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Association between mechanical ventilation and neurodevelopmental disorders in a nationwide cohort of extremely low birth weight infants

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ABSTRACT

Mechanical ventilation for preterm infants independently contributes to poor neurodevelopmental performance. However, few studies have investigated the association between the duration of mechanical ventilation and the risk for various developmental disorders in extremely low birth weight (ELBW) (<1000 g) infants. Using a large nationwide database, we did a 10-year retrospective follow-up study to explore the effect of mechanical ventilation on the incidence of cerebral palsy (CP), autism spectrum disorder (ASD), intellectual disability (ID), and attention-deficit/hyperactivity disorder (ADHD) in ELBW infants born between 1998 and 2001. Seven hundred twenty-eight ELBW infants without diagnoses of brain insults or focal brain lesions in the initial hospital stay were identified and divided into three groups (days on ventilator: ≦2, 3–14, ≧15 days). After adjusting for demographic and medical factors, the infants in the ≧15 days group had higher risks for CP (adjusted hazard ratio: 2.66; 95% confidence interval: 1.50–4.59; $p < 0.001$) and ADHD (adjusted hazard ratio: 1.95; 95% confidence interval: 1.02–3.76; $p < 0.05$), than did infants in the ≦2 days group. The risk for ASD or ID was not significantly different between the three groups. We conclude that mechanical ventilation for ≧15 days increased the risk for CP and ADHD in ELBW infants even without significant neonatal brain damage. Developing a brain-protective respiratory support strategy in response to real-time cerebral hemodynamic and oxygenation changes has the potential to improve neurodevelopmental outcomes in ELBW infants.

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1. Introduction

Using a ventilator has been a primary factor for decreasing the mortality of preterm extremely low birth weight (ELBW) (<1000 g) infants in the past three decades (Lau, Ambalavanan, Chakraborty, Wingate, & Carlo, 2013). Approximately 80% of ELBW infants depend on a ventilator to breathe for a few days to a few months after they have been born (Lemons et al., 2001). Although using a ventilator increases the survival of ELBW infants, prolonged dependence on one may cause adverse neurodevelopmental outcomes (Lemons et al., 2001; Vohr et al., 2000).

Preterm infants on a ventilator often simultaneously experience complicated morbidities and medications, such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), sepsis, and postnatal steroids, which may adversely affect their neurological development (Vohr et al., 2000). Therefore, their developmental outcomes are the result of the combined contribution of multiple medical risk factors. Studies have consistently indicated that even after adjusting for other risk factors, ventilator use itself is an independent risk factor for adverse neurodevelopment in preterm infants. For example, Brown, Doyle, Bear, and Inder (2006) found that longer dependence on a ventilator led to poorer muscle tone, reflexes, and spontaneous movement at term in very preterm infants below 32 weeks of gestation or less than 1500 g at birth (Brown, Doyle, Bear, & Inder, 2006). Similarly, other studies that longitudinally evaluated the development of very preterm infants reported that the number of days on a ventilator were a significant predictor of the mental and psychomotor developmental scores on the Bayley Scales of Infant Development (Bozynski et al., 1987; Kobaly et al., 2008; Saldir, Sarici, Bakar, & Ozcan, 2010; Thomas, Meinzen-Derr, Hoath, & Narendran, 2012; Trittmann, Nelin, & Klebanoff, 2013).

Little is known about the association between using a ventilator and the incidence of developmental disorders in preterm children except for cerebral palsy (CP). However, the literature reports controversial results about the effect of using a ventilator on the incidence of CP in preterm children. Drougia et al. (2007) found a significant association between the number of days on a ventilator and the incidence of CP only for the preterm cohort born between 1997 and 2003 but not for the cohort born between 1989 and 1996. The authors concluded that the birth period of the studied cohort affected the independent contribution of using a ventilator to the incidence of CP in preterm infants because of continuous modifications in perinatal care for this population over the past three decades. This seems to be supported by the findings of other studies. Studies with a sample born before 1997 consistently found no association between the duration of mechanical ventilation and the incidence of CP (Hansen et al., 2004; Tran, Gray, & O'Callaghan, 2005; Wilson-Costello et al., 1998); however, one other study (Powell, Kerkering, Barker, & Rozycki, 2006) with a sample born between 1996 and 2001 did find one. Additionally, methodological differences in the studies (sample size, gestational age of the enrolled sample, and confounders adjusted for) may also contribute to inconsistent findings between studies. Therefore, future studies with large samples born during the past two decades are needed to clarify the independent contribution of using a ventilator to CP incidence in the preterm population.

Few studies have investigated the effect of ventilator support on the risk of developmental disorders in ELBW infants. Therefore, we used a nationwide population-based database to explore the associations between the duration of using a ventilator and the risk of developmental disorders, specifically, CP, autism spectrum disorder (ASD), intellectual disability (ID), and attention-deficit/hyperactivity disorder (ADHD) in ELBW children. A 10-year retrospective follow-up was done on a cohort of ELBW infants born between 1998 and 2001.

2. Method

2.1. Data sources

Data, including ambulatory care claims, inpatient claims, and registration for beneficiaries, were obtained from Taiwan's National Health Insurance Research Database (NHIRD) provided by the Bureau of National Health Insurance (BNHI). Taiwan's National Health Insurance (NHI) program began in March 1995. By the end of February 1996, it covered 19.2 million Taiwanese residents (92%) (Chiang, 1997) and 97% of the total population had enrolled by the end of 2001 (Lu & Hsiao, 2003). The estimated coverage rate for those under 19 years old was around 98.7% in 2004 (Chen, Liu, Su, Huang, & Lin, 2007). Since 1996, the BNHI has anonymized patient registration files by deleting names and identification codes. The original claim data, coded based on The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (Buck, 2003) are left and constitute the content of the NHIRD. The BNHI does quarterly expert reviews on a random sample for every 50–100 ambulatory and inpatient claims to ensure the accuracy of the claims files (Cheng, 2003), and data retrieved from the NHIRD are considered to be complete and accurate (Chen, Chen, & Li, 2010; Sun et al., 2012).

Ethical approval for this study was obtained from the Institutional Review Board of Chi Mei Medical Center (10201-E02). We were allowed to access the databases by the Review Committee of the National Health Research Institutes (NHIRD-102-004).

2.2. Study population

Children with an ICD-9-CM code of 765.x1-765.x3 were born before 37 weeks of gestation (i.e., preterm) and weighed less than 1000 g at birth (i.e., ELBW). Therefore, a cohort born between January 1998 and December 2001, with a code of 765.x1-765.x3 were selected as the study population for this research. The exclusionary criteria were: (1) died during the initial hospital