in the Korean Neonatal Network (KNN). The KNN database provides maternal, delivery, and neonatal data until first patient discharge, and the data are collected by trained staff using a standardized operating procedure.<sup>10</sup> A total of 3508 VLBW infants born between January 1, 2013 and December 31, 2014 were reviewed. To reduce the skew of study outcomes because of other causes, we

AABR	Automated auditory brainstem response
BPD	Bronchopulmonary dysplasia
HR	Hazard ratio
IVH	Intraventricular hemorrhage
KNN	Korean Neonatal Network
NEC	Necrotizing enterocolitis
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
VLBW	Very low birth weight

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excluded infants with congenital respiratory or cardiovascular anomalies. Infants who had incomplete data or who transferred to other hospitals were also excluded.

The maternal variables included pregnancy-induced hypertension, oligohydramnios, and histologically confirmed chorioamnionitis. The neonatal variables included gestational age, birth weight, sex, immediate postnatal surfactant use for respiratory distress syndrome, pulmonary air leak, pulmonary hemorrhage, cumulative duration of invasive mechanical ventilation, respiratory support at 36 weeks of postmenstrual age, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bacterial sepsis, use of dexamethasone, pulmonary hypertension, periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), results of automated auditory brainstem response (AABR) before discharge, length of hospitalization, cumulative duration of parenteral nutrition, and survival to hospital discharge or death. We identified the cause of death for infants who died, and death from cardiorespiratory causes was indicated when infants expired from respiratory distress syndrome, persistent pulmonary hypertension, pulmonary hypoplasia, pulmonary hemorrhage, air leak syndrome, or BPD. For surviving infants, we collected data on weight, height, and head circumference at the time of discharge. The cumulative duration of mechanical ventilation was counted as each day that the infant received any respiratory support through an endotracheal tube because of respiratory insufficiency. Brief intubation for surgery with general anesthesia was not included in the calculation of mechanical ventilation duration. BPD was defined as the need for supplemental oxygen or positive pressure support at 36 weeks PMA, with moderate to severe BPD determined by the National Institutes of Health severity-based consensus definition of BPD.<sup>2,11</sup> The most severe stage of IVH based on the results of all brain ultrasound findings until first discharge was recorded regardless of the time of first observation or occurrence, as this information was not collected. IVH staging was determined according to Papile classification system.<sup>12</sup> NEC was defined according to a modified Bell staging classification. Bacterial sepsis was defined as a positive result for 1 or more bacterial cultures obtained from the blood of infants with clinical signs of infection or treated with appropriate antibiotics for 5 or more days or until death. Pulmonary hypertension was considered present only when accompanied by medical treatment after diagnosis based on echocardiography. PVL was diagnosed based on the results of brain ultrasound or MRI findings until first discharge. The cumulative duration of parenteral nutrition was the sum of the total days when any amino acids or lipids were provided intravenously before death or neonatal intensive care unit discharge.

The primary outcome was survival to hospital discharge or death. Secondary outcomes were various in-hospital morbidities, including BPD; pulmonary hypertension; ROP followed by laser coagulation; PVL; abnormal AABR results; weight, height, and head circumference at the time of discharge; and duration of parenteral nutrition and hospital stay.

The registration of data in the KNN was approved by the institutional review board of each participating center. In-

formed consent was obtained from the parents of each infant prior to participation in the KNN registry.

### Statistical Analyses

Demographic data were expressed as medians (IQR) or percentages. To assess the independent correlations between the cumulative duration of mechanical ventilation and each study outcome, we used ordinal regression (Polytomous universal model [PLUM]) analysis with adjustment for gestational age and birth weight. We then evaluated the hazard ratio (HR) according to increased durations of mechanical ventilation using Cox proportional regression analysis, with adjustment for factors that had a  $P < .10$  in the univariate analysis for all infants. We also evaluated the ORs of each categorical outcome according to increased durations of mechanical ventilation using multivariate logistic regression analysis, with adjustment for factors that had a  $P$  value of  $< .10$  in the univariate analysis for surviving infants. Correlations between continuous outcomes were analyzed using the Spearman test. In all analyses,  $P < .05$  was considered significant. Statistical analyses were conducted using SPSS v 21 (SPSS Inc, Chicago, Illinois).

## Results

During the 2-year study period, 3508 VLBW infants were registered in the KNN database. Of these infants, 260 were excluded for having congenital respiratory or cardiovascular anomalies ( $n = 48$ ), having insufficient data ( $n = 12$ ), or being transferred to other hospitals ( $n = 200$ ). We divided all the included infants into 5 groups according to their cumulative duration of mechanical ventilation: 7 days or less, 8-14 days, 15-28 days, 29-42 days, and more than 43 days. Of the 3248 VLBW infants, approximately 40% received mechanical ventilation for less than 1 week (41.1%;  $n = 1334$ ), and 20.4% ( $n = 662$ ) did not receive any type of invasive mechanical ventilation. Approximately 20% (18.4%;  $n = 598$ ) of infants needed mechanical respiratory support for more than 4 weeks, and 11% ( $n = 357$ ) required protracted mechanical ventilation for more than 6 weeks (Figure 1; available at [www.jpeds.com](http://www.jpeds.com)).

The demographic characteristics and morbidity rates for each group are provided in Table I (available at [www.jpeds.com](http://www.jpeds.com)). As lower gestational age and lower birth weight are predisposing factors for prolonged mechanical ventilation, we calculated correlation coefficients for each characteristic while adjusting for gestational age and birth weight. Histologic chorioamnionitis, history of surfactant treatment, air leak, seizure, stage 2 or higher NEC, bacterial sepsis, and postnatal use of dexamethasone were associated with a longer cumulative duration of mechanical ventilation (Table I).

### Primary Outcome

After adjusting for all confounding variables, the HR for all-cause death increased to 2.85 (95% CI 1.94-4.21) for infants who received mechanical ventilation for 15-28 days compared with those who received mechanical ventilation for 7 days or less, and it was 8.33 (95% CI 5.61-12.39) for infants who needed mechanical ventilation for more than 6 weeks (Table II).

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